جامعة بيرزيت
Birzeit University

The Most Commonly Used Drugs at the Primary Health Care Level in Palestine

Training and Self Learning Manual

2003

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Preface

The issue of drug availability and accessibility is a matter of immense concern for health services all over the world, especially in developing countries. Commonly, a large proportion of the health budget is spent on medications, often unnecessarily, and thus adding financial burdens on sometimes already over-burdened health care systems, and contributing to the problem of iatrogenic diseases as well. Over-prescribing, multi-drug prescribing, misuse of drugs, use of unnecessary expensive drugs and overuse of antibiotics and injections are cited in the literature as the most common problems of irrational use by prescribers as well as consumers.

Strategies aimed at improving the quality of primary health care services and reducing medical and health care costs are linked to the promotion of rational drug use. These considerations prompted the World Health Organization (WHO) to develop its policy for rational drug use, which by now is widely accepted as essential for improving health care quality and reducing health care costs at the same time. However, a rational drug policy is not merely the production of an Essential Drug list, although such a list is a step in the right direction, but only one of many. The essential drug concept entails series of orchestrated measures and steps encompassing the development of national drug policies, with selection, procurement, quantification, quality assurance, inventory control, distribution, financing, and rational drug use by prescribers supported by treatment guidelines, all integrated within an overall scheme. All these measures and steps entail a good amount of training/re-training, and effective supervision aimed at changing prescribing and dispensing practices at different levels.

Parallel to and in support of the initiative recently taken by the Palestine Ministry of Health in developing an Essential Drug List and Drug Formulary, the Institute of Community and Public Health embarked on field research to identify the most commonly used medications at the Primary Health Care level. The rationale for such an activity entailed the fact that drug misuse also takes place within the private sector which did not adopt the Palestine Ministry of Health Essential Drug List. The other rationale is that health professionals working in all health sub-sectors continue to need training and re-training in rational prescribing so that the old prescribing practices would diminish and new ones would replace them. While the List and the Formulary are very good steps taken in the right direction, they cannot solve the problem of antibiotic over-prescribing, for instance, nor the numerous other encountered problems engrained in local medical practices, and that to a large extent stem from insufficient knowledge of drugs and their appropriate use and lack of training in rational practices.

Thus combining many of the essential medications listed in the Palestinian Drug Formulary with selected others that were found to be very commonly used by private practitioners, this training aid and self/learning reference manual was compiled with the aim of providing the prescriber with essential information on the proper use of these commonly used medications. It specifically addresses the identified weaknesses in the current local prescribing and dispensing practices. Utilizing classical texts and references, including key WHO publications, the compilation led to the production of an initial draft. The initial draft was circulated for review and comments to about 20 local experts: physicians and pharmacists

specialized in particular fields, and working within the different sub-sectors of health services (governmental, UNRWA, NGO services and private practitioners). Much discussion, re-drafting and re-modification ensued, ending up with the production of the final version of this training/self-learning manual in 2003.

We hope that this initiative will contribute to improved practices by physicians, pharmacists and nurses in Palestine.

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June 2003

How to Use this Manual:

This manual is divided into 13 chapters organized according to therapeutic categories. Each of the chapters is divided into groups and subgroups to facilitate comparisons of drugs. Some drugs with multiple uses may be listed in more than one section of this manual.

Each chapter starts with an overview of the therapeutic category, then each drug is presented in the drug monographs that include:

- ***Drug summary:*** A small description of the drug.
- ***Indications:*** Approved indications, mainly on the primary care level.
- ***Contraindications:*** Specific conditions in which the drug should not be used.
- ***Dosage forms:*** Available dosage form on the primary health care level.
- ***Recommended dosage:*** Recommended dosage regimens and directions for administration.
- ***Use in special cases:*** Which includes use of these drugs in pregnancy, lactation, children, and patients who have any renal or liver disease.
- ***Precautions and warning:*** This section lists conditions in which use of the drug may be hazardous, and the medical team may need to use alternative dose regimens or drugs.
- ***Adverse drug reactions:*** Reported side effects of the drug.
- ***Interactions:*** A summary of documented drug-drug interactions.
- ***Overdosage:*** The clinical symptoms of toxicity or an accidental overdose, and initial method of treatment.
- ***Brands:*** The known brand names of the drug in the Palestinian market, and the companies that manufacturers them.

One can find the *abbreviations* and *pregnacy categories* included in the chapters in the first few pages. The *appendix* at the end of the manual include the Price list, the definitions, and general index.

The *Price List*, listing medications by generic name, brand name, concentration, dosage form, packaging and price list based on 2002 lists obtained locally (needless to say, the price list needs to be updated regularly, and we are setting up the infrastructure for such a task). This list represent an attempt at introducing several elements in the prescribing process at once: The use or remembering of generic names - a gradual process of using generic names of prescription is ultimately desired - the use of the correct dose and dosing interval - as we know that this is also a local problem - as well as paying attention to the cost, given that particular attention should be paid to the unit cost given the same drug quality, when prescribing. Note that local drug companies and wholesalers do produce price lists of available drugs, but those include merely the brand name and not the generic name nor the strength of the medication. These lists are used for commercial reasons at the level of the pharmacy, and are usually not accessible to doctors.

The *Reference List* includes the detailed books, and articles or journals that have been used to obtain the information compiled for the monographs.

The *Index* at the end provides a list of all the drugs that have been listed or mentioned in this reference. Brand names are written in *italic font*, while the proprietary/generic name in small letters.

The drugs mentioned in the Palestinian MOH EDL (2000) are indicated by $^{(P)}$, while the drugs mentioned in the WHO EDL 1999 are identified as $^{(WHO)}$ after each drug name. It should be emphasized that the resemblance with the previously mentioned lists is by the generic name ONLY, and not the concentration or dosage form.

Abbreviations

General Abbreviations	
ACE	Angiotensin-Converting Enzyme
AIDS	Acquired Immunodeficiency Syndrome
AST	Aspartate Amino-Transferase (*a high blood level of AST can occur with a heart attack or liver disease...*)
ALT	Alanine Amino Transferase
AV	Atrio-Ventricular
BBB	Blood Brain Barrier
B.P.	British Pharmacopoeia
BNF	British National Formulary
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC	Center for Disease Control
cGMP	cyclic Gaunine Mono-Phosphate
CHF	Congestive Heart Failure
Cl_{cr}	Creatinine Clearance
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CSF	Cerebrospinal Fluid
CVA	Cerebrovascular Accident (leads to a stroke)
CVS	Cerebrovascular System
e.g.	for example
ECG	Electrocardiogram: recording of the electrical activity of the heart
EEG	Electroencephalogram: measures the electrical current within the brain
ENT	Ear, Nose, and Throat
EPI	Expanded Program on Immunization
ERT	Estrogen Replacement Therapy
FDA	Food & Drug Administration

G6PD	Glucose-6-Phosphate Dehydrogenase
GABA	Gamma Aminobutyric Acid
GH	Growth Hormone
GI tract	Gastrointestinal Tract
GU	Genitourinary
GERD	Gastro-Esophageal Reflux Disease
GFR	Glomerular Filtration Rate
HDL	High-Density Lipoprotein(s)
Hgb	Hemoglobin
Hib	*Haemophilus influenzae* type B
HPA	Hypothalamic Pituitary Adrenocortical
I.U.	International Unit
ICD 10	The International Statistical Classification of Diseases and Related Health Problems, tenth revision
IOP	Intra-Ocular Pressure
IUD	Intra-Uterine Device
LDL	Low-Density Lipoprotein
LVF	Left Ventricular Failure
MAO	Mono-Amine Oxidase
MAOI	Mono-Amino Oxidase Inhibitor
meq	Milliequivalent
MI	Myocardial Infarction
mg	Milligram
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OC/ OCs	Oral Contraceptive/s
Oint.	Ointment
OTC	Over the counter
PKU	Phenylketonuria
PT	Prothrombin Time
REM	Rapid Eye Movement
RTS	Respiratory Tract System
SA	Sinoatrial
SLE	Systemic Lupus Erythematosus

S.O.B.	Shortness of Breath
SPF	Sun Protection Factor
SSRI	Selective Seretonin Reuptake Inhibitors
SR	Sustained Release
STD	Sexually Transmitted Diseases
Supp.	Suppository
Susp.	Suspention
Syr.	Syrup
t ½	Therapeutic half life
Tab./tabs.	Tablet, tablets
TCA	Tricyclic Antidepressants
TIA	Transient Ischemic Attack (Stroke)
*u*g or mcg	Microgram
U.S.P.	United States Pharmacopoeia
UNRWA	United Nations Relief and Works Agency
UNICEF	United Nations Children's Fund
UTI	Urinary Tract Infections
Vit.	Vitamin
WHO	World Health Organization
Company Name Abbreviations	
BMS	Bristol Meyer Squibb
BPC	Birzeit Palestine Company
Eastern Chem.	Eastern Chemical Company
GSK	Glaxo Smith Kline
HMR	Hoechst Marion Rousel
JCL	Jordan Chemical Laboratory./ Beit-Jala
JePharm	Jerusalem Pharmaceuticals Company
Pharmacare	Pharmacare Ltd. Company

Pharmacy Abbreviations	
a.c.	before meals
b.i.d.	two times a day
d	day
h., hrs.	hour, hours
h.s.	at night, or at bedtime
ID	intradermal
IM	intramuscular
IV	intravenous
min.	minute
mon.	month
PO	by mouth/ orally
prn / p.r.n.	when needed
q.d.	once every day
q.i.d.	four times daily
q.o.d.	every other day
q. 4 h.	every four hours
q. 4 w.	every four weeks
SC	subcutaneous
SL	sublingual
®	Brand name
Rx	Prescription
tbsp.	tablespoonful
t.i.d.	three times a day
tsp.	teaspoonful
wk	week
y., yrs.	year, years

Pregnancy Categories

Category	Explanation
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
B	Either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryonic effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs can not be used or are ineffective). There will be an appropriate statement in the "warnings" section of the labeling.
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of using the drug in pregnant women clearly outweighs any possible benefit. The dug is contraindicated in women who are or may become pregnant. There will be an appropriate statement the "contraindications" section of the labeling.

Chapter 1: ANALGESICS, ANTIPYRETICS, ANTI-INFLAMMATORY AND ANTIGOUT DRUGS

A) ANALGESIC, ANTIPYRETIC, AND ANTI-INFLAMMATORY AGENTS

1. **ACETYLSALICYLIC Acid (Aspirin)**
2. **PARACETAMOL (Acetaminophen)**
3. **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**
   (Ibuprofen, Diclofenac, Indomethacin, Piroxicam)

B) ANTIGOUT AGENTS

1. **Allopurinol**
2. **Sulfinpyrazone**
3. **Colchicine**

A) ANALGESICS, ANTIPYRETICS, AND ANTI-INFLAMMATORY AGENTS

In this section, drugs that have analgesic, anti-inflammatory and/or antipyretic action will be discussed. These are heterogeneous compounds, often chemically unrelated (although most of them are organic acids), but nevertheless share certain therapeutic actions and side effects. In many textbooks Aspirin is the prototype of this group; hence these compounds are often referred to as aspirin-like drugs. More frequently they are known as non-steroidal anti-inflammatory drugs (NSAIDs).

There is no internationally agreed upon classification of analgesics/antipyretics. Most textbooks classify them depending on their efficacy, dividing them into two groups; Non-narcotic analgesics (for the mild to moderate pain, some of which may also have antipyretic actions), and narcotic/opioid analgesics (which are principally used in the relief of severe pain, and may produce dependence). Many analgesics also have marked anti-inflammatory actions and therefore are used for the treatment of arthritis and other inflammatory conditions. Most exhibit their effect, at least in part, by the inhibition of prostaglandin synthesis.

At the primary health-care level, non-narcotic analgesics are of major concern because of their wide use.

Analgesics are drugs used to relieve pain-"pain killers". Pain is one of the most common symptoms, and one of the most frequent reasons why people seek medical care.

Antipyretic activity results in lowering the temperature, and is considered to involve the hypothalamus. Normal body temperature varies according to the individual's age, sex, level of physical and emotional stress, the environmental temperature, time of the day, and the anatomical site at which the temperature is measured. Body temperature may be measured at rectal, axillary, oral, or tympanic (ear canal) sites. The method used to measure the temperature should be indicated in the reported patient's temperature. Paracetamol, aspirin, and ibuprofen have similar antipyretic activity. Product selection should be based primarily on patient acceptance, the side effects of each agent, concurrent diseases that may prohibit the use of each agent, convenience of administration, and cost of therapy.

Anti-inflammatory agents are drugs that alleviate symptoms of inflammation, but do not necessarily deal with the cause.

NSAIDs have been shown to be as effective as aspirin (ASA), but not superior. **Cross-sensitivity** between aspirin and NSAIDs is high (can be up to 97% with ibuprofen). If a person is severely allergic to ASA, avoid use of NSAIDs.

Clinically, there are no clear guidelines to assist in selecting the most appropriate agent for a patient. Base for selection depends on clinical experience, patient convenience, side effects and cost.

NSAIDs' action is due to the inhibition of cyclo-oxygenase activity and prosta-glandin synthesis (see table 1.1) for specific indications). NSAIDs may mask usual signs of infection, therefore, cautious use in case there is an existing controlled infection. **Always take a detailed drug history prior to starting therapy to avoid cross-sensitivity effects.** Single ingredient preparations should be prescribed because compound preparations rarely have any advantage, and have a higher incidence of side effects.

Some current analgesic preparations contain medications that have been pulled off the market in developed countries, but are still used inappropriately at the primary care level. One example of such are pyralozones or butazones (phenylbutazone,

oxyphenbutazone). Dipyrone is a sodium sulphonate derivative of amidopyrine or aminopyrin, a member of the pyrazolone group of chemicals, marked by different generic and brand names: Analgin, Novalgin, Baralgan, Cibalgin, Metamizol . . . and many more. **No matter what it is called, it is no longer an accepted drug.** This medication has a potentially fatal risk of agranulocytosis; a severe loss of white blood cells, which leaves the victim susceptible to many diseases. Its use should be justified only in serious or life-threatening situations where no alternative anti-inflammatory medications have been effective.

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1) Acetylsalicylic Acid WHO,P

- ***DRUG SUMMARY:***

Acetylsalicylic Acid (ASA), **Aspirin**, is a salicylate that relieves headaches, muscular and joint pains, and reduces inflammation. ASA has been considered the drug of choice in the treatment of arthritis, but **its anti-inflammatory action occurs only when given in large doses (3-4 g/day)**. At these large doses, ASA produces adverse effects that are the **main disadvantage** when used for arthritis conditions. NSAIDs tend to be more appropriate for arthritis conditions. The mechanism of action of ASA is that it inactivates cyclooxygenase irreversibly, it inhibits prostaglandin synthesis and inhibits platelet aggregation.

- ***INDICATIONS:***

Used for pain, fever, inflammatory conditions such as rheumatic fever, rheumatoid arthritis, osteoarthritis, dys-manorrhea and symptomatic relief of the common cold pain and fever. It is used for reducing the risk of recurrent Transient Ischemic Attacks (TIA/stroke), or Myocardial Infarctions (MI/heart attack) at low doses.

- ***CONTRAINDICATIONS:***

In patients with history of hypersensitivity, asthma, peptic ulcer/dyspepsia, those with bleeding tendencies or disorders.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult:

350 - 650 mg q. 4 h. for minor aches and pain.

500 - 1000 mg q. 4-6 h.; max. 4 g/24 h., for moderate to severe pain.

75 - 325 mg/day q.d. continued indefinitely for: Ischemic stroke & TIA, and the prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris (*FDA, 1998*).

Child: Use not recommended, unless for certain conditions. (Refer to special cases).

Directions: Take with or after food to avoid GI disturbances (including ulcers).

*The drug is hydrolyzed in the stomach, and primarily absorbed in the stomach and upper small intestine. Peak level is within 15 minutes to 2 h., so patient should expect the drug effect to be noticed within 15 minutes from taking the medication.

*ASA should not be used for self-medication of pain for longer than 10 days in adults or 5 days in children, unless directed by a physician.

*ASA preparations should not be used if a strong vinegar-like odor is present.

- ***USE IN SPECIAL CASES:***

Pregnancy- Contraindicated at analgesic doses. ASA crosses the placenta, and may harm the fetus (Category D). Paracetamol may be a better choice for analgesia. ASA may be used in low doses (100 mg) as anticoagulant and for prophylaxis of pre-eclampsia in high-risk pregnant women. (*Refer to the anticoagulants in cardio-vascular chapter for further information about use)*.

Lactation- Salicylates are excreted in breast milk in low concentrations, but no adverse effects on infants have been reported. Use caution.

Children- Use is not recommended specially for undiagnosed fever when influenza is suspected, due to risk of Reye's syndrome (*a rare disorder presented by symptoms of encephalitis combined with evidence of liver failure*). This potentially fatal condition occurs following certain viral infections like chickenpox, or those with minor febrile illness. It is characterized by vomiting and lethargy that may progress to delirium and coma. Paracetamol should be used instead. (see recommended doses).

[Some of the USES IN SPECIAL CASES in children that ASA should be used in are Juvenile Arthritis (60-110mg/kg/d q.6-8 h.), Rheumatic Fever, and Kawasaki disease that are not usual cases seen at the primary health care level.]

Renal Disease- Caution in these patients, ASA may aggravate chronic kidney disease, fluid retention, increased risk of GI bleeding. In severe cases avoid. In minor cases reduce the dose. (50% of the dose is eliminated in the urine.)

Liver Disease- The drug is metabolized in the liver. Use caution in patients with impaired liver function, pre-existing hypoprothrombinemia and vitamin K deficiency may increase risk of bleeding.

- ***PRECAUTIONS AND WARNINGS:***

-Not to be taken on an empty stomach. Prolonged use (*see directrion*) requires medical supervision.

-Avoid ASA for at least 1 week prior to surgery. Patients should inform the dentist or doctor of taking this medication before doing any lab or dental work.

-Avoid alcohol while taking this medication since it increases the risk of GI ulceration and bleeding.

- ***ADVERSE EFFECTS:***

Dizziness, cinchonism (ringing in the ear), skin eruptions, epigastric discomfort, peptic ulceration and bleeding, increase bleeding tendency, hypersensitivity reactions.

- ***INTERACTIONS:***

Overview of ASA Drug-Drug Interaction	
Drug	**Interaction**
ACE inhibitors	Hypotensive and vasodilator effect of ACEI may be reduced Monitor patients, and discontinue ASA if possible.
Anti-coagulants	Anticoagulant effect enhanced. Effect of ASA on gastric mucosa and platelet function may enhance possibility of hemorrhage. Avoid concomitant use.
β-blockers	Their antihypertensive effectiveness may be decreased. Use with caution.
Cortico-steroids	Corticosteroids will reduce serum salicylate levels and decrease salicylate effectiveness. Monitor plasma salicylate concentration when adding or withdrawing corticosteroids.
NSAIDs	Pharmacological effects of certain NSAIDs may be decreased. Increased risk of GI disturbances if used concomitantly.
Oral hypo-glycemics	ASA increases hypoglycemia effect of sulfonylureas. Monitor the patient's blood glucose, if hypoglycemia occurs, decrease sulfonylurea dose.

- ***OVERDOSE:***

Can be fatal, particularly in children. Acute lethal dose is approximately 10-30 g for adults, and 4 g in children. Requires immediate referral to hospital. It presents with confusion, rapid deep breathing, sweating, tinnitis (noises in the ear), deafness followed in severe cases by unconsciousness. Induce vomiting if possible (patient is conscious) with syrup of ipecac. Activated charcoal decreases absorption if given within 2 hrs. after ingestion.

Chronic Salicylate toxicity may occur when > 100 mg/kg/d is ingested for 2 or more

days. It is more difficult to recognize and is associated with increased morbidity and mortality. Compared to acute poisoning, hyperventilation, dehydration, systemic acidosis and severe CNS manifestations occur more frequently. Treatment includes supportive measures.

- ***BRANDS:***

Acetosal (Rekah), Aspirin (Bayer), Aspro (Nicholas), Alka Seltzer (Agis), Baby Aspirin (JCL), Buffered Aspirin (Pennex), Bufsa (GAMA), Cartia (Smith Kline).

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2) Paracetamol WHO,P

- ***DRUG SUMMARY:***

Paracetamol or Acetaminophen (*N*-Acetyl-*p*-amino-phenol-APAP) is a non-narcotic CNS agent. It is equivalent to aspirin in relieving pain and reducing fever, but it has little effect on platelet function, does not affect bleeding time and generally produces no gastric bleeding or ulcers. It has no anti-inflammatory action in usual doses. Paracetamol reduces fever by direct action on the hypothalamus heat-regulating center with consequent peripheral vaso-dilatation, sweating and dissipation of heat.

- ***INDICATIONS:***

Used for pain and fever. Good substitute for ASA, when ASA is not tolerated or is contraindicated.

- ***CONTRAINDICATIONS:***

In patients with history of hypersensitivity. In patients with severe liver and kidney damage.

- ***DOSAGE FORMS:***

Tablets, capsules, suspension, suppositories.

- ***RECOMMENDED DOSAGE:***

Adult: PO: 325-650 mg q. 4-6 h. as needed; max. 4 g/24 hours.

Child: PO or PR: 10-15 mg/kg/dose.

AGE	DOSE *
0-3 mon	10mg/kg (5mg/kg if jaundiced)
3 mon-1 y	60-120 mg
1-5 y	120-250 mg
6-12 y	250-500 mg

** Martindale, 1996:82.*

* The doses may be repeated q. 4-6 h. not to exceed 4 doses in 24 hours.

Directions:

*Can be taken with fluids, but before meals or 2 hours after meal, 4 times daily for 2-3 days or as required.

*The drug is completely absorbed from the GI tract, less complete absorption takes place from rectal suppository.

*Peak effect occurs within 0.5-2 h., and duration is 3-4 h.

*If fever does not subside within 3 days, patient has to contact the physician.

- ***USE IN SPECIAL CASES:***

Pregnancy- Safe if used as directed (Category B). It is the drug of choice in pregnant women for aches and pains, or fever. It does cross the placenta, but no reports of harmful effects have been noted.

Lactation- APAP is excreted in low concentration in breast milk. No harm on infants has been noted. It is safe when used as recommended.

Children- Can be used prophylactically (30 min. before) in children receiving DPT vaccination to decrease incidence of fever and injection site pain. Use caution and do not exceed the recommended doses.

Renal Disease- Kidney tubular necrosis may occur with chronic use of very high doses of the drug (> 4 g/d).

Liver Disease- The drug is exclusively metabolized in the liver. Hepatotoxicity and severe hepatic failure occurred in chronic alcoholics following therapeutic doses. Avoid large dose in liver cases. (< 2 g/d is acceptable for these patients).

- ***PRECAUTIONS AND WARNINGS:***

-Do not exceed recommended doses. Chronic excessive use (> 4 g/d) eventually may lead to transient hepatotoxicity.

-If pain or fever persists for more than 3 days consult a physician.
-Use caution when patients are taking other drugs that might affect the liver.

- ***ADVERSE EFFECTS:***

If used as directed it rarely causes any side effects.
Heavy alcoholics and smokers are more susceptible to liver toxicity. Skin rashes and neutropenia are very rare.

- ***INTERACTIONS:***

Overview of APAP Drug-Drug Interaction	
Drug	**Interaction**
Alcohol*, *Barbiturates*, *Carba-mazepine*,** and ***Rifampin	The potential hepatotoxicity of APAP may be increased by large doses or long term use of the these agents due to hepatic microsomal enzyme induction

- ***OVERDOSE:***

Symptoms: Acute poisoning symptoms include nausea, vomiting, drowsiness, confusion, liver tenderness, low blood pressure, cardiac arrhythmia, jaundice and acute hepatic and renal failure.
Treatment: Refer to the emergency room as soon as possible. There are no early specific symptoms, careful monitoring of blood levels is needed to estimate potential for hepatotoxicity.
Oral N-acetylcysteine is a specific antidote for APAP toxicity. Administration of activated charcoal will adsorb acetylcysteine, so avoid administration. Follow special directions for administration of N-acetylcysteine antidote and monitor the patient for several days.

- ***BRANDS:***

Abrol (Rekah), Abrolet, (Rekah), Dexamol (Dexxon), Acamol (Teva), Acamoli (Teva), Aldolor (CTI), Febramol (BPC), Panadol (Whinthrop), Otamol (JePharm), Paracare (Pharmacare), Pamol (Eastern Chem.), Paramol (JCL), Paracetamol (Rekah), Paramolan (Trima), Razimol (Al-Razi), Tylenol (McNeil).

Table 1.1: NSAIDs of Summary of Indication [#]					
INDICATION	**Diclofenac**	**Ibuprofen**	**Indomethacin**	**Naproxen / Naproxen Na**	**Piroxicam**
Rheumatoid arthritis (RA)	✓	✓	✓	✓	✓
Osteoarthritis (OA)	✓	✓	✓	✓	✓
Ankylosing spondylitis	✓		✓	✓	
Mild to moderate pain	✘	✓		✓	
Primary dysmenorrhea		✓	✘	✓	✘
Juvenile rheumatoid arthritis	✘	✘		✓	✘
Tendinitis, Bursitis			✓	✓	
Acute gout			✓	✓	
Acute painful shoulder	✘		✓		
Pre-menstrual syndrome		✘		✘ / Naproxen Na	
Fever		✓		✘	
Migraine/Cluster headache			✘	✘	

✓- *Labeled use (approved by FDA for this indication)*
✘- *Unlabeled use (not approved by FDA for this specific indication, but is used by doctors.)*
Blank - is not usually used.
[#] *Drug Facts and Comparisons. 2000: p. 836.*

3) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

All NSAIDs are antipyretic, analgesic, and anti-inflammatory, but there might be some differences in their individual activities. Thus a patient may do well on one propionic acid (i.e. Ibuprofen) derivative, but not on another. The reasons for such differences are not fully understood, but differential sensitivity of enzymes in the target tissues may be the reason. When employed as analgesics, these drugs are usually effective against pain of low-to-moderate intensity. Although their maximal effect is much lower than opioids, they lack the unwanted effects of the opioids on the CNS, including respiratory depression and the development of physical dependence.

In addition to sharing many therapeutic activities, current NSAIDs share several unwanted effects. The most common is the tendency to induce gastric or intestinal ulceration that can sometimes be accompanied by anemia from the resultant blood loss. Other reported side effects include disturbances in platelet function, water retention, increased blood pressure, the delayed onset and prolongation of gestation or labor, and changes in renal function.

Newer agents of NSAIDs that are cyclooxygenase-2 (COX-2) inhibitors are being produced and sold on the market, as having lower GI side effects. Until further safety reports through post marketing

surveillance are studied, cost-benefit decisions should be made before recommending such agents.

In general, NSAIDs work only on symptomatic relief of fever, pain and inflammation associated with the disease.

a) Ibuprofen WHO

- ***DRUG SUMMARY:***

Ibuprofen (IBP) is a proprionic acid derivative. Comparable to aspirin (ASA) in its analgesic action, but higher doses are required for anti-inflammatory effect. It has been reported to have less GI symptoms than aspirin in equi-effective doses.

Cross-sensitivity with ASA and other NSAIDs has been reported. IBP inhibits platelet aggregation and prolongs bleeding time, but does not affect prothrombin or whole blood clotting times.

- ***INDICATION:***

Refer to table-1.1.

- ***CONTRAINDICATIONS:***

In patients who are hypersensitive where urticaria, severe rhinitis, bronchospasm, angioedema, are precipitated by ASA or other NSAIDs. Active peptic ulcer or bleeding abnormalities.

- ***DOSAGE FORMS:***

Tablets, suspension (100 mg/5ml), gel 5%.

- ***RECOMMENDED DOSAGE:***

Adult: 200-400 mg PO q. 4-6 h.,
max. 1800 mg/24 hours for pain and fever.
400-800 mg t.i.d. or q.i.d.; max. 3200 mg/d for inflammation.
Emulgel dose: A thin layer of the gel is applied to affected area as needed, up to three times daily.

Child: Use is not recommended for children under 6 months;

Doses of IBP in Children	
1-12 y: give 5-10 mg/kg q. 4-6 h. **or**	
6 - 11 mon. 25-50 mg	6 - 8 y. 125-250 mg
12 - 23 mon 50-100 mg	9 - 10 y. 150-300 mg
2 - 3 y. 75-150 mg	11 - 12 y. 200-400 mg
4 - 5 y. 100-200 mg	(all given q. 4-6 h. prn)

Maximum daily dose is 40 mg/kg/d.

Directions: IBP should be taken with food or milk if GI disturbances occur.

*80% of the drug is absorbed from the GI tract. Peak effect is 1-2 h.

*Onset for analgesia is 0.5 h., and for anti-rheumatic action is 7 days.

*If patient misses a dose, take as soon as they remember unless it is too close to the following dose, so they need to skip the following dose and continue with the usual schedule. Dose should not be doubled.

- ***USE IN SPECIAL CASES:***

Pregnancy- Better to avoid use (Category B). Paracetamol is a better choice for analgesia.

Lactation- Safe. IBP has not been detected in breast milk in analgesic doses.

Children- Safety and efficacy has not been established for children < 6 mon old. Normally, not recommended for children < 1 year or less than 7 kg.

Renal Disease- Use with caution. Reduce dose. NSAID metabolites are excreted by kidney into urine.

Liver Disease- Use with caution, and decrease the dose. The drug is metabolized in the liver. There is an increased risk of GI bleeding or fluid retention.

- ***PRECAUTIONS AND WARNINGS:***

-Patients with history of cardiac decompensation should be observed closely for evidence of fluid retention and edema.

-Instruct patient to report immediately any passage of dark tarry stool, coffee-ground emesis, blood or protein in urine. This can be an indication for GI bleeding. Medication should be stopped and patient should be re-evaluated.

-Caution if skin rash, itching, visual disturbances or persistent headache should occur.
-Caution in hypertension, chronic renal failure and patients with SLE. Advise patient not to drink alcohol, to avoid increased risk of GI ulceration and bleeding.

- ***ADVERSE EFFECTS:***

GI disturbances are most common; i.e. heartburn, nausea and dyspepsia, abdominal distress, gastritis and ulceration. Also, dizziness, drowsiness, jaundice, and fatigue may occur. Side effects are dose related. Incidence or aggravation of epilepsy and parkinsonism have been reported with use of NSAIDs.

- ***INTERACTIONS:***

Overview of Ibuprofen Drug-Drug Interaction	
Drug	**Interaction**
Oral anti-coagulants, and ***heparin***	May prolong bleeding time. Avoid concomitant use.
Lithium, ***digoxin*** and ***methotrexate***	Increased toxicity of these drugs with concomitant NSAIDs use. Monitor each drug serum levels and adjust dose as needed.

- ***OVERDOSE:***

Symptoms: May include drowsiness, dizziness, mental confusion, lethargy, vomiting, abdominal pain, tinnitus, convulsions, hypotension, tachycardia, and metabolic acidosis.
Treatment: Induce emesis or perform gastric lavage to recover undigested tablets, include supportive measures. Since NSAIDs are strongly bound to plasma, hemodialysis or peritoneal dialysis may be of little value. Charcoal tends to reduce the absorption of the drug.

- ***BRANDS:***

Adex 200 (Dexxon), Advil (Whitehall), Artofen (Teva), Brufen 400 (Boots), Ibufen (Dexxon), Isofen (BPC), Motrin (Upjohn), Nurofen (Boots), Trufen (JePharm).

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b) Diclofenac [P]

- ***DRUG SUMMARY:***

An acetic acid derivative. It has analgesic, antipyretic, and anti-inflammatory properties. At therapeutic doses it has little effect on platelet aggregation. Patients not responding to IBP can be given diclofenac instead. Do not co-administer with other NSAIDs or salisylates.

- ***INDICATION:***

Refer to table-1.1. (It is also used as an ophthalmic agent for cataract surgery).

- ***CONTRAINDICATION:***

Same as IBP.

- ***DOSAGE FORMS:***

Tablets, sustained release tablets, suppositories, emulgel and ampoules.

- ***RECOMMENDED DOSAGE:***

Adult: 75-150 mg/24h given by mouth in divided doses. Total daily dose should not exceed 150 mg/d, such doses have not been studied.
Suppository form is given in a dose of 75-100 mg each evening.
The emulgel form 1% should be applied to painful site, 2-4 gm, 3-4 times daily. Therapy should be reviewed after 14 days.
Child: Not recommended for children < 1 y. unless JRA.
Child > 1 y. for RA: 1-3 mg/kg in divided doses by mouth or rectum.

Directions: Diclofenac is readily absorbed from the GI tract, and 50-60% reaches the systemic circulation. Peak effect is within 2-3 h.
*Absorption is delayed by food, take with a full glass of water. For chronic use take after food to avoid GI problems.

*Sustained release forms are given once or twice daily.
*If simple GI disturbances occur, an antacid may be used, but not administered at the same time of the drug intake.
*If patient misses a dose, this dose should be taken as soon as remembered, unless it is too close to the following dose, so skip and maintain schedule. Do not double the dose.

- ***USE IN SPECIAL CASES:***

Pregnancy- Should not be used unless there are compelling reasons for doing so, (Category B).
Lactation- Do not use in nursing mothers because of possible effects on infant's cardiovascular system.
Children- Use in child < 1 year is not recommended. Safety and efficacy in children have not been established.
Renal Disease- NSAID metabolites are eliminated by the kidneys, 50-60% excreted in urine. Reduce dose to avoid accumulation.
Liver Disease- Effects are not known. Metabolism of the drug occurs in liver. Use caution to avoid increased risk of GI bleed.

- ***PRECAUTIONS, WARNINGS & OVERDOSE:***

Same as IBP.

- ***ADVERSE EFFECTS:***

Similar to IBP, but with higher incidence.

- ***INTERACTIONS:***

See overview table.

Overview of Diclofenac Drug-Drug Interaction	
Drug	**Interaction**
Lithium*, *digoxin and ***methotrexate***	Increased toxicity of these drugs with concomitant NSAIDs use. Monitor each drug serum levels and adjust dose as needed.
Diuretics	May decrease blood pressure lowering effects of diuretics. May lead to an increase in serum K^+, if using K^+ sparing diuretics.

- ***BRANDS:***

Abitren (Abic), Betaren/Betaren S.R (Dexxon), Diclofen (JePharm), Rhumacare (Pharmacare), Rufenal (BPC), Voltin (Eastern Chem.), Voltaren/ Voltaren S.R. (Ciba-Geigy).

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c) Indomethacin P

- ***DRUG SUMMARY:***

A very potent arylacetic acid NSAID derivative. Because of its high potential to cause side effects when used in high doses, it should be carefully considered for active disease unresponsive to adequate trials with salicylates. It has equal or a little superior action than naproxen, but higher incidence of side effects. This medication will enable reduction of steroid doses in severe forms of Rheumatoid Arthritis. (In this case reduce steroid dose slowly!).

- ***INDICATION:***

Refer to table-1.1 in the beginning of this chapter. (Also used as IV for Patent Ductus Arteriosus in premature infants.)

- ***CONTRAINDICATION:***

Same as IBP.
Also in patients with recent rectal bleeding or proctitis if using suppositories.

- ***DOSAGE FORMS:***

Capsules, suppositories, gel.

- ***RECOMMENDED DOSAGE:***

Adult: ★ ***Rheumatoid Arthritis:***
25-50 mg b.i.d. or t.i.d., or 75 mg sustained release 1-2 times a day; max. 200 mg/d.
★ ***Dysmenorrhea:*** up to 75 mg daily.
★ ***Acute Gout*:** 50 mg t.i.d. until pain is tolerable (usually within 2-3 days), then taper off to 25 mg t.i.d. until total resolution of attack.
(If administering both PO and rectal dosage forms combined, dose should not exceed 200 mg/d).
Child: Not recommended due to effect on liver function.
Directions: Administer immediately after meals, or with food, milk or antacid to minimize GI side effects. (*Food or antacid may cause somewhat delayed and reduced*

absorption, but advantage of safety outweighs risk of impaired absorption.)
*If patient misses a dose, take as soon as remembered unless it is too close to the following dose, so skip and maintain schedule. Never double doses.

- ***USE IN SPECIAL CASES:***

Pregnancy- Category B in the 1st and 2nd trimester, and D in 3rd trimester.
Lactation- Use not recommended.
Children- Contraindicated for children < 14 yrs. Hepatotoxicity including fatalities has occurred in children with juvenile rheumatoid arthritis when taking this medicine.
Renal Disease- Use caution.
Liver Disease- Use caution, better to use lower doses, high risk of GI bleeding.

- ***PRECAUTION AND WARNINGS:***

Same as IBP. Indomethacin has been reported to aggravate depression or other psychiatric disturbances, epilepsy and parkinsonism. Extreme caution should be taken in susceptible patients. In case of hemorrhoids, caution use or avoid rectal administration.

- ***ADVERSE EFFECTS:***

Same as IBP, but with higher incidence.

- ***INTERACTIONS:***

*Same as IBP, as well as:

Overview of Specific Indomethacin Drug-Drug Interaction	
Drug	**Interaction**
Probenecid	Increases in plasma concentration of indomethacin; enhancing the pain relief effect, but increasing its adverse effects. Use caution.
Sympatho-mimetics	Concomitant use may result in increased blood pressure. Monitor patient.

- ***OVERDOSE:***

Treatment is symptomatic and supportive. The stomach should be emptied as quickly a possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit or unconscious, gastric lavage should be performed. Once the stomach has been emptied, 25-50 gm of charcoal may be given. Follow patient for several days because of GI ulceration and hemorrhage complications.

- ***BRANDS:***

Indocaps (JCL), Indocin (Merk), Indocin (Eastern Chem.), Indolin (BPC), Indomed/ Indomed S.R. (Assia), Indopharm (JePharm), Indotard (CTI), Indovis (CTI).

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d) Piroxicam

- ***DRUG SUMMARY:***

An oxicam NSAID derivative. Is as effective as naproxen, and has a prolonged duration of action which permits once daily administration. Use is not recommended unless other NSAIDs have failed or patient compliance would be improved with once daily dose.

- ***INDICATION:***

Refer to table-1.1, at the beginning of this chapter.

- ***CONTRAINDICATIONS:***

Same as IBP.

- ***DOSAGE FORMS:***

Capsules, suppositories.

- ***RECOMMENDED DOSAGE:***

Adults: 10-20 mg PO 1-2 times/day.
For acute gout, 40 mg initially, then 40 mg daily in single or divided doses for 2 days, then 20 mg q. d. for 7-14 days.
Child: Not to be used.
Directions: Take with or after food. Peak effect is 3-5 hrs. for analgesia, and 2-4 weeks for anti-rheumatic action. Onset is 1 h. for analgesia, and 7 days for anti-rheumatic action. Duration is 48-72 hrs.
*If patient misses dose, it should be taken as soon as remembered unless it is too close to the following dose, so skip and maintain schedule. Do not double dose.

- ***USE IN SPECIAL CASES:***

Pregnancy- Category B in 1st and 2nd trimester, and Category D in 3rd trimester.
Lactation + Children- Not established.
Renal Disease- Use with caution to avoid risk of accumulation.
Liver Disease- Use with caution to avoid risk of GI bleedings.

- ***PRECAUTIONS AND WARNINGS, ADVERSE EFFECTS, INTERACTIONS AND OVERDOSE:*** All Similar to IBP.
- ***BRANDS:***

Felcol (Eastern Chem.), Feldene (Pfizer), Pirox (JePharm).

B) ANTIGOUT AGENTS

Gout is a disorder of uric acid metabolism. It is manifested by hyper-uricemia, acute or chronic recurrent arthritis, and deposits of monosodium urates. Although hyper-uricemia is a precursor of gout, it is not a disease by itself, and not diagnostic of gout. The diagnosis of acute gouty arthritis is confirmed when large numbers of polymorphonuclear leukocytes and mono-sodium urate crystals are demonstrated in synovial fluid aspirated from the inflamed joint.

Most acute attacks have no obvious precipitating events, but trauma, excessive alcohol intake, drug induced (in therapy of diuretics, aspirin, anti-tuberculosis agents like pyrazinamide or ethambutol), or initiation of a hyperuricemic agent may contribute to an acute attack.

In an acute attack, the goals of treatment are to immediately relieve pain and inflammation, and not to decrease the serum uric concentration. This can be effectively treated by a NSAID; i.e. indomethacin or naproxen. *(refer to individual drug monographs for more details)*. **Aspirin should not be used**, since salicylates increase urate concentration. Acute attacks should never be treated with allopurinol or uricosurics (probenecid, sulfinpyrazone), this may prolong the attack indefinitely. Colchicine is an alternative to NSAIDs in patients with heart failure.

After the initial attack of acute gout, the interval between subsequent attacks varies from a few days to several years. Some patients may never experience another acute attack. Antihyperuricemic medications should be initiated only when gouty patients have frequent acute attacks, urate tophi, or evidence of renal damage. **Therapy starts when the acute attack completely subsides**. Once started, such therapy usually is continued indefinitely. Initiation of treatment may precipitate an acute attack therefore the colchicine or an NSAID could be used prophylactically for at least one month after the hyperuricemia has been corrected. If an acute attack develops while the patient is taking treatment, the treatment should be continued at the same dosage, and treatment for the acute attack should be initiated on its own.

1) Allopurinol WHO,P

- ***DRUG SUMMARY:***

Allopurinol is an agent that inhibits uric acid synthesis by inhibiting xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine (end product of purine catabolism) to uric acid, so it reduces endogenous uric acid production. **It is used for patients who overproduce uric acid**. It has no analgesic, anti-inflammatory, or uricosuric actions, therefore, it is not useful for acute gouty attacks and may actually aggravate and prolong it.

- ***INDICATIONS:***

To control primary hyperuricemia that accompanies severe gout, and to prevent possibility of flare-ups of acute gouty attack. To prevent recurrent calcium oxalate stones, prophylactically to reduce severity of hyperuricemia associated with

antineoplastic and radiation therapies, both of which greatly increase plasma uric acid levels in the body.

- ***CONTRAINDICATIONS:***

Hypersensitivity, patients who have developed a severe reaction should not be restarted on the drug. Discontinue medication at first appearance of skin rash or other signs of allergic reactions. Contraindicated as initial treatment for acute gouty attack, or for asymptomatic hyperuricemia.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★***Hyperuricemia;***

100 mg daily initially, may be increased by 100 mg/wk; max. 800 mg daily.

Serum uric acid level of ≤ 6 mg/dl should be attained.

★***Control of gout, and secondary hyperuricemia;***

200-300 mg/day for mild gout,

400-600 mg/day for moderate to severe.

Initially 100 mg daily as a single dose, after food, gradually the dose is increased over 1-3 wks according to the plasma or urinary uric acid concentration to about 300 mg. Usual maintenance dose is 200-600 mg/d.; max. 800 mg daily.

★***Recurrent calcium oxalate stones;***

200-300 mg/day in single or divided doses, as well as modification in the diet.

★***Renal impairment:***

Creatinine Clearance (Cl_{cr})	Recommended Dose
Cl_{cr} 60 ml/min.	200 mg/day
Cl_{cr} 40 ml/min.	150 mg/day
Cl_{cr} 20 ml/min.	100 mg/day
Cl_{cr} 10 ml/min.	100 mg on alternate days
Cl_{cr} < 10 ml/min.	100 mg 3 times a week.

Child: ★ ***Secondary hyperuricemia***

(associated with malignancy or neoplastic therapy),

(6-10 y): 100 mg PO t.i.d.

(< 6 y): 50 mg PO t.i.d. *or* 10 mg/kg/day divided q. 6 h.

Directions: Doses of > 300 mg/day should be divided, taken with food or milk.

*Normal serum levels of uric acid are usually achieved in 1-3 weeks, with a normal range being 3.6-8.5 mg/dl for men, and 2.3-6.6 mg/dl for women.

*A sudden decrease in serum level can precipitate an acute gouty attack, start with low dose and increase by 100 mg/week.

*It is advisable to maintain sufficient fluid intake to yield a daily urinary output of at least 2 L. The patient needs to drink at least 10-12 glasses of water daily.

*Advise patient to contact health care provider if any of these symptoms occur; skin rash, painful urination, blood in the urine, irritation of the eyes, or swelling of the lips and mouth occurs. Discontinuation of the medication may be recommended.

*Advise patient to limit high-purine foods: kidney, liver, anchovies, sardines, salmon, meat soups, peanuts, dried peas and beans, cauliflower, peppers and spinach.

*For oxalate stone treatment, need to avoid foods such as tea, chocolate, spinach, nuts, beets, figs, and excessive Ca intake. Also need to increase oral fluids and dietary fiber intake.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly needed (Category C). There are no adequate and well-controlled studies in pregnant women.

Lactation- Allopurinol and its metabolites have been detected in breast milk. No adverse reactions have been reported, but use with caution.

Children- Allopurinol is rarely indicated for use in children, with the exception to those with hyperuricemia secondary to malignancy or certain rare inborn errors of purine metabolism.

Renal Disease- Need to reduce dosage for patients with renal disease, to avoid accumulation of allopurinol and its metabolites. For moderate to severe renal impairment refer to recommended doses.

Liver Disease- Use caution. Perform periodic liver function tests during early stages of

therapy, particularly in patients with preexisting liver disease.

- ***PRECAUTIONS AND WARNINGS:***

-Hypersensitivity; need to discontinue drug at first appearance of skin rash or other signs of allergic reactions. In some cases, rash may be followed by more severe reactions such as fever, exfoliative, urticarial or purpuric lesions, irreversible hepatotoxicity and rarely, death.

-Need to emphasize the importance of increasing fluid intake to avoid the theoretic possibility of formation of xanthine calculi under the influence of allopurinol therapy.

- ***ADVERSE EFFECTS:***

Drowsiness, headache, nausea, vomiting, diarrhea, abdominal discomfort, photo-sensitivity, urticaria, pruritic maculo-papular rash, jaundice, increased alkaline phosphatase, AST and ALT liver enzymes, hepatotoxicity, xanthine renal calculi, agranulocytosis, aplastic anemia, bone marrow depression have all been reported.

- ***INTERACTIONS:***

Overview of Allopurinol Drug-Drug Interaction	
Drug	**Interaction**
ACE inhibitors	Captopril co-administration may increase risk of toxicity; it is better to space-out time interval of drug administration.
Alcohol	May inhibit renal excretions of uric acid; warn patient against drinking alcohol.
Ampicillin and ***amoxicillin***	Co-administration increases risk of skin rash. Start allopurinol therapy after antibiotic therapy has been completed for a couple of weeks.
Antacids; Aluminum hydroxide	May inhibit the GI absorption of allopurinol. This effect can be avoided by administering allopurinol 3 or more hours before Aluminum hydroxide.
Thiazides	May increase the risk of allopurinol toxicity and hypersensitivity, (especially with impaired renal function); so use caution.
Warfarin	Allopurinol may enhance anti-coagulant effect of warfarin, use with caution.
Large doses of vitamin C	May increase the possibility of kidney stone formation due to urinary acidification.

- ***OVERDOSE:***

Symptoms may include headache, nausea, vomiting, epigastric pain, jaundice and other adverse side effects.

Treatment: Need to evaluate patient, and a dose reduction may be necessary if not discontinuation of the medication.

In accidental overdose, need to induce vomiting if it has not occurred already. Refer to hospital for supportive or symptomatic care.

- ***BRANDS:***

Allopurinol (Abic), Alloril (Dexxon), Caplenal (Berk), Uricnase (BPC), Zylol (Teva), Zyloric (GlaxoWellcome).

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2) Sulfinpyrazone

- ***DRUG SUMMARY:***

A potent pyrazolidine derivative, uricosuric agent for gout. At therapeutic doses promotes urinary secretion of uric acid and reduces serum urate levels by competitively inhibiting renal tubular re-absorption of uric acid. **It is used for patients who are under-excretors of uric acid**. As it has no apparent analgesic or anti-inflammatory activity, it is not used for relief of acute gout.

- ***INDICATIONS:***

Maintenance therapy in chronic gouty arthritis and tophaceous gout. Unlabeled uses include; drug induced hyperuricemia, and to decrease platelet aggregation.

- ***CONTRAINDICATIONS:***

Hypersensitivity to butazones or other pyrazoles, active peptic ulcer, or symptoms of GI inflammation or ulceration, as well as blood dyscrasias.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★ ***Use in gout;***

100-200 mg 1-2 times a day, for 1 wk, then increase to 200-400 mg twice a day increased over 1-3 wks. It may be reduced to 200 mg after serum urate levels are controlled. Maximum dose is 600 mg/d, rarely 800 mg/d.

Child: Use not commonly indicated for children.

Directions: May cause GI upset, take with food, milk, or an antacids if needed.

*Patient needs to increase fluid intake to at least 10-12 glasses (8 ounces each) daily if possible.

*Sulfinpyrazone therapy should be continued without interruption even when the patient has an acute gouty attack, which may be treated with full therapeutic doses of the appropriate anti-inflammatory agent.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly needed and when the potential benefits outweigh the potential hazards to the fetus (Category C).

Lactation- Avoid use, unless clearly needed and potential benefits outweigh potential hazards to the nursing infant.

Children- Not commonly prescribed for children.

Renal Disease- Use caution. Renal failure has occurred in predisposed patients. Assess renal function periodically to avoid complications.

Liver Disease- Use caution. This drug is metabolized to active and inactive metabolites in the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in patients who had a history of peptic ulcer, may reactivate or aggravate peptic ulcer.

-Need blood cell counts, as well as renal function evaluation periodically.

-Sulfinpyrazone may increase the frequency of acute gouty attacks during the first 6-12 months of therapy, even when serum urate levels appear to be controlled. The physician may prescribe colchicine prophylactically, concurrently during the first 3-6 months to decrease the severity of the acute attack.

- ***ADVERSE EFFECTS:***

Most frequent include: upper GI disturbances, nausea, diarrhea, blood loss, reactivation or aggravation of peptic ulcer, precipitation of acute gout attacks. Less frequently: rash and jaundice. Rarely: blood dyscrasias, i.e. anemia, agranulocytosis, aplastic anemia, bronchoconstriction in patients with aspirin-induced asthma.

- ***INTERACTIONS:***

Overview of Sulfinpyrazone Drug-Drug Interaction

Drug	Interaction
Salicylates	These suppress/antagonize the uricosuric action of sulfinpyrazone. Do not administer aspirin or salicylates to patients. *(These do not antagonize allopurinol, but are nevertheless NOT indicated in gout.)*
Sulfonyl-ureas	May be displaced by sulfin-pyrazone, increasing risk of hypoglycemia.
Theophylline	***Theophylline*** plasma clearance may be increased, thus lowering plasma levels. Monitor patient closely to determine dosage adjustments if needed.
Verapamil	Increase in clearance and decrease in bioavailability may occur. Use with caution.
Warfarin	Anticoagulant activity of ***warfarin*** will be enhanced. Hemorrhage could occur. Use extreme caution.

- ***OVERDOSE:***

Symptoms include: Nausea, vomiting, diarrhea, epigastric pain. Labored respiration, convulsion, and coma may

occur. Possible symptoms seen after over-dosages may include anemia, jaundice or ulceration. There is no specific antidote for treatment. Induce vomiting if possible. Refer to a hospital emergency room for general supportive care.

- ***BRANDS:***

Anturane (Ciba), Pyrocard (Trima).

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3) Colchicine WHO,P

- ***DRUG SUMMARY:***

An antigout agent that is not an analgesic, not a uricosuric, and will not prevent progression of gout to chronic gouty arthritis. Its exact mechanism of action is not clear, but it reduces inflammatory response to the deposited crystals and also diminishes phagocytosis. Its prophylactic, suppressive effect helps reduce the incidence of acute attack. It is a good alternative to NSAIDs, and probably as effective. It is of value in patients with heart failure since unlike NSAIDs it does not induce fluid retention, also it can be given to patients receiving anticoagulants.

- ***INDICATIONS:***

For pain relieve of **acute attacks of gout**. Short term prophylaxis during initial therapy with allopurinol or uricosuric drugs. It is also used for amyloidosis, Behcet's syndrome, Familial Mediterranean fever, idiopathic thrombocytopenic purpura, primary biliary cirrhosis, and various skin disorders.

- ***CONTRAINDICATIONS:***

Hypersensitivity to colchicine, serious GI, renal, hepatic or cardiac disorders, blood dyscrasias, and pregnancy.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★ ***Use in gout;***

1 mg PO initially, given at the first warning of an acute attack, followed by 0.5-1 mg q. 2-3 h. till relief of pain is obtained, or vomiting or diarrhea occur; max. 10 mg/day.

One should wait 3 days before initiating a second course to minimize the possibility of cumulative toxicity.

★ ***Use as prophylaxis or maintenance of recurrent gouty arthritis;***

0.5-1 mg PO once or 3 times daily.

★ ***Use in Familial Mediterranean fever;***

1-3 mg/day, to prevent frequency and severity of acute febrile episodes and to prevent amyloidosis.

Child: Not commonly prescribed for children, unless under direct specialist supervision for rare cases.

Directions: Treatment should be started at the first sign of an attack, and stopped as soon as pain is relieved or at the fist sign or vomiting or diarrhea.

*Medication should be discontinued if the patient reports any of the following: rash, sore throat, fever, unusual bleeding, bruising, weakness, numbness or tingling.

- ***USE IN SPECIAL CASES:***

Pregnancy- Contraindicated use (oral: Category C, parenteral: D). Colchicine can cause fetal harm, and should be avoided.

Lactation- Avoid use, unless clearly needed and potential benefits outweigh potential hazards to the nursing infant. It is not known if this drug is excreted in breast milk.

Children- Safety and efficacy not established.

Renal + Liver Diseases- Use caution in mild cases, there is an increased risk of toxicity. Use is contraindicated in severe cases of hepatic/renal dysfunction.

- ***PRECAUTIONS AND WARNINGS:***

For patients receiving long-term therapy, periodic blood count should be performed.

Hepatic and renal function impairment: increased colchicine toxicity. Myopathy and neuropathy have been noted in patients with altered renal function.

- ***ADVERSE EFFECTS:***

GI effects; vomiting, diarrhea, abdominal pain and nausea may occur, especially with maximum doses, and particularly

troublesome in the presence of peptic ulcer or spastic colon. Bone marrow depression with aplastic anemia, agranulocytosis, myopathy, loss of hair, reversible azospermia (fertility impairment), hypersensitivity, and dermatoses have all been reported.

- ***INTERACTIONS:***

Overview of Colchicine Drug-Drug Interaction	
Drug	**Interaction**
Cyclosporin	Increased risk of nephrotoxicity and myotoxicity due to increased plasma cyclosporin concen-tration. Observe patients closely for severe adverse effects if coadministration is necessary, and adjust the dose accordingly.
Erythromycin	May increase serum colchicine concentration; toxicity may occur. Use with caution.

- ***OVERDOSE:***

Symptoms: Usually there is a latent period of several hours between overdosage and symptom onset. First symptoms to appear include nausea, vomiting abdominal pain and diarrhea. Myocardial injury, profound shock and respiratory failure, leukopenia, alopecia may also occur.

Treatment: Begin with gastric lavage (if not too much time has passed), and measures to prevent shock. Hemodialysis or peritoneal dialysis may be used. Continue with supportive measures.

- ***BRANDS:***

Colchicine (RAFA, Abbott).

Chapter 2: CARDIOVASCULAR DRUGS

A) ANTIHYPERTENSIVES
1. **Diuretics**
2. **Beta-Blockers**
3. **ACE Inhibitors**
4. **Calcium Channel Blockers**

B) ANTI-ARRHYTHMICS
1. **Amiodarone**
2. **Lidocaine**
3. **Quinidine**

C) ANTIANGINA
1. **Isosorbide Dinitrate**

D) ANTICOAGULANTS
1. **Aspirin**
2. **Warfarin**

E) CONGESTIVE HEART FAILURE DRUGS
1. **Digoxin (Digitalis Glycoside)**

F) LIPID LOWERING DRUGS
1. **Fibric Acids**
2. **Bile Acid Sequestrants**
3. **HMG-CoA Reductase Inhibitors**

A) ANTIHYPERTENSIVES

The actual level of blood pressure that can be considered hypertensive is somewhat difficult to define; it depends on a number of factors, including the patient's age, sex, race, and life style. In general, hypertension is defined as a systolic blood pressure (**SBP**) that is ≥ 140 mmHg diastolic blood pressure (**DBP**) of ≥ 90 mmHg.

Hypertension is classified into three stages as indicated in table-2.1. Patients are divided into risk groups based on their blood pressure as well as to the presence or absence of target organ disease and additional risk factors (*for further information see: Report of the Joint National Committee- JNC 6-1997, and the WHO-ISH 1999 guidelines, note that the JNC 7-2003 report has changed the categories, but will not be adopted in this chapter*).

Life style modification is the first step in therapy for most patients, this includes, weight reduction if overweight, regular physical activity on regular bases, reduction of sodium intake, adequate intake of potassium, calcium and magnesium, limited alcohol intake and smoke cessations.

Periodic blood pressure measurements should be done for patients after starting with life style modifications, then the initiation of antihypertensive therapy. Drug therapy should be individualized, especially that there are several groups of pharmacological therapy as seen on table 2.2. But in general, for uncomplicated hypertension a diuretic and/or a beta-blocker are the first choice of treatment. For patients with other health problems such as diabetes mellitus or heart failure, starting with Angiotensin converting enzyme (ACE) inhibitors might be more appropriate. See table 2.3, as well as each drug monograph for specific indications.
The aim of antihypertensive therapy is to lower and maintain blood pressure to a level within the normal range of the patient's age and sex.

In the following pages the most commonly prescribed categories will be discussed.

Table-2.1. Classification of Blood Pressure For Adults > 18 Years of Age

Category	SBP (mmHg)		DBP (mmHg)
Optimal	< 120	and	< 80
Normal	< 130	and	< 85
High normal	130 - 139	or	85-89
Hypertension *			
Stage 1 (Mild)	140 - 159	or	90 - 99
Stage 2 (Moderate)	160 - 179		100 - 109
Stage 3 (Severe)	> 180	or	> 110

*Based on the average of ≥ 2 readings taken at each of ≥ 2 visits after an initial screening.
*When systolic and diastolic blood pressures fall into different categories select the higher category to classify the individual's blood pressure status.
Reference: Drug Facts & Comparisons 2000, Treatment Guidelines, p. A-5.

There are three general approaches for the pharmacological treatment of primary hypertension. These approaches are summarized in table-2.2.

Table-2.2: Pharmacological Approaches to Treatment of Hypertension	
CATEGORIES	**EXAMPLE**
I. Diuretics to reduce blood volume:	
A. Thiazide diuretics	Hydrochlorothiazide
B. Loop diuretic	Furosemide
C. Potassium sparing diuretics	Spironolactone
II. Drugs that interfere with the renin-angiotensin system:	
A. Converting enzyme inhibitors	Captopril
B. Angiotensin-receptor antagonists	Saralasin
III. Drugs that decrease peripheral vascular resistance and/or cardiac output:	
A. Direct vasodilators	
1. Calcium channel blockers	Nifedipine Verapamil Diltiazem
2. Potassium channel activators	Minoxidil
3. Elevation of cGMP	Nitroprusside
4. Others	Hydralazine
B. Sympathetic nervous system depressants	
1. α-Blockers	Prazosin
2. β-Blockers (Non-selective) (β_1 selectivity)	 Propranolol Atenolol
3. Norepinephrine synthesis inhibitors	Metyrosine
4. Norepinephrine storage inhibitors	Reserpine
5. Transmitter release inhibitors	Guanethidine
6. Centrally acting (decrease sympathetic outflow)	α-Methyldopa

Table-2.3: Comparison of the Clinical Effects of Antihypertensive Drugs					
Feature	**β-Blockers**	**Thiazide Diuretics**	**ACE Inhibitors**	**Ca antagonists**	**α-Blockers**
Efficacy in coexisting disease states					
-Angina pectoris	✓	✗	✗	✓	✗
-CHF/LVF	✗	✓ [a]	✓		✓
-Supraventricular arrhythmias	✓	✗	✗	✓ [b]	✗
-Raynaud's phenomenon	✗	✗	✗	✓	✓
-Asthma	✗	✓	✓	✓	✓
Effect on the heart rate	↓	↔	↔	↔↑	↔
Effect on total peripheral resistance	↑, ↓ [c]	↔	↓	↓	↓
Effect on left ventricular hypertrophy	↓	↔ **or** ↑	↓	↓	↓
Effect on serum lipids	Generally adverse [d]	Adverse	Neutral/ favorable	Favorable	Favorable
Effect on glycemic control	Generally adverse [e]	Adverse	None	Generally none	None

a. A loop diuretic may be more suitable if CHF/LVF is predominant.
b. Some agents only (verapamil)
c. β-blockers initially cause a reflex increase in total peripheral resistance followed by a decrease towards or slightly below pretreatment levels with long term use. However, β-blockers with vasodilator activity (labetalol or celiprolol) cause a reduction in total peripheral resistance.
d. Not all β-blockers have adverse effects on the serum lipid profile (carvediolol, labetalol, pindolol) have not shown any adverse effects.
e. β-blockers may mask some of the warning signs of hypoglycemic episodes.
f. Symbols: ✓: indicated use, ✗: not indicated, ↔: no significant effect, ↑: effect increased, ↓: decreased.
** References:* *Speight & Holford. Avery's Drug Treatment, 4th ed. Adis International, New Zealand,1997. Drug Facts & Comparisons, 2000, p. A9.*

1) DIURETICS

Diuretics are agents that increase the rate of urine formation, as the term used "for diuresis". They are divided into Thiazide, Loop and Potassium-sparing diuretics, each working on a specific segment of the renal system. One drug from each group will be discussed as the prototype.

a) Thiazide Diuretics:

Hydrochlorothiazide WHO,P

- ***DRUG SUMMARY:***

Hydrochlorothiazide is a very potent **thiazide diuretic**, classified as a cardio-vascular, antihypertensive agent. It is the drug of choice for primary hypertension. Thiazides mainly increase excretion of Na and Cl, by inhibiting their reabsorption from the thick ascending limb of Loop of Henle and the early distal tubules.

(Other drugs in this group include Benzthiazide, Chlorothiazide, Chlorthalidone, Indapamide, Metolazone, etc.).

- ***INDICATIONS:***

Thiazides are mainly used to relieve edema due to heart failure and, in lower doses, to reduce blood pressure.

- ***CONTRAINDICATIONS:***

Anuria, hypercalcemia, severe renal and hepatic impairment, hepatic coma or precoma, hypersensitivity to thiazides or other sulfonamides, Addison's disease, porphyria.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★***For Edema;***

Start with 50-100 mg PO daily.

Maintenance 25-50 mg on alternate days.

★***For Hypertension;***

25 mg PO daily, can be increased to 50-75 mg if necessary. In elderly patients, an initial dose of 12.5 mg may be sufficient.

Directions: It can be taken with food or milk to reduce GI upset.

*It acts within 1-2 h. of oral administration, and has a duration of 12-24 h.

*It is advisable to eat a banana or have a glass of orange juice to prevent hypokalemia.

*It should be administered early in the morning after eating. If it is to be given in two doses, schedule the second dose no later than 3 pm., so diuresis does not interfere with sleep.

***100 mg PO doses for hypertension** are rarely recommended. Doses > 25 mg/d in older patients, or > 50 mg in young patients do not increase blood pressure lowering effect of the medication (plateau effect).

- ***USE IN SPECIAL CASES:***

Pregnancy- Diuretics are not used to treat hypertension in pregnancy since they might affect placental perfusion due to decreasing the extracellular volume. Thiazides may cause neonatal thrombocytopenia (Category B).

Lactation- The amount excreted in breast milk is too small to be harmful to nursing infant; large doses may suppress lactation.

Children- Not established.

Renal Disease- If there is a moderate renal dysfunction, avoid thiazide diuretics. If the GFR < 25 ml/min. one should use loop diuretics (furosemide), which will be more effective. Thiazides are not effective in these cases.

Liver Disease- Use with caution since hypokalemia may precipitate coma. Also there will be a risk of hypomagnesemia in the case of alcoholic cirrhosis.

- ***PRECAUTIONS AND WARNINGS*:**

-It may cause **hypokalemia**. Potassium supplements may be recommended in these cases: symptomatic hypokalemia, patient with an abnormal resting ECG, patient with history of arrhythmias, ischemic disease or severe heart failure, during concomitant digitalis therapy, and with planned general anesthesia. For prevention, potassium chloride doses of 2-4 g (approx. 25-50 mmol) PO per day are suitable in patient taking a normal diet. Smaller doses must

be used if there is renal insufficiency (common in elderly). If patient can't tolerate side effects, do not use thiazide diuretics, and switch to a potassium sparing diuretic.

-Aggravation of diabetes and gout may occur. May raise LDL-cholesterol, and drop HDL-cholesterol. Take caution in the case of bronchial asthma, hepatic cirrhosis, renal dysfunction, and history of SLE.

- ***ADVERSE EFFECTS:***

Impotence (reversible on withdrawal of treatment), hypokalemia, hypomagnesemia, hyponatremia, hypercalcemia, hypochloremic alkalosis, hyperuricemia, gout, hyperglycemia, and increases in plasma cholesterol concentration.

- ***INTERACTIONS:***

Overview of Thiazide Drug-Drug Interaction	
Drug	**Interaction**
Analgesics	Diuretics increase the risk of nephrotoxicity of NSAIDs. Use with caution.
Anion-exchange resins	Cholestyramine reduces the absorption of thiazide diuretics. Give them at least two hours apart.
Anti-arrhythmics	Toxicity of many antiarrhythmic drugs increased if hypokalemia occurs. Use with caution.
Anti-depressants	Increased risk of postural hypotension with TCAs.
Anti-diabetics	Hypoglycemic effect is antagonized by thiazide diuretics. Use with caution.
Anti-histamines	Hypokalemia increases the risk of ventricular arrhythmia with astemizole & terfenadine.
Calcium salts	Risk of hypercalcemia. Avoid use concomitantly.
Cardiac glycosides	Increased toxicity if hypokalemia occurs.
Cortico-steroids	Increased risk of hypokalemia; antagonism of diuretic effect. Use with caution.
Lithium	Lithium excretion reduced by thiazides. Monitor patients.
Sex hormones	Estrogens and combined OCs antagonize diuretic effect. Counsel women on use of alternative method instead of hormonal therapy if needed.

- ***OVERDOSE:***

Symptoms: changes due to plasma volume depletion *(e.g. orthostatic hypotension, dizziness, drowsiness, etc.)*, and signs of K deficiency *(e.g. confusion, dizziness, muscular weakness, GI disturbances).*

Treatment: Perform gastric lavage or induce emesis, give activated charcoal. Avoid cathartics since they may enhance electrolyte and fluid loss. Always refer the patient for further investigations.

- ***BRANDS:***

Esidrex (Ciba-Geigy), Disothiazide (Dexxon).

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b) Loop Diuretics

Furosemide WHO,P

- ***DRUG SUMMARY:***

Loop diuretics are used in pulmonary edema due to left ventricular failure and in patients with long standing heart failure who no longer respond to thiazides. These drugs inhibit the reabsorption of Na and Cl ions from the ascending Loop of Henle in the renal tubule, and are powerful diuretics. Hypokalemia may develop, and care is needed to avoid hypotension. It is a good choice for patients who do not respond to thiazide diuretics, or have impaired renal function.

The most important example of these diuretics is furosemide/frusemide. It is a powerful diuretic that acts within 1 hour of oral administration and diuresis is complete within 6 hours. The degree of diuresis associated with these drugs is dose related.

(Other drugs in this group include Ethacrynic acid, Bumetanide and Torsemide).

- ***INDICATIONS:***

Edema, oliguria due to renal failure, and hypertension.

- ***CONTRAINDICATIONS:***

Precomatose states associated with liver cirrhosis; porphyria; history of hypersensitivity to furosemide; anuria; increasing oliguria; fluid and electrolyte depletion states; and hepatic coma.

- ***DOSAGE FORMS:***

Tablets, injection.

- ***RECOMMENDED DOSAGE:***

Adult: ★*For Edema;*

Initially, start with 40 mg PO in the morning adjusted as necessary according to patient's response.

Maintenance for mild cases: 20 mg PO daily, or 40 mg on alternate days.

Some patients may require doses of 80 mg or more daily given in 1 or 2 doses.

(Only in very severe cases dose may be titrated up to a maximum of 600 mg/d; in such case a specialist in this field is needed).

★*For Hypertension;*

40-80 mg PO daily either alone or in conjunction with other antihypertensives.

Child: ★*For Edema and Hypertension;*

1-3 mg/kg PO daily may be increased according to response but for a maximum of 40 mg/24 h. Doses over 6 mg/kg are not recommended.

Directions: Furosemide can be taken with food or milk to reduce possibility of gastric irritation.

*Drug effects are evident within 30 min. to 1 hr. after an oral dose, and lasts for about 4-6 h.

*Schedule doses to avoid nocturia and sleeping disturbance (example: when given once daily it should be administered in the morning; when given twice daily it should be given at 8 am. and 2 pm.).

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use. Diuretics are not usually used to treat hypertension during pregnancy, since it might affect placental perfusion thus decreasing the extracellular volume (Category C).

Lactation- Furosemide is excreted in breast milk. Because of the potential adverse reactions in nursing infants, decide whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Renal Disease- In case of moderate renal impairment, higher doses of furosemide may be needed. In renal failure, use is contraindicated.

Liver Disease- Avoid use in severe cases of liver dysfunction. Hypokalemia may precipitate coma; potassium-sparing diuretics should be used to prevent this; increased risk of hypomagnesemia in alcoholic cirrhosis.

- ***PRECAUTIONS AND WARNINGS:***

-These agents are potent diuretics; excess amounts can lead to profound diuresis with water and electrolyte depletion. Careful medical supervision is required and dosage should be individualized.

-Caution use in case of infants, elderly patients, hepatic cirrhosis, nephrotic syndrome, cardiogenic shock associated with MI, history of SLE, history of gout, patients receiving digitalis glycosides or potassium-depleting steroids.

- ***ADVERSE EFFECTS:***

Hyponatremia, hypokalemia, hypochloremic alkalosis, increased calcium excretion, hypotension; less commonly nausea, GI disturbances, hyperuricemia and gout may occur; and hyperglycemia (less common than thiazides).

- ***INTERACTIONS:***

Overview of Loop Diuretics Drug-Drug Interaction	
Drug	**Interaction**
Analgesics	Diuretics may increase the risk of nephrotoxicity of NSAIDs, if used for long periods of time. Monitor patients, especially those at risk of kidney disease.
Anti-arrhythmics	Toxicity of many anti-arrhythmic drugs might increase if hypokalemia occurs. Use caution.
Anti-depressants	Increased risk of postural hypotension with TCAs. Warn patients against suddenly changing posture to upright position (when standing up) to avoid feeling dizzy and falling.
Anti-diabetics	Hypoglycemic effects of antidiabetic drugs may be antagonized by furosemide. Use caution.
Anti-histamines	Hypokalemia increases the risk of ventricular arrhythmia with astemizole and terfenadine. Avoid use with such antihistamines.
Cardiac glycosides	Increased toxicity if hypokalemia occurs.
Cortico-steroids	Increased risk of hypokalemia; antagonism of diuretic effect.
Lithium	Loop diuretics reduce lithium excretion, but they are safer than thiazides.
Sex hormones	Estrogens and combined OCs antagonize diuretic effect. Counsel women on use of alternative method instead of hormonal therapy if needed.

- ***OVERDOSE:***

Symptoms: Acute profound water loss, volume and electrolyte depletion, dehydration, reduction of blood volume, and circulatory collapse with a possibility of vascular thrombosis and embolism.
Treatment: Replace fluid and electrolyte losses by careful monitoring of the urine and electrolyte output and serum electrolyte levels. Always refer the patient for further investigations.

- ***BRANDS:***

Diasix (JCL), Furovite (Vitamed), Fusid (Teva), Lasix (Hoechst), Miphar (Pharbita), Urix (BPC).

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c) Potassium Sparing Diuretics

Spironolactone WHO,P

- ***DRUG SUMMARY:***

Potassium-sparing diuretics are another class of diuretics that have been used to avoid hypokalemia associated with thiazide and loop diuretics. Spironolactone is a potassium sparing-diuretic that acts by antagonizing aldosterone. It is of value in the treatment of the edema of cirrhosis of the liver, and is effective in edema of heart failure, particularly when congestion has caused hepatic engorgement. It is also used in Conn's syndrome (primary hyper-aldosteronism). Good choice for patients who are very susceptible to hypokalemia complications, or can not tolerate the other diuretic agents.
(Other agents in this group include Amiloride and Triamterene).

- ***INDICATIONS:***

Edema and ascites in cirrhosis of the liver, malignant ascites, nephrotic syndrome, congestive heart failure; primary aldos-teronism.

- ***CONTRAINDICATIONS:***

Hyperkalemia, severe renal impairment; pregnancy and breast-feeding; Addison's disease; and porphyria.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★***For Edema;***
25-200 mg/24 hrs. PO in divided doses; continued for at least 5 days; dose adjusted to optimal response; if no response, a

thiazide or a loop diuretic may be added without changing spironolactone dosage.

★***For Hypertension;***

50-100 mg/24 hrs. PO in single or divided doses; continued for at least 2 wks.; dose adjusted to optimal response.

★***For Primary Aldosteronism;***

100-400 mg/day in divided doses.

Child: ★***For Edema;***

3.3 mg/kg/day PO in single or divided doses continued for at least 5 days; dose needs to be adjusted till optimal response.

★***For Hypertension;***

1-2 mg/kg PO given twice daily.

Directions: Administer with food to enhance absorption.

*Tablets may be crushed (unless package advises against) before administration and taken with fluid of patient's choice.

*It may produce drowsiness and lack of coordination; observe caution while driving or performing other tasks requiring alertness, coordination or physical dexterity, until effects of the medication is fully known.

- ***USE IN SPECIAL CASES:***

Pregnancy- Do not use. Spironolactone or its metabolites may cross the placenta barrier. Feminization occurs in male rat fetuses. In general diuretics are not used to treat hypertension in pregnancy since it might affect placental perfusion due to decrease of extracellular volume (Category D).

Lactation- One of the metabolites of spironolactone appears in breast milk, an alternative method of infant feeding should be instituted when using spironolactone.

Renal Disease- use with caution. Use of spironolactone may cause a transient elevation of BUN, especially in patients with preexisting renal impairment. The drug may cause mild acidosis.

Liver Disease- use with caution, since it is metabolized in the liver.

- ***PRECAUTIONS AND WARNINGS*:**

-Use caution with patients with BUN of 40 mg/dl or greater and if there is a hepatic disease since it is metabolized in the liver.

- ***ADVERSE EFFECTS*:**

GI disturbances, gynecomastia and hyperkalemia.

- ***INTERACTIONS:***

Overview of Spironolactone Drug-Drug Interaction

Drug	Interaction
Ammonium chloride	Combination of spironolactone and acidifying doses of ammonium chloride may produce systemic acidosis. Avoid concomitant use.
Aspirin	Diuretic effect of spironolactone may be antagonized by aspirin and other salicylates. Avoid concomitant use.
Potassium supplements	Hyperkalemia may result from the use of spironolactone along with potassium supplements. Avoid concomitant use.
ACE inhibitors	Both medications may cause hyperkalemia that might cause complete heart block. Do not use together.

- ***OVERDOSE:***

Symptoms: The most likely signs are dehydration and electrolyte imbalances. Other symptoms may include GI cramping, vomiting, diarrhea, headache, drowsiness, and mental confusion.

Treatment: discontinue therapy and observe patient closely. Induce emesis or perform gastric lavage. Treatment is symptomatic and supportive. If hyperkalemia occurs, emergency procedures are to be implemented.

- ***BRANDS:***

Aldactone (Searle), Aldosprine (Teva), Sincomen (Schering).

2) BETA – BLOCKERS

β-adrenergic receptor blocking agents competitively antagonize the responses to catecholamines that are mediated by the β-receptors. Some agents are more selective than others, and all have differences in their pharmacokinetic profiles. β-blockers are the drugs of choice in: youth, hyperkinetic circulation, angina pectoris, post-myocardial infarction (cardioprotective effect), migraine head-aches, senile tremor. Table-2.4 gives an overview of drugs in this class and indicates the selectivity in their action

Table- 2.4: Summary of Available β-Blockers

Drug	Adrenergic receptor blocking activity
Acebutolol	β_1 (β_2 at higher doses) (ISA* activity)
Atenolol	β_1 (β_2 at higher doses)
Bisoprolol	β_1 (β_2 at higher doses)
Esmolol	β_1 (β_2 at higher doses)
Metoprolol	β_1 (β_2 at higher doses)
Oxprenolol	β_1 β_2 (ISA activity)
Pindolol	β_1 β_2 (ISA activity)
Propranolol	β_1 β_2 (non-selective)
Timolol	β_1 β_2 (non-selective)
Labetolol	β_1 β_2 α_1

**ISA- Intrinsic Sympathomimetic Activity; tend to cause less bradycardia than other β-blockers, and may cause less coldness of the extremities.*
-Other drugs produced include: Carteolol, Celiprolol, Nadolol, Penbutolol, Sotalol.
Reference: Drug Facts & Comparisons, 2000, p. 468.

a) Propranolol P

- ***DRUG SUMMARY:***

Propranolol is a non-selective β-blocker of both cardiac (β_1) and bronchial (β_2) adrenoreceptor blocking activity. As a result of blocking β_1-receptors within the heart, the following effects will occur: reduction of the heart rate, reduction of myocardial irritability (class II anti-arrhythmic agents), and reduction of the force of myocardial contraction. Propranolol also blocks bronchodilator effect of catecholamines leading to bronchoconstriction.

- ***INDICATIONS:***

Management of cardiac arrhythmias; myocardial infarction; tachyarrhythmias associated with digitalis intoxication, for anesthesia and thyrotoxicosis; angina pectoris due to coronary atherosclerosis; in the treatment of hypertension alone or in combination with other anti-hypertensive agents; and for migraine prophylaxis.

- ***CONTRAINDICATIONS:***

It is contraindicated in the following cases:
1. Greater than first-degree heart block.
2. CHF or Cardiogenic shock.
3. Significant aortic or mitral valvular disease.
4. Bronchial asthma or bronchospasm.
5. Allergic rhinitis during pollen season.
6. Concurrent use of adrenergic augmenting psychotropic drugs or within two weeks of MAO inhibitors therapy.
7. Sick sinus syndrome.

- ***DOSAGE FORMS:***

Tablets

- ***RECOMMENDED DOSAGE:***

Adult: ★***For Hypertension***;
Initially 40-80 mg PO b.i.d.; increased at weekly intervals to 160-320 mg/24hrs in divided doses; max. 640 mg/d.
★***For Angina***;
40 mg PO b.i.d. or t.i.d.; may need 120-320 mg/24 h in divided doses; max. 320 mg/d.
★***For Arrhythmias***;
10-30 mg PO, t.i.d. or q.i.d. up to 320 mg/d.
★***For Acute MI***;
40 mg 4 times a day for 2 to 3 days then 80 mg twice daily; max. 240 mg/d or
180-240 mg/24 h. in divided doses.
★***For Migraine Prophylaxis***;
40-80 mg in divided doses daily; increased at weekly intervals; may require up to 160-

240 mg/d. If there is no response after 4-6 weeks then therapy should be discontinued.

Child: ★*For Hypertension*;

1 mg/kg/24h PO in 2 divided doses, increased to 2 to 4 mg/kg/24hrs.

Directions: It is recommended to be taken before meals and at bedtime. Food enhances bioavailability of propranolol, so **advise patients to be consistent with regard to taking propranolol with food or on an empty stomach to minimize variations in absorption.**

*If a dose is missed, take as soon as remembered. If too close to next dose, ignore and continue with the regimen. The next dose should not be doubled.

- ***USE IN SPECIAL CASES:***

Pregnancy- If it is administered in the third trimester it may cause intra-uterine growth retardation, neonatal hypoglycemia, and bradycardia; risk greater in severe hypertension (Category C).

Lactation- Propranolol is excreted in breast milk but in concentrations too low to have significant side effects on nursing child compared to other β-blockers. Peak concentrations occur 2-3 hours after a dose. Although no reported toxicity effects have been noted with β-blockers, the child should be observed specially if the drug is used for long term. The American Academy of Pediatrics considers propranolol to be compatible with breast-feeding.

Children- Safety is not established.

Renal Disease- In severe cases, start with small dose; higher plasma concentrations after oral administration; may reduce renal blood flow and adversely affect renal function in severe impairment.

Liver Disease- Reduce oral dose.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in special risk patients with: peripheral arterial insufficiency, patients prone to non-allergenic bronchospasm (e.g. chronic bronchitis, emphysema), major surgery, renal and hepatic impairment, Myasthenia Gravis, Wolff-Parkinson-White syndrome.

-Diabetes mellitus, since β-blockers prevent premonitory signs of hypoglycemia in diabetics and may also augment hypoglycemia by interfering with catecholamine-induced glycogenolysis. On the other hand propranolol may block insulin release from the pancreas with resulting hyperglycemia. Use caution in patients prone to hypoglycemia.

-Avoid abrupt withdrawal in angina.

- ***ADVERSE EFFECTS*:**

Bradycardia, heart failure, bronchospasm, peripheral vasoconstriction, gastrointestinal disturbances, fatigue, sleep disturbances, rare reports of rashes and dry eyes (reversible on withdrawal).

- ***INTERACTIONS:***

Overview of β-Blockers Drug-Drug Interaction	
Drug	**Interaction**
Alcohol & anesthetics	Enhance the hypotensive effect. Use with caution and warn patient of this effect.
NSAIDs	Antagonize hypotensive effect. If the patient has to take an NSAID, advise to use caution and move slowly when changing postural positions, to decrease the chances of dizziness or falling.
Anti-arrhythmics	Increased risk of myocardial depression and bradycardia and increased risk of lidocaine toxicity. Do not administer concomitantly.
Rifampicin	Accelerates the metabolism of propranolol. Do not administer at the same time.
Antidiabetics	Enhances the hypoglycemic effect (masking of warning signs such as tremor). Use caution.
Anti-psychotics	Plasma concentration of chlorpromazine is increased by propranolol. Dose adjustment is required if patient has increased side effects.
Anxiolytics & hypnotics	Enhance the hypotensive effect of β-blockers.

Cardiac glycosides	Propranolol may potentiate bradycardia due to digoxin.
Cortico-steroids & sex hormones	(Estrogens and combined OC). Antagonism of the hypotensive effect of propranolol.
Muscle relaxants	Propranolol enhances the effect of muscle relaxant.
Sympatho-mimetics	Severe hypertension with adrenaline and noradrenaline; Severe hypertension is also possible with sympathomimetic anorectics and cough and cold remedies.
Theophyl-line	β-blockers should be avoided on pharmacological grounds (bronchospasm).
Thyroxin	Metabolism of propranolol is accelerated with thyroxin (reduced effects). Dose adjustment of propranolol may be needed.
Cimetidine	Plasma concentration of propranolol is increased by cimetidine. Do not administer at the same time.
Calcium-channel blockers	Increased risk of bradycardia and AV block with diltiazem; severe hypotension and heart failure occasionally with nifedipine; asystole, severe hypotension, and heart failure with verapamil. They should not be used together.

- ***OVERDOSE:***

Therapeutic overdoses of β-blockers may cause lightheadedness, dizziness, and possibly syncope due to impaired circulation secondary to bradycardia and hypotension; heart failure may be precipitated or exacerbated.

Acute massive overdoses must be managed in hospital and expert advice should be obtained. Maintenance of a clear airway and adequate ventilation is mandatory.

- ***BRANDS:***

Blocardril 10 (BPC), Deralin (Abic), Slow Deraline (Abic), Prolol (Dexxon).

b) Atenolol WHO, P

- ***DRUG SUMMARY:***

In therapeutic doses atenolol selectively blocks β_1-adrenergic receptors located chiefly in cardiac muscle. With large doses preferential effect is lost and inhibition of β_2-adrenergic receptors (especially in bronchial and vascular musculature) may lead to increased airway resistance, especially in patients with asthma. It is less lipophilic (lipid soluble) than propranolol thus it does not readily cross the blood-brain barrier, therefore it is not associated with mental depression. It is not as heavily metabolized in the liver. It has a longer antihypertensive effect than propranolol thus permitting once-a-day dosing.

- ***INDICATIONS:***

Used in the management of hypertension (1st choice drug) as a single agent or concomitantly with other antihypertensive agent, especially a diuretic. As an anti-arrhythmic agent and for thyrotoxicosis.

Treatment of stable angina pectoris and MI.

- ***CONTRAINDICATIONS:***

Atenolol is contraindicated in the following cases:

1. Sinus bradycardia.
2. Greater than first degree heart block.
3. Uncontrolled cardiac failure.
4. Cardiogenic shock.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★*For Hypertension*;

50 mg PO once daily initially, used alone or added to a diuretic, may be increased to 100 mg/d. The full effect is seen within 1-2 weeks. Doses over 100 mg/day are unlikely to produce any further benefit.

★*For Angina*;

50-100 mg PO daily in 1 or 2 doses.

★*For Arrhythmias*;

50-100 mg PO daily.

★***For MI***:
Patient would be under emergency treatment where IV doses would be administered, then switched to PO as needed.

Directions: If necessary, tablet may be crushed (unless manufacture's package strictly advises against that) before administration and taken with fluid of patient's choice.
*If patient misses a dose, it should be taken as soon as remembered. If too close to next dosing time, just continue with the regimen. The next dose should not be doubled.

- ***USE IN SPECIAL CASES:***

Pregnancy- If atenolol is administered in the 3rd trimester it may cause intra-uterine growth retardation, neonatal hypoglycemia, and bradycardia; risk is greater in severe hypertension (Category C).
Lactation- Monitor infant; possible toxicity due to β-blockade but amount of most beta-blockers excreted in milk is too small to affect the infant. Atenolol is excreted in higher amounts than propranolol.
Children- Not established.
Renal Disease- In the case of moderate renal impairment, one should reduce the dose of atenolol, since atenolol is excreted unchanged in the urine. If it is severe (Cl_{cr} < 15), start with a small dose; higher plasma concentrations after oral administration; may reduce renal blood flow and adversely affect renal function in severe impairment; max dose is 25 mg/d.
Liver Disease- It is not metabolized in the liver. So there is no need for dosage adjustment in the case of hepatic dysfunction.

- ***PRECAUTIONS AND WARNINGS:***

Use with caution in the following cases:
-Hypertensive patient with CHF controlled by digitalis and diuretic.
-Asthmatic patient.
-Diabetic patient. (Refer to propranolol)
-Impairment of renal function.

- ***ADVERSE EFFECTS, INTER-ACTIONS, OVERDOSE:***

Refer to propranolol.

- ***BRANDS***

Apo-atenol (Apotex), Ateni (Generics), Normiten (Abic), Corotenol (JePharm), Normalol (Dexxon).

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3) ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

The essential effect of these agents on the renin-angiotensin system is to inhibit conversion of the relatively inactive angiotensin I to the active angiotensin II by blocking the angiotensin converting enzyme (ACE). The converting enzyme inhibitors are highly specific drugs. Although they inhibit the degradation of Bradykinin and potentiate its hypotensive action, the principal pharmacological and clinical effects of ACE inhibitors are quite specific at the level of the enzyme. In addition, recent studies suggest that ACE inhibitors may also affect other enzymes, including those involved in the generation of prostaglandins.

Many agents on the market are in this group, which differ in their pharmacokinetic profiles, but do not add much benefit over each other. Table-2.5 compares some of the locally available drugs.

Captopril will be the prototype for discussion on ACE inhibitors group.

Table-2. 5: Available ACE Inhibitors Chart of Comparisons						
Drug	**Prodrug**	**Pharmacokinetic Parameters[a]**				**Principal route(s) of elimination**
		t_{max} (h)	$t_{1/2}$ (h)	Vd (L)	PB (%)	
Benazepril	Yes	1.5	2-3 (22)[b]	8.4	> 95	Renal
Captopril	No	1.0	2.0	49 [c]	30	Renal
Cilazapril	Yes	3.0	2(40-50)	35	-	Renal
Enalapril	Yes	3-4	5 (35)[b]	-	50	Renal
Lisinopril	No	6.0	12 (30)[b]	124	< 1	Renal
Quinapril	Yes	2.0	2-3	-	97	Renal
Ramipril	Yes	3.0	3.0 (110)[t]	90	56	Renal/Hepatic

[a] Values shown are for active metabolite if compound is a prodrug.
[b] Terminal phase elimination half-life. [C] At steady state.
Abbreviations: t_{max} = time to peak plasma concentration, $t_{1/2}$ = elimination half-life, Vd = apparent volume of distribution, PB = protein binding.
-Other produced drugs in this group include: *Delapril, Fosinopril, Moexiprol, Perindopril, Spirapril, Trandolapril, Zofenopril.*

Reference: Speight & Holford. Avery's Drug Treatment, 4th ed. Adis International, New Zealand 1997.

a) Captopril WHO,P

- ***DRUG SUMMARY:***

Captopril is an angiotensin-converting enzyme (ACE) inhibitor, cardiovascular, antihypertensive, vasodilating agent. It lowers blood pressure by specific inhibition of the angiotensin-converting enzyme that leads to the formation of angiotensin-II that is a vasoconstrictor. ACE inhibitors have been considered for treatment of hypertension when thiazides and beta-blockers are contraindicated, not tolerated, or fail to control blood pressure. ACE inhibitors are a good choice for hypertension in insulin-dependent diabetics and for patients with cardiac heart failure.

- ***INDICATIONS:***

Used in mild to moderate essential hypertension alone or with thiazide therapy; severe hypertension resistant to other treatment.
For congestive heart failure (CHF) in conjunction with digitalis and diuretics.
Also in diabetic nephropathy in insulin-dependent diabetes.

- ***CONTRAINDICATIONS:***

It is contraindicated in the following cases: Hypersensitivity to ACE inhibitors, known or suspected renovascular disease, aortic stenosis or outflow tract obstruction, porphyria, and pregnancy.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★***For Hypertension***;
Initially, 12.5 mg b.i.d. would be started if using it alone.
Initially 6.25 mg b.i.d. if used in addition to a diuretic, in elderly, or in renal impairment.
Usual maintenance dose is 25 mg b.i.d.; max. 50 mg t.i.d. (rarely: 50 mg t.i.d. is used as in severe hypertension).
★***For Heart Failure***;
Initially 6.25-12.5 mg t.i.d.
Start as early as 3 days after infarction, then increase over several weeks to 150 mg in divided doses; max. 450 mg/day.

Directions: Administration of first dose in therapy should be started at night, at bedtime to avoid hypotensive side effects.

*Food decreases its absorption; so it should be taken one hour before meals or 2 hours after meals.

*If a dose is missed, it should be taken as soon as remembered. If too close to second dosing time, it should be ignored and the patient should continue with the usual regimen. The next dose should not be doubled.

- ***USE IN SPECIAL CASES:***

Pregnancy- The use of ACEIs during the 2nd and 3rd trimesters has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, renal failure and death. When pregnancy is detected, ACEIs should be discontinued as soon as possible. (Category C in 1st trimester, Category D in 2nd & 3rd trimesters).

Lactation- Use with caution. It is excreted in breast milk, but in amounts too small to be harmful to the nursing infant. Use the lowest possible dose of drug. Peak concentration levels occur at 4 hrs, so nursing should be avoid then.

Children- Safety of captopril in children has not been established.

Renal Disease- ACE inhibitors are excreted by the kidney, and occasionally cause impairment of renal function which may progress and become severe. At particular risk are those with pre-existing renal disease or impairment, the elderly, those with bilateral renal artery stenosis.

Note:-

Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics or use of potassium-containing salt substitutes increase the risk of hyperkalemia. Renal function and electrolytes should be checked before starting an ACE inhibitor, and monitored during treatment.

-In general, with mild renal impairment, reduce dose and monitor response, but avoid if possible. In the case of renal impairment, even mild, hyperkalemia and other side effects are more common (but specialized role in some forms of renal disease).

Liver Disease- Some hepatic metabolism occurs, but it seems to be safe to be used in hepatic disease.

- ***PRECAUTIONS AND WARNINGS***

-Use caution if administered with diuretics.

-First dose may cause hypotension especially in patients: taking diuretics, on a low sodium diet, on dialysis, or dehydrated.

-Monitor renal function before and during treatment (refer to USE IN SPECIAL CASES).

-ACE inhibitors should be used with particular caution in patients with peripheral vascular disease or generalized atherosclerosis, as such patients may have clinically silent renovascular disease.

-White cell counts and urinary protein estimations are needed.

-In the case of patients on dialysis, avoid the combination of ACEI therapy with the use of high flux polyacrylonitrile membranes, since anaphylactic reactions have been reported.

-Take caution in patients receiving immunosuppressants or other drugs that cause leukopenia or agranulocytosis, coronary or cerebrovascular disease.

- ***ADVERSE EFFECTS:***

Persistent dry cough, throat discomfort, voice changes are very common. Taste disturbances (loss of taste), sore mouth, abdominal pain, rash, angioedema, hypotension; proteinureai, thrombo-cytopenia, neutropenia, agranulocytosis, hyperkalemia (all are more common in renal impairment); increases in liver enzymes, liver damage, and cholestatic jaundice; renal impairment.

- ***INTERACTIONS:***

Overview of ACEI Drug-Drug Interaction	
Drug	**Interaction**
Alcohol, anesthetics, anxiolytics, hypnotics, muscle relaxants (baclofen), corticosteroids, & anti-depressants	Enhance the hypotensive effect. Use with caution.
β-blockers, Ca-channel blockers, nitrates, & levodopa	Enhance the hypotensive effect. Use with caution.
Analgesics	Antagonize the hypotensive effect and increased risk of renal failure with NSAIDs; hyperkalemia with Indo-methacin and possibly other NSAIDs.
Anti-psychotics	Severe postural hypotension with chlorpromazine and possibly other phenothiazines. Avoid concomitant use.
Cardiac glycosides	Plasma concentration of digoxin possibly increased by captopril. Monitor closely when initiating captopril therapy. May need to reduce dose of glycoside.
Diuretics	Enhanced hypotensive effect (can be extreme); hyperkalemia with potassium-sparing diuretics. Use with caution.
Lithium	ACE inhibitors reduce excretion of lithium (increase its plasma concentration).
Potassium salts	Patients will be at increased risk of hyperkalemia. Avoid concomitant use.
Sex hormones	Estrogen and combined oral contraceptives antagonize hypotensive effect. Dose adjustment of ACE inhibitors may be needed if patient not responding to therapy.
Uricosurics	Probenecid reduces excretion of captopril. Use with caution.

- ***OVERDOSE:***

Hypotension is the most common symptom of overdose. Systolic blood pressure of 95-80 mmHg in hypertensive patients have been reported. Treatment includes usual supportive measures, with correction of hypotension being the primary choice.

- ***BRANDS:***

Capoten (Squibb), Cardopril (BPC), Inhibace (Pharmabest).

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4) CA CHANNEL BLOCKERS

Calcium channel blockers (less correctly called Ca antagonist) interfere with the inward displacement of Ca ions through the slow channels of active cell membranes. They influence the myocardial cells, the walls within the specialized conduction system of the heart, and the cells of the vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses with the heart may be depressed, and coronary or systemic vascular tone may be diminished. They should be **avoided in heart failure** because they may further depress cardiac function and cause clinically significant deterioration. Ca channel blockers differ in their action, therefore their therapeutic effects are much variable within the group as compared to the other classes of drugs.

(Drugs in this category include: Nifedipine, Verapamil, Diltiazem, Isardipine, Felodipine, Nicardipine, Nisoldipine, and Nimodipine).

The major agents that will be discussed include nifedipine, verapamil and diltiazem.

a) Nifedipine [WHO,P]

- ***DRUG SUMMARY:***

Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries (hypotensive effect), in greater effect than that produced by verapamil or diltiazem and usually results in reflex tachycardia. It has more influence on vessels and less on the myocardium than does verapamil, and unlike verapamil has no anti-arrhythmic activity. It rarely precipitates heart failure.

- ***INDICATIONS:***

Prophylaxis and treatment of angina; hypertension; Raynaud's phenomenon.

- ***CONTRAINDICATIONS:***

Cardiogenic shock; advanced aortic stenosis; and porphyria.

- ***DOSAGE FORMS:***

Tablets, soft gelatin capsules.

- ***RECOMMENDED DOSAGE:***

Adult: ★***Use for Angina;***

10-20 mg PO t.i.d. up to 180 mg/24 hrs.

★***Use for Hypertension;***

10-20 mg t.i.d. up to 180 mg/24 hrs. or 30-90 mg sustained release once/day.

★***Use for Hypertensive Emergency;***

10-20 mg PO q. 20-30 min. if necessary.

Child: Safety and efficacy not established.

Directions: In a hypertensive emergency, nifedipine capsule may be swallowed whole or contents may be given SL. Puncture capsule with a pin and squeeze contents under the tongue (puncture about 10 times). The punctured capsule may also be chewed.

*If a dose is missed, it should be taken as soon as remembered. If too close to second dosing time, it should be ignored and the patient should continue with the usual regimen. The next dose should not be doubled.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use during pregnancy unless clearly indicated (Category C). May inhibit labor (and has been used for treatment in premature labor under intensive observation).

Lactation- Amount excreted in breast milk is too small to be harmful, but manufacturers advise to avoid. Delay breast-feeding by 3-4 hrs after a dose, to decrease the amount of drug ingested by infant.

Renal Disease- In the case of moderate renal impairment, start with a small dose; reversible deterioration in renal function has been reported.

Liver Disease- Reduce dose in case of hepatic impairment.

- ***PRECAUTIONS AND WARNINGS:***

Withdraw medication if ischemic pain occurs or existing pain worsens shortly after initiating treatment; heart failure or significantly impaired left ventricular function; severe hypotension; diabetes mellitus; may inhibit labor.

- ***ADVERSE EFFECTS:***

Adverse side effects that may occur: headache, flushing, dizziness, lethargy; also gravitational edema, rash, nausea, increased frequency of micturition, eye pain, gum hyperplasia, tachycardia and palpitation, tremor, leg cramps; depression has been reported as well as teleangectasia.

- ***INTERACTIONS:***

Overview of Nifedipine Drug-Drug Interaction

Drug	Interaction
Anti-arrhythmics	Increased risk of bradycardia, AV block, and myocardial depression. Nifedipine reduces plasma concentration of quinidine.
Anti-bacterials	Rifampicin possibly increases metabolism of nifedipine (reduce plasma concentration).
Anti-diabetics	Nifedipine may occasionally impair glucose tolerance. Use with caution and warn diabetic patients.
Anti-epileptics	Nifedipine increases plasma concentration of phenytoin. Effect of nifedipine reduced by carbamazepine.

Antihyper-tensives & Anti-psychotics	Enhanced hypotensive effects. Warn patient.
β-blockers	Occasionally severe hypo-tension and heart failure with nifedipine. Safer to avoid use concomitantly unless clearly indicated.

- ***OVERDOSE:***

Symptoms include nausea weakness, dizziness, drowsiness, confusion and slurred speech. Hypotension, bradycardia and AV block may occur. Death can occur.
Treatment: If the patient is seen shortly after oral ingestion of nifedipine, employ emetics or lavage and cathartics. Dialysis is not likely to help since these drugs are highly protein-bound. Treatment is supportive. Refer the patient for further control and investigation.

- ***BRANDS:***

Adalat (Bayer), Angilat (BPC), Aprical (Rentshler), Corotrend (Siegfried), Osmo-Adala (Pharma-Clal), Pressolat (Agis), Megalat (Agis).

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b) Verapamil WHO,P

- ***DRUG SUMMARY:***

Verapamil inhibits the calcium ion influx through slow channels into cells of myocardial and arterial smooth muscles (both coronary and peripheral blood vessels). It dilates coronary arteries and arterioles and inhibits coronary artery spasm; thus myocardial oxygen delivery is increased (antianginal effect). It decreases and slows SA and AV nodes conduction (antiarrhythmic effect) without effect on normal arterial action potential or intraventricular conduction. By vaso-dilatation of peripheral arterioles, drug decreases peripheral vascular resistance and reduces arterial BP at rest. It reduces the cardiac output and it may slightly decrease the heart rate. It may precipitate heart failure and exacerbate conduction disorder.

- ***INDICATIONS:***

- Supraventricular arrhythmias.
- Angina.
- Hypertension.

- ***CONTRAINDICATIONS:***

Hypotension, bradycardia, second- and third-degree heart block, sick sinus syndrome, cardiogenic shock, cardio-megaly, sino-atrial block; history of heart failure or significantly impaired left ventricular function, even if controlled by therapy; Wolff-Parkinson-White syndrome including atrial flutter or fibrillation; porphyria, digitalis toxicity.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult:

★***For Supraventricular Arrhythmias;***
40-120 mg PO, 3-4 times daily.
★***For Angina;***
80-120 mg 3 times daily.
★***For Hypertension;***
240-480 mg PO daily in 2-3 divided doses.

Directions: Administer oral dose with food to reduce gastric irritation.
*Sustained action dosage forms should not be opened, crushed or chewed. Capsule should be swallowed as a whole
*If a dose is missed, it should be taken as soon as remembered. If too close to second dosing time, it should be ignored and the patient should continue with the usual regimen. The next dose should not be doubled.

- ***USE IN SPECIAL CASES:***

Refer to Nifedipine. Verapamil crosses the placenta.
In lactation, verapamil or its metabolites have not shown any adverse effects on nursing children.

- ***PRECAUTIONS AND WARNINGS:***

-Caution use in the following cases: 1st degree heart block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, or left ventricular failure present); aortic stenosis, as well as in patients with hepatic and renal impairment.

- ***ADVERSE EFFECTS:***

Constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, and ankle edema. Other reported effects include pruritis, AV block, bradycardia, and rarely gynecomastia and gingival hyperplasia after long term treatment.

- ***INTERACTIONS:***

Overview of Verapamil Drug-Drug Interaction	
Drug	**Interaction**
Anesthetics	Verapamil increases hypotensive effect of general anesthetics and risk of AV delay.
Anti-arrhythmics	Increased risk of bradycardia, AV block, and myocardial depression. Verapamil raises plasma concentration of quinidine (extreme hypotension may occur).
Anti-bacterials	Rifampicin increases metabolism of verapamil (reduce plasma concentration).
Anti-depressants	It increases plasma concentration of imipramine and other tricyclics.
Anti-epileptics	The effect of carbamazepine is enhanced by verapamil; effect of verapamil reduced by phenobarbitone and phenytoin.
Anti-hypertensives	Enhanced hypotensive effects. Caution patients to slowly change position when standing up or sitting down, so they won't feel dizzy.
Anti-psychotics	Enhanced hypotensive effects. Use with caution.
Beta-blockers	Asystole, severe hypotension, and heart failure. It should be usually avoided.
Cardiac glycosides	Plasma concentration of digoxin may be increased by verapamil, also there will be an increased risk in AV block and bradycardia.
Lithium	Neurotoxicity may occur without any increase in plasma lithium concentration. Monitor patients taking Li.
Theophylline	Verapamil enhances the effect of theophylline. Use caution, monitor patient response closely when starting therapy.

- ***OVERDOSE:***

Refer to nifedipine.

- ***BRANDS:***

Ikacor/Ikapress (Teva), Verac (Dexxon).

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c) Diltiazem

- ***DRUG SUMMARY:***

A slow calcium channel blocking, cardio-vascular agent. It is effective in most forms of angina; the longer acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contraindicated or ineffective. It has a less negative inotropic effect than verapamil and significant myocardial depression occurs rarely. Nevertheless because of the risk of bradycardia it should be used with caution in association with beta-blockers. It does **not** alter total serum calcium levels.

- ***INDICATIONS:***

Prophylaxis and treatment of angina and hypertension (long acting formulations).

- ***CONTRAINDICATIONS:***

Severe bradycardia, left ventricular failure, second- or third-degree AV block (unless pacemaker fitted), sick sinus syndrome; pregnancy; and porphyria.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★***For Angina;***

30 mg PO q.i.d.; may increase q. 1-2 d. as required; usual dose range 180-360 mg/day in 3-4 divided doses. Sustained release doses: start with 120-180 mg once daily; then titration may be carried out over a 7-14 day period to 360-480 mg/d.

★***For Hypertension;***

60-120 mg sustained-release b.i.d. (usual range: 240-360 mg/d).

Child: No recommendations.

Directions: Administer oral drug before meals and at bedtime.

*If using sustained release forms, do not chew, open or crush the tablet. Swallow as whole.

- ***USE IN SPECIAL CASES:***

Pregnancy- May inhibit labor. Manufacturers advise that diltiazem is teratogenic in animals, therefore should not be used in pregnant women (Category C).

Lactation- Significant amount is excreted in breast milk but not known to be harmful to the nursing infant. Benefit-risk ratio should be made on whether do discontinue the drug or stop breast-feeding.

Children- Diltiazem safety and efficacy not established.

Renal Disease- Start with smaller dose.

Liver Disease- Reduce dose in hepatic impairment.

- ***PRECAUTIONS AND WARNINGS:***

-Reduce dose of diltiazem in hepatic and renal impairment; heart failure or significantly impaired left ventricular function, mild bradycardia (avoid if severe), first degree AV block, or prolonged PR interval.

- ***ADVERSE EFFECTS:***

Bradycardia, sino-atrial block, atrio-ventricular block, hypotension, malaise, headache, flushing, gastrointestinal disturbances, constipation, ankle edema; rarely rashes (toxic erythema reported); altered liver function tests; hepatitis, amnesia and depression have been reported.

- ***INTERACTIONS:***

Same as nifedipine. *[Refer to nifedipine.]*

- ***OVERDOSE:***

Refer to verapamil.

- ***BRANDS:***

Dilatam/Dilapress (Abic), Levozem (Dexxon).

B) ANTIARRHYTHMICS

The exact mechanisms underlying rhythm disturbances are complex, and for the most part, unknown. Arrhythmia may result from abnormal impulse formation (automaticity), abnormal impulse conduction, or a combination of both processes.

Accurate diagnosis and appropriate therapy of disturbances in cardiac rhythm require gradual analysis of patient's history (specially relating to new use of drugs affecting the heart), physical exam as well as laboratory and ECG results. Diagnosis of such cases is usually done by a cardiologist.

The most widely used classification of antidysrhythmic drugs is based on the electrophysiologic action, (refer to table 2.6 on classification).

At the primary level, physicians will not prescribe such medications, but they may see patients who are taking such drugs. Therefore, knowledge about these agents is needed.

Table- 2.6: Classification of Antiarrhythmic Drugs	
Class I	Drugs with local anesthetic effects and membrane stabilizing properties. These are subdivided depending on the magnitude of their effects on the different cardiac phases.
Type IA	Affecting both atrial and ventricle muscle. ***Quinidine**, Procainamide, Moricizine, Disopyramide.*
Type IB	Usefulness is confined to ventricular rhythm disorders. ***Lidocaine**, Tocainide, Mexiletine, Phenytoin.*
Type IC	Indicated primarily in ventricular dysrhythmias, can be used in atrial arrhythmia. *Encainide, Flecainide, Lorainide, Propafenone.*
Class II	β-adrenergic blocking agents, general myocardial depressants for both supraventricular and ventricular rhythm disturbances. ***Propranolol**, Esmolol, Acebutolol.*
Class III	No membrane stabilizing effects, selectively increases action potential duration. ***Amiodarone**, Bretylium, Sotalol.*
Class IV	Calcium channel blockers, and others. ***Verapamil**, Adenosine.*

[#] *The drugs in bold have been discussed in this chapter.*

1) Amiodarone

- ***DRUG SUMMARY:***

Amiodarone is an iodine-containing benzofuran derivative that possesses cardiac electrophysiological actions that differ fundamentally from those of currently available antiarrhythmic agents. It is a Class III antiarrhythmic with a very long half-life.

Toxicity associated with amiodarone has led the FDA to recommend that the drug be reserved for use in patients with life-threatening arrhythmias.

- ***INDICATIONS:***

It is used for the treatment of both ventricular and supraventricular arrhythmias.

Mainly used for the treatment of tachycardia associated with the Wolff-Parkinson-White syndrome. Also it can be used in the following arrhythmias when other drugs are ineffective or contra-indicated; paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation.

- ***CONTRAINDICATIONS:***

Sinus bradycardia, SA heart block; unless pacemaker fitted; avoid in severe conduction disturbances or sinus node disease; avoid IV use in severe respiratory failure, circulatory collapse, severe arterial hypotension, congestive heart failure; thyroid dysfunction; pregnancy and breast feeding; iodine sensitivity; and porphyria.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★*For Arrhythmias;*

Loading dose (*administered initially in hospital*): 800-1600 mg/d PO in 1-2 doses for 1-3 wks. Maintenance dose: 400-800 mg/d PO in 1-2 doses.

Child: No recommendations.

Directions: GI symptoms occur commonly during high-dose therapy, especially with loading doses. Symptoms usually respond to dose reduction or to administration in divided doses and with food, including milk.

* Use the lowest effective dose to prevent the occurrence of side effects.

*Be alert to pulmonary toxicity presenting with; progressive dyspnea, fatigue, cough, pleuritic pain and fever.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only if no alternative is available (Category D). If it is given in the second or third trimester there will be a possibility of neonatal goiter.

Lactation- Avoid use even though no adverse effects were observed. Breast feeding should be avoided in mothers currently taking the drug or have taken it chronically within the past several months.

Children- Safety and efficacy for use in children have not been established, therefore amiodarone is not recommended for use.

Renal Disease- With moderate renal impairment, Iodine will be accumulated and there will be a risk of thyroid dysfunction.

Liver Disease- It is contraindicated in severe hepatic impairment.

- ***PRECAUTIONS AND WARNINGS:***

-Liver function and thyroid function tests required in long-term therapy. Amiodarone interferes with tests of thyroid function.

-Use caution in heart failure, renal impairment, elderly, severe bradycardia and conduction disturbances in excessive dosage.

-IV use may cause moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdose).

-Also take caution in the case of congestive heart failure, electrolyte imbalance, and preexisting lung disease.

- ***ADVERSE EFFECTS:***

Reversible corneal microdeposits (sometimes with night glare); peripheral neuropathy and myopathy (usually reversible on withdrawal), bradycardia and conduction disturbances; phototoxicity; blue-grey discoloration of the skin (specially nose and ears), hyper- or hypothyroidism; diffused pulmonary alveolitis and fibrosis; hepatitis; anaphylaxis on rapid injection, also bronchospasm or apnea in respiratory failure.

- ***INTERACTIONS:***

Overview of Amiodarone Drug-Drug Interaction	
Drug	**Interaction**
Other anti-arrhythmics	Increased myocardial depression risks. Use with caution.
Anti-coagulants	Metabolism of nicoumalone and warfarin inhibited (enhanced anticoagulant effect). Monitor patient closely.
Anti-epileptics	Metabolism of phenytoin inhibited (increased plasma concentration). Monitor blood levels of patient closely.
Anti-histamines	Increased risk of ventricular arrhythmias with astemizole and terfenadine. Avoid use of these antihistamines while on therapy.
β-blockers	Increased risk of bradycardia, AV block, and myocardial depression.
Calcium-channel blockers	Diltiazem and verapamil increase risk of bradycardia, AV block, and myocardial depression. Use with caution.
Cardiac glycosides	Increased plasma concentration of digoxin (half digoxin maintenance dose).
Diuretics	Toxicity increased if hypokalemia occurs. Monitor patient closely, especially when starting them on the medication.
Ulcer-healing drugs	Cimetidine increases plasma concentrations of amiodarone. Use with caution, do not administer at the same time-interval if needed. Other ulcer healing medication have not shown this interaction, but no sufficient data is available.

- ***OVERDOSE:***

The most likely effects of amiodarone overdose are: hypotension, cardiogenic shock, bradycardia, AV block, and hepatotoxicity.

Treatment includes usual supportive measures. In addition, monitor the patient's cardiac rhythm and blood pressure; if bradycardia occurs, a β-adrenergic agonist may be used. Always refer the patient.

- ***BRANDS:***

Amiodacore (CTI), Cordorone (Labaz/ C.T.S.), Procar (Unipharm).

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2) Lidocaine WHO,P

- ***DRUG SUMMARY:***

It was introduced as a local anesthetic and is still used extensively for that purpose. In contrast to quinidine and procainamide, lidocaine acts primarily on disturbances of ventricular origin and has a narrow spectrum of antiarrhythmic effects. Use is only in injection form, in clinical settings. Indicated for ventricular arrhythmias especially after an MI. No adequate and well controlled studies available on pregnancy (Category B), lactation or use in children.

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3) Quinidine WHO,P

- ***DRUG SUMMARY:***

Quinidine, a *Cinchona* derivative, is a class IA antiarrhythmic, cardiovascular agent. It acts as a depressant of myocardial excitability, conduction velocity and contractility. There are differences in the anhydrous quinidine alkaloid content among the various salts. Make sure that the patient does not switch brands without your consultation. It should be prescribed only when other agents have failed or cannot be available. Quinidine, may itself precipitate rhythm disorders, so it should be **used on specialist advice only**.

C) ANTIANGINA

Angina pectoris is a symptom of myocardial ischemia, which is usually secondary to atherosclerosis of the coronary arteries. Although angina usually implies severe chest pain or discomfort, its presentations are variable. Angina may occur predictably with strenuous exercise (stable angina), or at other times unexpectedly with little or no exercise (unstable angina). Both reflect underlying narrowing of coronary arteries. Classical Prinzmetal variant angina (vasospastic angina) occurs in patient without coronary heart disease, and is due to a spasm of the coronary artery that decreases myocardial blood flow.

Specific treatment of ischemic disease is directed toward improving myocardial oxygen supply, reducing myocardial oxygen demand, and treating precipitating factors or concurrent disorders that may aggravate ischemia. The selection of an effective therapeutic regimen depends on the severity of symptoms, the presence of associated disease (e.g. pulmonary or renal disease) the patient's age and activity level, and the underlying pathophysiologic mechanism that is responsible for the ischemia.

Nitrates remain important first-line agents for the treatment of angina. They have different mechanisms of action that result in vasodilatation action. Nitrate tolerance and reduction in therapeutic response may occur with all the nitrate preparations. To restore antianginal efficacy, nitrates need to be absent from the body for several hours, therefore, patients need a nitrate-free interval of at least 10-12 hours to enhance treatment efficacy. When nitrates cannot be discontinued, even for a

short time, increased doses may be required to overcome tolerance.

Beta-adrenergic blockers (i.e. propranolol, metoprolol) are also important in the management of stable angina. They reduce the frequency of anginal episodes by reducing myocardial oxygen demand, and raise the anginal threshold. Choice of selective or non-selective β_1- or β_2 antagonists depends on individual patients; type of angina, concurrent cardiac problems, side effects, etc. (refer to β-blockers in antihypertensive section).

Calcium channel blockers (i.e. nifedipine, verapamil, diltiazem) are also used as antiangina agents. The antianginal effects of these agents are due to direct coronary vasodilatation and an improvement in the efficiency of myocardial performance. They are indicated in the management of stable and unstable angina, and are the agents of choice in patients unable to tolerate β-adrenergic antagonists and nitrates. Refer to individual monographs for each drug. (Refer to calcium channel blockers in antihypertensive section.)

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1) Isosorbide Dinitrate WHO,P

- ***DRUG SUMMARY:***

Isosorbide dinitrate, a short-acting nitrate, is one of the most effective drugs for providing rapid symptomatic relief of angina. It is active sublingually, and is more stable than glyceryl trinitrate for those who only require nitrates infrequently. It is also effective when given PO for prophylaxis; although the effect is slower in onset, it may persist for several hours. Duration of action up to 12 hrs is claimed for modified-release preparations. Isosorbide mononitrate is a major active metabolite of the dinitrate that attributes to the activity, and is available in the market as a separate preparation.

- ***INDICATIONS:***

Prophylaxis and treatment of angina; left ventricular failure.

- ***CONTRAINDICATIONS:***

Marked anemia, head trauma, cerebral hemorrhage, closed angle glaucoma.

- ***DOSAGE FORMS:***

Tablets, skin patches.

- ***RECOMMENDED DOSAGE:***

Adult: ★***For Angina;***

Sublingually: 5-10 mg.

By mouth: 30-120 mg in divided doses.

★***For Ventricular Failure;***

40-160 mg PO, up to 240 mg if required.

Directions: Regular oral forms are best taken on an empty stomach (one h. before meals or two hrs. after meals).

*Patient should not eat, drink, talk, or smoke while sublingual tablet is under tongue. Sublingual tablet should be placed under the tongue at first sign of anginal attack. If pain is not relieved, repeat dose at 5 to 10 min. intervals to a maximum of 3 doses. Beware of possible MI.

*Patient should be sitting while taking rapid-acting forms of isosorbide dinitrate (sublingual and chewable tablets) because of the possibility of fainting.

*If tolerance should develop in treating angina, establish a short drug free period of 10-12 hrs. If the drug cannot be discontinued for a short period of time, reduce dosing intervals, i.e. if giving 3-4 times/d, give 2-3 times/d.

*Patients using SL preparations should always carry the pills with them.

- ***USE IN SPECIAL CASES:***

Pregnancy- Safety for use during pregnancy has not been established. Use only when clearly needed and when the potential benefits outweigh the potential hazards to the fetus (Category C).

Lactation- Exercise caution when administering to a nursing woman. It is not known whether nitrates are excreted in breast milk. No available data.

Children- Safety and efficacy for use in children have not been established.

Renal + Liver Disease- Use caution. In case of liver disease use of the **mononitrate** is recommended instead of the dinitrate form.

- ***PRECAUTIONS AND WARNINGS:***

-Take caution in the case of **hypotensive conditions**, with concomitant use of medications that cause hypotension, and in the case of hyperthyroidism.

-In some patients there is a possibility of developing tolerance (reduced therapeutic effects). Refer to directions.

- ***ADVERSE EFFECTS:***

Throbbing headache, flushing, dizziness, postural hypotension, and tachycardia. These are more prominent at the beginning of treatment, and will be reduced with time.

- ***INTERACTIONS:***

Overview of Isosorbide Dinitrate Drug-Drug Interaction	
Drug	**Interaction**
Alcohol, anesthetics, anxiolytics, hypnotics, β-blockers, Ca-channel blockers, muscle relaxants (baclofen), cortico-steroids, dopa-minergics (levodopa), anti-psychotics, diuretics, & anti-depressants	All these drugs enhance the hypotensive effect. Need to warn your patients if taking any of these during the time of nitrate therapy.
Analgesics	NSAIDs antagonize the hypotensive effect. Use with caution.
Anti-depressants	Tricyclics may reduce effect of sublingual nitrates (owing to dry mouth).
Sex hormones	Estrogen and combined OC antagonize hypotensive effect. Use with caution.

- ***OVERDOSE:***

Signs and symptoms result mainly from vasodilation and methemoglobinemia; also, hypotension, tachycardia, flushing, perspiring skin, vertigo, syncope, vomiting (possibly with colic and bloody diarrhea), dizziness, moderate fever and paralysis, as well as convulsions and death due to cardiovascular collapse.

If nitrates were ingested, induce emesis or perform gastric lavage followed by charcoal administration; however, nitrates are usually rapidly and completely absorbed. Gastric lavage may be of use if the medication has only recently been swallowed. Passive movement of the extremities may aid venous return. Refer to emergency room for symptomatic care.

- ***BRANDS:***

Cordil (Dexxon)**,** Isocardide (Sam-On), Isordil (Wyeth Ayerst), Isotard (CTI/C.T.S.).

D) ANTICOAGULANTS

Blood coagulation resulting in the formation of a stable fibrin clot involves a cascade of proteolytic reactions involving the interaction of clotting factors, platelets and tissue materials. Although most cases of thromboembolic disease are idiopathic, several clinical conditions have been associated with and increased risk of thrombosis. Such factors include: inherited deficiencies of factors like antithrombin III, protein C, and protein S, and clinical conditions that may predispose patients like pregnancy, malignancy, immobilization, congestive heart failure, cigarette smoking, or immunologic disorders.

Prior to initiation of anti-coagulant therapy, patients must be screened for the presence of relative contraindications to therapy (*refer to table 2.7*) because the failure to detect such contraindications could result in fatal hemorrhage.

Aspirin and warfarin will be discussed in this section.

Table- 2.7: Relative Contraindications to Anticoagulant Therapy
Active bleeding (e.g., active peptic ulcer disease).
Bleeding tendency (e.g., hemophilia, thrombocytopenia).
Uncontrolled hypertension.
Cerebrovascular hemorrhage.
Recent surgery or invasive procedures (e.g. arterial or lumbar puncture).
Pericarditis or pericardial effusion.
Severe trauma.
Pregnancy (primarily related to warfarin).
Patients prone to falling (e.g., elderly or debilitated patients).
Inadequate laboratory facilities.
Unsatisfactory patient compliance.

1) Aspirin WHO,P

- ***DRUG SUMMARY:***

Aspirin is recommended in treatment of cardiovascular, cerebrovascular and rheumatologic conditions. Studies have shown that it is effective in the treatment of TIA, ischemic stroke, angina, acute MI, recurrent MI with low doses of 50-365 mg, depending on case.

Low-dose aspirin may also help in preventing pre-eclampsia/toxemia in pregnant women. The rationale for use of ASA prophylaxis is the inhibition of synthesis of prostaglandin thromboxane, which has been found to be elevated in severe pre-eclampsia. As of today, studies do not support the routine use of low-dose aspirin in pregnant women for prevention of pre-eclampsia or its complications. Further studies are needed.

Doses: a single dose of ASA is given as soon as possible after an ischemic event: 150-300 mg after MI, and 300 mg after TIA/stroke. After the initial dose, maintenance treatment with aspirin ranges from 75-325 mg daily, depending on case.

(For other details on ASA, refer to analgesics chapter).

2) Warfarin WHO,P

- ***DRUG SUMMARY:***

Warfarin, a coumarin derivative anti-coagulant, indirectly interferes with blood clotting by depressing hepatic synthesis of vitamin K-dependent coagulation factors. Has no effect on already synthesized circulating coagulation factors or on circulating thrombi. It does not reverse ischemic tissue damage, and has no effect on platelets. It takes 2-3 days for the anticoagulant effect to develop fully.

- ***INDICATIONS:***

Prophylaxis for embolization in patients with rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient brain ischemic attacks.

- ***CONTRAINDICATIONS:***

Pregnancy, peptic ulcer, severe hypertension, bacterial endocarditis, hemorrhagic tendencies, vitamin C or K deficiency, hemophilia, active bleeding, open wounds, severe hepatic or renal disease.

Note: Oral anticoagulant should not be used in cerebral thrombosis or peripheral arterial occlusion, but may be of value in patients with transient brain ischemic attacks whether due to carotid or vertebrobasilar arterial disease. If these patients also have severe hypertension, anticoagulants are contraindicated, and antiplatelet drugs are an alternative.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: Whenever possible, the base-line prothrombin time should be determined before the initial dose is given. Treatment is very highly individualized. Control dosage by periodic determination of Prothrombin Time (PT) or the International Normalized Ratio (INR).

Induction dose: The typical induction dose is 10 mg daily for 2 days. On the other hand, less than 10 mg should be given if base-line prothrombin time is prolonged, abnormal liver-function tests, patient in cardiac failure, parenteral feeding, less than average body weight, or over 80 years of age.

Maintenance dose: It depends upon the prothrombin time. The currently recommended therapeutic ranges are: PT ratio of 1.3 to 1.5; and INR of 2 to 3 except for cases of mechanical prosthetic valves and recurrent systemic embolism where therapeutic ranges are PT 1.5 to 2, and INR 3 to 4.5

The daily maintenance dose of warfarin is usually 3 to 9 mg (taken at the same time each day or every other day).

Directions: Tablet may be crushed before administration and taken with fluid of patient's choice.

*If a dose is missed, it should be taken as soon as remembered. Do not double the dose on the next dosing scheduled time.

**It is essential that the PT or INR be determined: daily or on alternate days in early days of treatment, then at longer intervals (depending on response) then up to every 8 weeks.*

- ***USE IN SPECIAL CASES:***

Pregnancy- Oral anticoagulants are teratogenic and should not be administered specially in the first trimester of pregnancy (Category D). Women at risk of pregnancy should be warned of this danger; difficult decisions may have to be made, particularly in women with prosthetic heart valves or with a history of recurrent venous thrombosis or pulmonary embolism.

Lactation- Use caution. Warfarin appears in breast milk in an inactive form. Infant nursed by warfarin-treated mothers had no changes in their PT. Warfarin has been considered safe for use.

Children- Safety and efficacy in children < 18 years old have not been established. Heparin use might be safer. Use of oral anticoagulants in children is only indicated in children with rare thromboembolic disorders secondary to other diseases.

Renal Disease- Use with caution. If there is severe renal impairment this drug should be avoided.

Liver Disease- Use with caution. If there is severe hepatic impairment it should be avoided.

- ***PRECAUTIONS AND WARNINGS:***

-Need to use caution in special risk patients such as: hepatic and renal disease, recent surgery, alcoholism, during menstruation, and nursing mothers.

-Table 2.8 is a list of endogenous factors that may increase or decrease prothrombin time response (enhance or decrease anticoagulant effect respectively).

- ***ADVERSE EFFECTS:***

Hemorrhage from any tissue or organ.

- ***INTERACTIONS:***

Note: Change in patient's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (*especially involving green leafy vegetables; lettuce, cabbage, spinach, broccoli…*) may also affect warfarin control as well as herbal and botanical (*ie. garlic, ginseng, licorice, capsicum*) preparations.

***Phenytoin** and **cholestyramine** may enhance or reduce warfarin anticoagulant effect. Do not administer at the same time, and monitor patients blood levels closely.

***Antiplatelet drugs:** Aspirin increases risk of bleeding due to antiplatelet effect. Avoid use. Warn patient not to take OTC medications containing aspirin.

See table on list of drugs-interactions.

Table 2.8
Endogenous factors that may increase prothrombin time response **(enhance anticoagulant effect)**
Carcinoma. Congestive heart failure. Collagen diseases. Hepatic and renal insufficiency. Diarrhea. Fever. Pancreatic disorders. Mal-nutrition. Vitamin K deficiency. Alcoholism.
Endogenous factors that may decrease prothrombin time response **(decrease anticoagulant response)**
Edema. Hypothyroidism. Hyperlipidemia. Hypercholesterolemia. Chronic alcoholism. Hereditary resistance to coumarin therapy.

*The following is **a list of drugs** that exhibit hazardous **interactions with warfarin** and they should not be given concomitantly:*

Enhance Warfarin Effect
Alcohol. *Anabolic steroids.* *Analgesics:* e.g. aspirin increases risk of bleeding due to antiplatelet effect. *Antiarrhythmics*: e.g. amiodarone, quinidine. *Antibacterials*: e.g. chloramphenicol, cotrimoxazole, erythromycin, metronidazole, sulfonamides. Others as tetracycline, trimethoprim, and ampicillin may enhance warfarin effect. *Antifungals:* e.g. miconazole. *Ulcer-healing drugs:* e.g. cimetidine. *Influenza vaccine*.
Reduce Warfarin Effect
Antibacterials: e.g. Rifampicin. *Antiepileptics:* e.g. carbamazepine, phenobarbitone. *Antifungals:* e.g. griseofulvin. *Barbiturates.* *Oral contraceptives.* *Vitamin K:* major changes in diet (especially involving vegetables).

- ***OVERDOSE:***

Early symptoms include: excessive menstrual bleeding, melena, oozing from superficial injuries, bleeding from gums after brushing teeth, excessive bruising. Hemorrhage is the principal adverse effect. Other symptoms may include nausea, vomiting, headache, and malaise.

Treatment includes discontinuation of therapy with the medication. If necessary give small doses of oral phytomenadione (Vit. K_1) 2.5 to 10 mg. In persistent bleeding or severe hemorrhage cases refer to emergency room for supportive care as needed.

- ***BRANDS:***

Coumadin (Taro).

E) CONGESTIVE HEART FAILURE DRUGS

Heart failure is the inability of the heart to maintain an adequate output to meet the metabolic demands of the body.

The clinical manifestations of heart failure vary depending on the rapidity of decompensation, underlying etiology, and age of the patient. Signs and symptoms of low cardiac output include fatigue, exercise intolerance, decreased peripheral perfusion decreased urine output, confusion and lethargy, and ultimately shock.

Precipitating factors that cause heart failure include: coronary artery disease, hypertension, dilated cardiomyopathy (due to toxins like alcohol, viral or parasitic infection or collagen vascular disease), valvular heart diseases, restrictive cardio-myopathy, constrictive cardiomyopathy, and high-output heart failure due to chronic anemia, atrioventricular shunts or thyrotoxicosis.

Nonpharmacologic therapeutic measures are important to employ in conjunction with the specific pharmacological measures. These include:

A) Restriction of physical activity and bed rest to reduce myocardial workload. Simple exercise to improve functional capacity in selected patients. Need to decrease emotional stress.
B) Weight loss, specially in obese patients,
C) Dietary sodium restriction (≤ 2.0 g Na^+/day), and fluid and water restriction (≤ 1.5 L/day).
D) Discontinuation of negative inotropic medications (e.g. beta-adrenergic antagonists, verapamil, diltiazem, type IA and IC antiarrhythmics) if possible.
E) Complete cessation of cigarette smoking is also important to optimize oxygen-carrying capacity and to reduce the risk of coronary disease.

Pharmacological therapy principles include: control of sodium and fluid retention, vasodilator therapy and inotropic support, in conjunction with the non-pharmacologic measures.

Diuretics are first line drugs. Their goal is to produce a maximum net loss of 0.5 to 1.0 liter of fluid per day to prevent intravascular volume depletion. Need to monitor patients for complications of electrolyte imbalances and volume depletion. Hypokalemia may be life threatening in patients receiving digoxin or predisposed to ventricular arrhythmias.

Digitalis glycosides are used to increase myocardial contractility. The principal actions of the cardiac glycosides are: an increase in the force of the myocardial contraction and a reduction of the conductivity of the heart. Digoxin is most efficacious in management of heart failure associated or caused by atrial fibrillation or flutter (or other supraventricular tachycardias that respond to digoxin), or in patients with dilated left ventricles and impaired systolic function. Other cardiac agents may be used depending on the patients' condition. Always refer patients to a specialist for further management when patient is not responding to initial treatments.

Since the Renin-angiotensin system becomes increasingly more active in cardiac failure, **ACE inhibitors** are being promoted with a diuretic (thiazide or loop diuretics since they potentiate the blood pressure lowering effects of ACEI) to be first-line. The beneficial effects of these drugs have been demonstrated in mild, moderate and severe dysfunction. Since they are less toxic and do not require as much monitoring, their use has been accepted widely. They have a particularly valuable role when cardiac failure develops during or after a myocardial infarction.

1) Digoxin WHO,P

- ***DRUG SUMMARY:***

The most widely used glycoside of *digitalis lanata*, acts by increasing the force and velocity of myocardial systolic contraction; increases contractility (positive inotropic effect). Action is more prompt and less prolonged than that of digitalis and digitoxin. In patients with mild failure a loading dose in not required, and a satisfactory plasma concentration can be achieved over a period of about a week.

- ***INDICATIONS:***

Heart failure and supraventricular arrhythmias (particularly atrial fibrillation).

- ***CONTRAINDICATIONS:***

Digitalis hypersensitivity, ventricular fibrillation, ventricular tachycardia unless due to congestive heart failure, supraventricular arrhythmias caused by Walff-Parkinson-White syndrome.

Note: Full digitalizing dose is not given if the patient has received digoxin during the previous week, or if slowly excreted cardiotonic glycoside has been given during previous 2 weeks.

- ***DOSAGE FORMS:***

Tablets, elixir (0.05mg/ml).

- ***RECOMMENDED DOSAGE:***

Adult: ★*Digitalizing Dose;*

10-15 μg/kg (1-1.5 mg) PO/IV in divided doses over 24-48 hrs.

★Maintenance dose;

125-250 micrograms daily, (elderly 125 *u*g)

Children: should be treated and monitored by a pediatrician/cardiologist. Premature and newborn infants display considerable variability in tolerance, and are very sensitive; therefore doses are individualized according to infant's degree of maturity.

Directions: Make sure that the patient will not stop taking the medication without the doctor's consultation.

*If the patient misses a dose, it should be taken as soon as remembered. If too close to the next dose, it could be ignored and the required dosing schedule should be continued.

*Warn patient about the possible side effects. In case symptoms are severe or unmanageable, the patient should report to you as soon as possible, to manage the toxicity effects.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly indicated (Category C). It passes through the placenta and has been used to treat fetal tachycardia and CHF.

Lactation- Use with caution. The amount appearing in breast milk is too small to be harmful, and no data of adverse effects have been reported in nursing infant.

Renal Disease- Digoxin excretion is delayed in renal insufficiency since it is eliminated by the kidneys. Doses will need adjustment depending on Cl_{cr} and lean body weight, maintenance dose will be lowered.

Liver Disease- No dosage adjustment is required.

- ***PRECAUTIONS AND WARNINGS:***

Cautious use in: renal insufficiency, hypokalemia, advanced heart disease, acute MI, incomplete AV block, cor-pulmonale, hypothyroidism, lung disease. Dose should be reduced in the case of elderly patients.

- ***ADVERSE EFFECTS:***

Anorexia, nausea, vomiting, diarrhea, abdominal pain, visual disturbances, headache, fatigue, drowsiness, confusion, delirium, hallucination, arrhythmias, and heart block.

- ***INTERACTIONS:***

Overview of Digoxin Drug-Drug Interaction

Drug	Interaction
Analgesics	NSAIDs may exacerbate heart failure, reduce GFR and increase plasma-cardiac glycoside concentrations. Avoid concomitant use.
Anion-exchange resins	Digoxin absorption is reduced by cholestyramine and colestipol. Administer 2 hours after or before taking resins.
Anti-arrhythmic drugs	Plasma concentration of digoxin is increased by amiodarone, propafenone, and quinidine (use half the maintenance dose of digoxin).
Anti-bacterials	Erythromycins enhance the effect of digoxin. Use caution.
Anthyperten-sives	Captopril possibly increases plasma concentration of digoxin
Anti-malarials	Quinine, chloroquine, and hydroxychloroquine raises plasma concentration of digoxin. Use half the maintenance dose of digoxin.
β-blockers	Increased risk of AV block and bradycardia.
Calcium-channel blockers	Plasma concentration of digoxin increased by diltiazem, nicardipine, and verapamil; increased AV block and bradycardia with verapamil.
Diuretics	Increased toxicity occurs with acetazolamide, loop diuretics, and thiazides; effects of digoxin enhanced by spironolactone.
Muscle relaxants	Arrhythmias with suxameth-onium. Avoid concomitant use.

Potassium	K antagonizes digitalis preparations. A decrease in K level favors digoxin binding, increasing likelihood of digitalis toxicity. Increased K level decreases digitalis binding and decreases digitoxin effect. Be very careful.

- ***OVERDOSE:***

Symptoms of toxicity include exaggerated side effects.

In the case of overdose one should discontinue digoxin until all signs of toxicity are abolished. Always refer the patient for further medical investigation and symptomatic care.

- ***BRANDS:***

Digoxin-Zori (Teva), Lanoxin (Glaxo Wellcome).

F) LIPID LOWERING DRUGS

The relationship between the risk of atherosclerotic heart disease and serum lipoprotein is well established. Elevated levels of total cholesterol and low-density lipoprotein (LDL), and low levels of high-density lipoprotein cholesterol (HDL) are associated with increased risk for cardiac disease. See table-2.9 for classification of blood cholesterol levels.

Table-2.9: Classification of Blood Cholesterol Levels in Adults

Classification	Total Chol.	LDL Chol.	HDL Chol.	TGs
Desirable blood concentration (mg/dl)	< 200	< 130	≥ 35	Male: 40-160 Female: 35-135
Borderline-high (mg/dl)	200-239	130-159		
High (mg/dl)	≥ 240	≥ 160		

Drug Facts and Comparisons, 2000, p. 532.

Table 2.10 lists the common risk factors for heart disease. If no family history of high cholesterol levels, ask about any medication intake that might contribute to elevating their cholesterol or triglycerides (TGs) levels, such as: alcohol intake, OCs, corticosteroids, nicotinic acids, spironolactone or thiazide diuretics.

Table- 2.10: Cardiac Risk Factors

Male sex
Family history of CHD
Cigarette smoking
Hypertension
HDL-cholesterol below 35 mg/dl (on more than one measurement)
Diabetes mellitus
Hypothyroidism
Presence of cerebrovascular or peripheral vascular disease
Severe obesity (> 30 % over-weight)

The rationale for therapy is to reduce the risk of atherosclerotic cardiovascular disease. **Diet, weight loss and exercise are the most important therapy to start with.** Diet is the initial therapy, and in most cases, should be tried for several months before drug therapy is considered. Cessation of smoking and reduction of blood pressure are also important.

Lipid lowering agents should be reserved for patients in whom severe hyperlipidemia is inadequately controlled by the modified fat diet. Choice of medication depends on the individual patient and type of disorder. Some drugs are used to lower cholesterol, others lower both cholesterol and triglycerides.

WHO recognizes the value of the lipid lowering drugs, but has not included any specific agent on the EDL.

Bile sequestrant resins (cholestyramine and colestipol) are usually first-line choice, while HMG-CoA reductase inhibitors (Fluvastatin, lovastatin, paravastatin, and simvastatin) and fibric acid derivatives (bezafibrate, clofibrate and gemfibrozil) are second choice. (Long term safety and efficacy for second line agents have not been established.)

Table- 2.11: Effects of Selected Antihyperlipidemic Drugs on Serum Lipids and Lipoproteins

Drug	Lipids		Lipoproteins		
	Cholesterol	Triglycerides	VLDL	LDL	HDL
Cholestyramine	↓	→↑	→↑	↓	→↑
Clofibrate	↓	↓	↓	→↓	→↑
Gemfibrozil	↓	↓	↓	→↓	→↓
Lovastatin	↓	↓	↓	↓	↑
Nicotinic Acid	↓	↓	↓	↓	↑
Probucol	↓	→	↓	↓	↑
Simvastatin	↓	↓	↓	↓	↑

↓- decrease, ↑- increase, →- unchanged.
Adapted from Drugs Facts and Comparisons 2000, p. 532.

Measurement of LDL-cholesterol levels should be at 4-6 wks, and at 3 mons. If the response is inadequate, refer this patient to a lipid disorder specialist. Experience with combination therapy is limited.

For menopausal women with high serum cholesterol, estrogen replacement therapy can be considered as an alternative choice, since estrogen lowers LDL and raises HDL cholesterol levels.

Table 2.11 summarizes the effects of selected antihyperlipidemic drugs on serum lipids and lipoproteins.

1) Fibric Acids

a) Bezafibrate

- ***DRUG SUMMARY:***

It belongs to a group known by the clofibrate group (refer to introduction). It can be regarded as broad-spectrum lipid-modulating agent in that although their main action is to decrease serum TGs they also tend to reduce LDL-cholesterol and to raise HDL-cholesterol. This group can cause a myositis-like syndrome, especially in patients with impaired renal function. In addition, clofibrate predisposes to gallstones by increasing biliary cholesterol excretion; it is therefore only indicated in patients who have had a cholecystectomy.

- ***INDICATIONS:***

Hyperlipidemias types IIa, IIb, III, IV, and V in patients who have not responded adequately to diet and other appropriate measures.

- ***CONTRAINDICATIONS:***

Hypoalbuminemia, primary biliary cirrhosis, gall bladder disease, nephrotic syndrome, pregnancy and breast feeding, and severe renal or hepatic impairment.

- ***DOSAGE FORMS:***

Tablets

- ***RECOMMENDED DOSAGE:***

Adult: 200 mg PO t.i.d., may be reduced to 200 mg b.i.d. in hypertriglyceridemia.

Directions: It may be taken with or after food if GI upset occurs.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid in the case of pregnancy since there is a theoretical possibility of interference with embryonic growth and development due to anticholesterol effect. Strict birth control procedures must be exercised by women of child-bearing potential. Since no controlled studies on women have been performed, weigh the possible benefits of the drug to the patient against possible hazards to the fetus.

Lactation- Avoid. No available data, but animal studies suggest drug excretion into breast milk.

Children- Safety and efficacy in children have not been established.

Renal Disease- If there is mild to moderate renal impairment, reduce dose since it might cause further deterioration in renal function. If there is severe renal impairment, avoid bezafibrate.

Liver Disease- Avoid in severe liver disease.

- ***PRECAUTIONS AND WARNINGS:***

Some patients might not be responsive to clofibrate or its derivatives.

There has been no indication that these drugs cause a reduction in the incidence of fatal myocardial infarctions in patients. Be selective when choosing patients to start on therapy.

- ***ADVERSE EFFECTS:***

Nausea, abdominal discomfort; rarely myositis-like syndrome, pruritis, urticaria, impotence; and headache reported.

- ***INTERACTIONS:***

Overview of Bezafebrate Drug-Drug Interaction	
Drug	**Interaction**
Anti-coagulants	Enhancement of effect of nicoumalone and warfarin.
Anti-diabetics	May improve glucose tolerance and have positive additive effect. Monitor glucose levels if therapy is started.

- ***OVERDOSE:***

Symptoms include excessive side effects. Institute symptomatic supportive measures.

- ***BRANDS:***

Bezalip (Boehringer), Norlip (Unipharm).

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2) Bile Acid Sequestrants

a) Cholestyramine

- ***DRUG SUMMARY:***

A quaternary ammonium anion exchange resin (bile acid sequestrant) used for its cholesterol-lowering effect.

- ***INDICATIONS*:**

As adjunct to diet therapy in management of patients with primary hypercholestrolemia (type IIa hyperlipidemia), with a significant risk of artherosclerotic heart disease and MI. Also has been used for relief of pruritus associated with partial biliary obstruction, and to control diarrhea caused by excess bile acids in colon for hyperoxaluria.

- ***CONTRAINDICATIONS:***

Hypersensitivity to bile acid sequestering resins and in complete biliary obstruction.

- ***DOSAGE FORMS:***

Tablets, powder.

- ***RECOMMENDED DOSAGE:***

Adult: ***★For Hypercholesterolemia and Hyperlipoproteinemia;***

4-8 g PO b.i.d. to q.i.d., a.c. and h.s.

May need up to 24 g/d; max. 32g/d).

Directions: Medication is taken before meals, and at bedtime.

*If using powder, dissolve one packet, or one level scoop in at least 120-180 ml of water or other preferred liquid. Permit drug to hydrate by standing without stirring 1-2 min., then stir until suspension is uniform. Rinse glass with small amount of liquid to ensure entire dose is taken.

*Determine cholesterol level frequently during the first few months of therapy. Serum levels are reduced within 24-48 hrs., and continue to decline for a year. If response is unsatisfactory after 3 months of treatment, the drug is usually withdrawn. *(See Precautions and Warnings).*

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly needed, and the potential benefit outweighs the potential hazards to the fetus (Category C). Safety for use during pregnancy has not been established. Even though these agents do not get absorbed systematically, they interfere with fat-soluble vitamins that are essential to the growing fetus.

Lactation- Exercise caution. The possible lack of proper fat-soluble vitamin absorption may have an effect on the nursing infant.

Children- Doses have not been established in children. Safety and efficacy in children < 6 yrs old are not established.

Renal Disease- Use with caution.

Liver Disease- Use with caution. Cholestyramine interferes with absorption of fat-soluble vitamins and may aggravate malabsorption in primary biliary cirrhosis.

- ***PRECAUTIONS AND WARNINGS:***

-Carcinogenesis: The incidence of intestinal tumors in studies was greater in cholestyramine-treated rats than in controls. Before instituting therapy, vigorously attempt to control serum cholesterol by an appropriate dietary regimen and weight reduction.

-Resins may interfere with normal fat absorption of digestion and may prevent absorption of fat-soluble vitamins A, D, E, and K. Chronic use of resins may be associated with increased bleeding time due to vitamin K deficiency. Supplementation with the vitamins may be given in a water miscible form or administered parenterally if needed.

-Reduction of serum or red cell folate has been reported with chronic administration. Consider supplementation with folic acid if needed.

-Use caution with patients with preexisting constipation. Fecal impaction may occur, and hemorrhoids may be aggravated. Need to avoid constipation (causing strain on defecation) in patients with symptomatic coronary artery disease. Increased fluid intake may be sufficient, if not, the patient can use a laxative or stool softener.

- ***ADVERSE EFFECTS:***

Most common are: constipation, and in severe cases may be accompanied by fecal impaction and aggravation or bleeding of hemorrhoids. Others may be, abdominal pain, flatulence, bloating sensation, nausea, indigestion, heartburn, belching, urticaria, asthma, and general backache or joint pains.

- ***INTERACTIONS:***

Note:
Most medications should be taken at least 1 hour before, or 4-6 hours after cholestyramine- or colestipol- administration.

Overview of Cholestyramine Reported Drug-Drug Interaction

Drug	Interaction
Anti-coagulants	The anticoagulant effect may be decreased by cholestyramine.
Digitalis glycosides	Serum level of glycosides may be reduced, reducing the therapeutic effect.
Analgesics	Piroxicam elimination is enhanced, and paracetamol absorption is reduced leading to subtherapeutic effects.
Propranolol	The plasma concentration of propranolol and its metabolite is reduced.
Thiazide diuretics	Absorption and serum level of thiazides may be decreased.
Thyroid Hormones	Loss of efficacy of thyroid and potential hypothyroidism with concurrent use of cholestyramine.
Vitamins A, D, E, K	Malabsorption may occur with chronic use of resins.

- ***OVERDOSE:***

The chief potential harm would be GI tract obstruction. Location and degree of obstruction and status of gut motility determine treatment. No ill effects have been reported.

- ***BRANDS:***

Chol-Less (Rafa), Questran (Bristol Labs/ Mead Johnson).

3) HMG-COA Reductase Inhibitors

a) Simvastatin

- ***DRUG SUMMARY:***

Simvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), classified as a cardiovascular, lipid lowering agent. It is more potent than lovastatin. A response is noted within 1-2 wks.

[Several statins have been shown to reduce fatal and myocardial infarction, stroke, the need for coronary by-pass surgery and all-cause mortality. (WHO EDL. 1997)].

- ***INDICATIONS:***

Hypercholesterolemia, familial hyper-cholestrolemia.

- ***CONTRAINDICATIONS:***

Hypersensitivity to these agents, pregnancy and nursing mothers, active liver disease.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: 5-40 mg q.d.

Directions: Can be given without regard to meals. Better given in the evenings.

* Liver function tests should be performed q. 4-6 wks. during the first 3 mons. of therapy, then every 6-8 wks. for the next year. (PT may be prolonged).

- ***USE IN SPECIAL CASES:***

Pregnancy- Contraindicated use (Category X). Evidence in skeletal malformation in animal studies has been reported.

Lactation- It is not known if simvastatin is excreted in human breast milk, but because of the potential for serious adverse reaction in nursing infants it is inadvisable to use it.

Children- Safety and efficacy in children < 18 years old have not been established. Avoid use.

Renal Disease- Use with caution. Higher systemic exposure of simvastatin may occur in severe renal insufficiency.

Liver Disease- Avoid use in patients who consume substantial quantities of alcohol or who have a history of liver disease.

- ***PRECAUTIONS AND WARNINGS:***

-Use with caution in patients who consume substantial quantities of alcohol or who have a history of liver disease. Liver function tests should be performed in all patients before initiating therapy. Elevations of liver enzymes should be monitored closely. If levels of transaminase rise to 3 times the normal levels and are persistent, discontinue the drug.

-Carcinogenesis/fertility impairments, have been noted in animal studies of these agents at high doses.

- ***ADVERSE EFFECTS:***

Angina, dizziness, headache, vertigo, insomnia, nausea, vomiting, diarrhea, flatulence, photosensitivity, transient elevations of liver transaminases, rhabdo-myolysis, gynecomastia and erectile dysfunction, progression of cataracts.

- ***INTERACTIONS:***

Overview of Simvistatin Major Drug-Drug Interaction	
Drug	**Interaction**
Warfarin	The anticoagulant effect of warfarin may be increased. Monitor prothrombin time.
Cyclosporin	Increased risk of Myopathy or rhabdomyolysis may occur with concurrent administration.

- ***OVERDOSE:***

Few cases of overdosage have occurred with simvastatin, no patients had any specific symptoms, and all recovered. Treat symptomatically as required.

- ***BRANDS:***

Simovil (Assia/Riesel), Zocor (Merck).

Chapter 3: GASTRO-INTESTINAL DRUGS

A) ANTACIDS & ULCER-HEALING MEDICATION
- **1) Mg/Al Salts**
- **2) Ranitidine**
- **3) Omeprazole**

B) ANTISPASMODICS/ANTICHOLINERGICS
- **1) Hyocine N-Butyl Bromide**

C) ANTIEMETICS
- **1) Metaclopramide**
- **2) Meclizine/Meclozine**

D) DRUGS USED IN DIARRHEA
- **1) Oral Rehydration Salts**
- **2) Anti-Diarrheal - Loperamide**

E) LAXATIVES
- **1) Bisacodyl**
- **2) Castor Oil**
- **3) Glycerine**
- **4) Psyllium**

F) ANTI-HEMORRHOIDAL
- **1) Mentioned Formula - Anusol**

A) ANTACIDS & ULCER HEALING MEDICATION

Gastro-intestinal tract (GIT) disorders are very common. Important clues to determine what type of problem is present can be found by asking patients about time of symptoms occurrence (in relation to meals and night time), if pain is localized, if symptoms are acute or chronic . . . etc.
The following table shows some common GIT disorders with the associated symptoms and characteristics:

Summary of Selected GI Disorders
Gastroesophageal Reflux Disease
Heartburn/pain in lower chest. Pain is worse after meals & when lying down. Pain may wake patient at night. Pain is often relieved by antacids. Pain may be worse after certain foods, smoking, alcohol, caffeine, and medications that reduce lower esophageal sphincter tone.
Gastric Ulcer
Variable epigastric pain. Unpredictable pattern. Food may worsen pain. Weight loss is common. May be relieved by antacids. History of chronic NSAID use.
Duodenal Ulcer
Aching epigastric pain. Well-localized, predictable pattern. Begins 1-2 hrs. after eating, worse before next meal. Relieved by food or antacids. Weight gain common. May wake patient at night. History of smoking.
Acute Gastritis
Burning epigastric pain. Possible association with anorexia, nausea, and vomiting. History of alcohol binge or NSAID use.

There are many factors that disrupt the gastric mucosal barrier, which lead to acid-peptic disorders. These factors include: Helicobacter pylori (*H. pylori*) bacteria, drugs, e.g. NSAIDs, corticosteroids, alcohol, caffeine and smoking. Healing can be promoted by minimizing these factors when possible.

The primary aim of pharmacological therapy for such disorders has been either to neutralize existing acid (using antacids), reduce the secretion of acid (using anticholinergic agents, H_2-antagonists or proton pump inhibitors), or to eradicate *H. pylori* bacteria. Table-3.1 indicates a summary of the most common therapeutic classes, their mechanism of action and some examples.

Antacids are useful for the short-term relief of indigestion, heartburn and excessive eating and drinking, as well as for the long-term management of gastro-esophageal reflux and peptic ulcer disease. They give symptomatic relief, promote healing and reduce reoccurrence. There are 2 kinds of antacids. *Absorbable antacids*: these provide rapid, complete neutra-lization, but continuous use may cause milk-alkali syndrome that can progress to irreversible kidney damage if unrecognized. Examples include sodium bicarbonate, calcium carbonate. *Non-absorbable antacids* are relatively unsoluble salt of weak bases and have fewer side effects. They interact with gastric HCL forming non-absorbable salts thus increasing gastric pH. Examples like Aluminium hydroxide and Magnesium hydroxide.

Dual and triple therapy regimens have been implemented to provide higher eradication rates. Dual therapy such as use of amoxicillin plus omeprazole, or clarithromycin plus omeprazole have an overall lower efficacy rates compared to triple therapy. Also after treatment failure, in patient who remain *H. pylori* positive resistance has developed. Therefore, experts no longer advocate dual therapy as first-line treatment (Gitnick, 1997). The effectiveness of regimens may be due to antibiotic resistance. Therefore, the

patients' prior antibiotic exposure should be considered when selecting a regimen.

Examples of used regimens adopted from Drug Facts and Comparisons are shown in table-3.2.

Table-3.1: Summary of the Most Common Therapeutic Classes for Treatment of Ulcers

Therapeutic Class	Mechanism of Action	Example	Notes
Antacids	Neutralize existing acids, without affecting the amount or rate of gastric secretion. They react with acids to form salt and water.	Na bicarbonate, Ca carbonate, Aluminium salts, Magnesium salts.	These products differ in potency, GI side effects, systemic complications and drug interactions.
H_2-antagonists	Reduce acid secretion without enhancing mucosal defenses.	Cimetidine, Ranitidine, Famotidine, Nizatidine.	These products are almost equally effective with some differences in side effects.
Proton pump inhibitors	Blocks the final step in acid production.	Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole.	These products are comparable in effective-ness with some differences in drug-drug interactions.

Table-3.2: Regimens Used in the Eradication of *H. Pylori*

Regimens	Dosing	Duration [1]	Eradication
Metronidazole Omeprazole Clarithromycin	500 mg twice daily with meals 20 mg twice daily with meals 500 mg twice daily with meals	1 - 2 weeks	87% to $\geq$ 91%
Amoxicillin Omeprazole Clarithromycin	1 gram twice daily with meals 20 mg twice daily with meals 500 mg twice daily with meals	1 - 2 weeks	77% to 83%

[1] *Extending therapy to 10-14 days in the above regimens may provide additional benefit. H_2 blockers may be used with two antibiotics, but a longer treatment course (10-14 days), higher antibiotic doses and 3 times daily administration are required.*

Reference: Drug Facts and Comparisons, 2000; A-10,11.

1) Mg/Al Salt [WHO,P]

- ***DRUG SUMMARY:***

Many commercially available antacid products contain a combination of aluminium (Al) and magnesium (Mg) salts, hydroxide, trisilicate. Because constipation from Al and diarrhea from Mg are dose related, combining these two agents allow for a potent neutralizing capacity with lower doses of each agent. The constipating effect of Al should balance the diarrheal effect of Mg, and vice versa. These agents do not cause alkalosis or rebound hyperacidity as $NaHCO_3$.

- ***INDICATIONS:***

Hyperacidity; symptomatic relief of stomach upset, dyspepsia, heartburn, acid indigestion, GERD, and hyperacidity associated with peptic ulcer.

- ***CONTRAINDICATIONS:***

Known sensitivity to any of the components of the products.

- ***DOSAGE FORMS:***

Tablets, suspension.

- ***RECOMMENDED DOSAGE:***

Adult: ★*For Indigestion and Heart Burn;*
1 or 2 tabs or 1 or 2 tbsp. when needed.
★*For Ulcers*;
Take 1-2 tabs or 1-2 tbsp., one hour a.c. and at h.s.

Child: Use is not recommended.

Directions: Antacids should be taken 1 h. after meals when needed, which will give a duration of action for up to 3 hrs.

*If using the suspension, shake bottle well before use.

*Chewable tablets should be chewed well, and followed by a full glass of water.

***Advise patient to contact physician if relief of heartburn or indigestion is not obtained, or if any sign of bleeding such as black tarry stool or/and "coffee ground" vomitus occur.** This could be an indication of a serious problem or GI bleed.

*Warn patient that smoking and alcohol may increase their risk of peptic ulcer disease, and they should stop these habits if possible to avoid such problems.

*Warn patient of possible drug interactions. (*Refer to drug interactions*).

- ***USE IN SPECIAL CASES:***

Pregnancy- This type of antacid are generally considered safe during pregnancy as long as chronic high doses are avoided. It is better to avoid use unless clearly needed.

Lactation- Safe if using in small dose, for a very short period of time. Avoid use chronically, the cations are secreted in breast milk, and can cause side effects in the neonate such as hypermagnesemia.

Children- Such products are not intended for children < 6 yrs. old.

Renal Disease- Patient with renal disease are **susceptible to toxicity** of antacid (especially products containing Mg and Al) due to decreased clearance. Use caution, and reduce doses. Avoid chronic use of such product.

Liver Disease- Use caution.

- ***PRECAUTIONS AND WARNINGS:***

-Prolonged use or aluminium-containing antacid may result in hypophosphatemia, especially in patients with inadequate phosphate intake. Severe forms of this can lead to anorexia, malaise, muscle weakness, and osteomalacia.

- ***ADVERSE EFFECTS:***

Diarrhea (usually due to Al) or constipation (due to Mg) may occur.

- ***INTERACTIONS:***

Patient should space doses of antacids at least 2 hrs apart from interacting drugs.

Summary of Mg-Al Combination Drug Interactions

DRUG	Effect	DRUG	Effect
Benzodiazepines	↓	Ketconazole	↓
Captopril	↓	Levodopa	↑
Corticosteroids	↓	Phenothiazines	↓
Digoxin	↓	Quinidine	↑
Fluoroquinolones	↓	Salicylates	↓
H_2-antagonist	↓	Sulfonylureas	↑
Hydantoins	↓	Tetracyclines	↓
Iron salts	↓	Valproic acid	↑

↓ Pharmacological effect decreased by antacid
↑ Pharmacological effect increased by antacid

- ***OVERDOSE:***

No intentional overdose with antacids has been reported. If a child took an overdose of antacid, take immediately to the emergency room for supportive care. Do not induce vomiting at home.

- ***BRANDS:***

Maalox (Rorer), Magnagel (JePharm), Simigel (BPC), Stomagel (JCL).

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2) Ranitidine WHO,P

- ***DRUG SUMMARY:***

An H_2-receptor antagonist; antisecretory, GI agent. It is a potent antiulcer drug that competitively and reversibly inhibits histamine action at the H_2-receptor sites on parietal cells, thus reducing acid secretion. Ranitidine has no analgesic effect, and should not be taken for relieve of intermittent epigastric pain.

- ***INDICATIONS:***

Short-term treatment and maintenance therapy of active, benign gastric and duodenal ulcers. For hypersecretory conditions (Zollinger-Ellison syndrome), and GERD.

- ***CONTRAINDICATIONS:***

Hypersensitivity to ranitidine, or other H_2-antagonists.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★*For Duodenal, Gastric Ulcers and GERD:*
150 mg PO b.i.d. or 300 mg PO h.s.
★*Maintenance Therapy:*
150 mg PO h.s.
★*Zollinger-Ellison syndrome:*
150 mg PO t.i.d. Doses up to 6 g daily in divided doses have been used.
Child: Use is not recommended.
Directions:
*Food does not reduce oral ranitidine absorption or serum concentrations, so can take medication without regard to food.
*Patients should not use OTC remedies for gastric distress or pain without physician's advice (e.g. antacids reduce ranitidine absorption). If antacid is required in addition, administer the antacid 2 hrs. before or after ranitidine intake.
*Symptoms are usually relieved within 1 week. Most patients have healed ulcers by 4 weeks, however; if healing cannot be confirmed, treatment may be continued for up to 8 weeks. Advise patient to complete course of therapy as needed.
*Smoking has been shown to decrease ranitidine efficacy and adversely affects ulcer healing. Urge patient to stop smoking. This is more important in preventing ulcer recurrence than the medication.

- ***USE IN SPECIAL CASES:***

Pregnancy- Administer only when clearly needed and potential benefit outweighs potential risk. There are no well-controlled studies in pregnant women (Category B).
Lactation- Ranitidine is excreted in breast milk. No reports of adverse effects documented, but use caution if need to administer to nursing mothers.
Children- Not recommended. Safety and efficacy are not established.
Renal Disease- May need to reduce dose. The drug is excreted primarily via the kidneys, and decreased creatinine clearance (CL_{cr}) may occur. CL_{cr} is monitored if renal dysfunction is present. When less than 50 ml/min, can reduce dose to 150 mg gradually to once every 24 hours.
Liver Disease- Caution, the drug is metabolized by the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Symptomatic response to ranitidine therapy does not preclude the presence of gastric malignancy.
-Use caution in patients with hepatic and renal diseases.

- ***ADVERSE EFFECTS*:**

Headache, malaise, dizziness, insomnia, agitation, depression (mainly in the elderly) may occur (due to penetration through the BBB, but less than cimetidine).

Occasionally gynaecomastia has been reported (with other H_2 antagonists). Rarely constipation or diarrhea, nausea, abdominal pain, rash, thrombocytopenia, and hepatotoxicity or anaphylaxis have occurred.

- ***INTERACTIONS:***

**Ranitidine weakly binds to cytochrome P450 (an enzyme responsible for oxidation reactions in the mitochondria), therefore serious drug interactions are less than cimetidine. Raise of aminotranferase may be observed.*

Overview of Ranitidine Drug-Drug Interaction	
Drug	**Interaction**
Sulfonyl-ureas-(glipizide)	H_2-antagonists in general inhibit sulfonylurea hepatic metabolism causing accum-ulation of sulfonylureas resulting in hypoglycemia but this is mainly seen in cimetidine. Ranitidine has been reported to increase the hypoglycemic effect of glipizide. Monitor blood glucose and adjust dosage of sulfonylurea as necessary.
Warfarin	Ranitidine may interfere with warfarin clearance, increasing its effects. Do not administer concomitantly.

- ***OVERDOSE:***

Symptoms: There is no experience with deliberate over-dose. In animals, toxic doses caused rapid respiration, tachycardia, muscle tremor, vomiting pallor of mucous membranes or redness, miosis and diarrhea.
Treatment: Induce emesis and employ supportive therapy.

- ***BRANDS:***

GI-Care (Pharmacare), Randin (JePharm), Ratidine (BPC), Zantab (Teva), Zantac (Glaxo Wellcome).

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3) Omeprazole

- ***DRUG SUMMARY:***

Omeprazole is a substituted benzimidazole, which does not exhibit anticholinergic or H_2-antagnostic properties. It belongs to the class of antisecretory compounds: a gastric proton pump inhibitor. It blocks the final step in acid production. Onset of action occurs within 1 hour. Omeprazole, as with other agents in this group, is a new drug with limited use due to its high costs and lack of sufficient long-term studies. But it can prevent NSAID-associated ulcers specially in very elderly patients for whom NSAIDs can't be withdrawn.

- ***INDICATIONS:***

Short-term use (4-8 weeks) for gastro-esophageal reflux disease, gastric and active duodenal ulcers, and erosive esophagitis. Used if there is a poor response to H_2-receptor antagonists in treating GERD. Long-term use should be limited to conditions such as Zollinger-Ellison (ZE) syndrome, multiple endocrine adenomas, and systemic astocytosis. It is indicated with amoxycillin or clarithromycin to eradicates *H. pylori* (refer to introduction).

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Capsules.

- ***RECOMMENDED DOSAGE:***

Adult: ★*Duodenal ulcer & GERD (GERD if poorly responsive to H_2 antagonists):* 20 mg PO q.d. for 4-8 wks.
★*Gastric ulcer:* 40 mg q.d. for 4-8 wks.
★*Hypersecretory conditions:* the dose should be individualized. Initial dose is 60 mg/d. Doses up to 120 mg t.i.d. have been administered. Daily doses > 80 mg should be divided. Some patients with Zollinger-Ellison syndrome have been treated continuously for > 5 yrs.
Directions: Take one capsule before eating. Antacids may be used concomitantly.

*Do not open, crush, or chew capsule. Take as whole with full glass of water.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use. Omeprazole passes the blood-placenta barrier. In animal studies, toxicity to the fetus has been noted. Use only when benefit justifies the risk to the fetus (Category C).

Lactation- Avoid use. It is not known if omeprazole is excreted in breast milk. Lactating women should discontinue lactation prior to taking this drug.

Children- Avoid use. Safety and efficacy in children has not been established.

Renal Disease- Use caution, even though no dosage adjustment is necessary. 80% of drug is excreted in urine.

Liver Disease- The drug is metabolized in the liver. In liver diseases, not more that 20 mg daily should be administered.

- ***PRECAUTIONS AND WARNINGS:***

-Symptomatic response to therapy with omeprazole does not preclude gastric malignancy.

-The safety and efficacy for treatment in humans for more than 8 weeks is not established. Carcinogenesis; it has been noted in animal studies that there is a higher (increase of) incidence with long-term use (more than 2 years).

- ***ADVERSE EFFECTS:***

Omeprazole is generally well tolerated. Most common side effects include headache, dizziness, fatigue, diarrhea, abdominal pain, nausea, and rash.

Erythema, fever, chest pain, pancreatitis, acute inerstitial nephritis, glucosuria, anemia, thrombocytopenia, hypoglycemia, bronchospasm, as well as testicular pain have been noted.

- ***INTERACTIONS:***

Overview of Omeprazole Drug-Drug Interaction	
Drug	**Interaction**
Diazepam*, *Phenytoin and ***Warfarin***	Increased plasma concentrations of these drugs when used concomitantly with omeprazole have been noted, avoid administering any of these medications with omeprazole.
Drugs where gastric pH is important	Omeprazole may interfere with absorption of drugs where gastric pH is important, because of its profound and long lasting inhibition of gastric acid secretion (i.e. ketoconazole, ampicillin esters, iron salts).

Propranolol or ***Theophylline:*** No reports of interactions with these drugs.

- ***OVERDOSE:***

Reports have been rare.

Symptoms: Confusion, drowsiness, blurred vision, tachycardia, headache, dry mouth, and flushing.

Treatment: No specific antidote is known. Can administer syrup of ipecac to induce vomiting before reaching the hospital. Treatment should be symptomatic and supportive. Since omeprazole is extensively protein bound, it is not readily dialyzable.

- ***BRANDS:***

Losec (Abic), Locid (JePharm), Mepral (BCP), Prelosec (Astra Merk).

B) ANTISPASMODICS/ ANTICHOLINERGICS

Anticholinergic agents (agents that decrease/antagonize/prevent the effect of the neurotransmitter acetylcholine), also known as antimuscarinic drugs (*i.e. atropine/hyoscyamine, scopolamine/ hyoscine, belladonna alkaloids, tridihexethyl, dicyclomine . . . etc.*). These agents are used primarily as antispasmodics by decreasing smooth muscles tone

(motility) in the GI, biliary and urinary tracts. These antimuscarinc/antispasmodic drugs may be useful as adjunctive treatment in non-ulcer dyspepsia, in the irritable bowel syndrome, and in diverticular disease.

1) Hyocine N-butyl Bromide [P]

- ***DRUG SUMMARY:***

A quaternary ammonium compound, classified as an antimuscarinic/ anti-cholinergic, antispasmodic agent. It is a more powerful suppressant of salivation than atropine, and usually slows rather than increases heart rate, especially in low doses.

- ***INDICATIONS:***

Antispasmodic for GIT and UT disorders characterized by smooth muscle spasm. Also, can be used for motion sickness and dysmenorrhea.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug, narrow-angle glaucoma, prostatic hypertrophy, obstructive disease of the GI (i.e. paralytic illues, severe ulcerative colitis, pyloric obstruction), tachycardia, or myasthenia gravis.

- ***DOSAGE FORMS:***

Tablets, injection.

- ***RECOMMENDED DOSAGE:***

Adult: Orally: 20 mg 4 times daily.
IM or IV (acute spasm): 20 mg, repeated after 30 min. if necessary
Child (6-12 y): 10 mg PO t.i.d.

Directions: Taken 30 to 60 min. a.c.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use. Safety for use has not been established (Category C). Parenteral administration before onset of labor has caused CNS depression and hemorrhage in the neonate.
Lactation- Better to avoid in nursing mothers as it is excreted in breast milk. Risk-benefit decisions must be considered.
Children- Do not use in children less than 6 years old.
Renal Disease- Use with caution, drug is excreted in urine, bile and feces unchanged.
Liver Disease- Use with caution, drug metabolized in the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Use in geriatrics: The elderly may respond to usual doses of the drug with excitement, agitation, drowsiness, or confusion. They are more susceptible to the antimuscarinic side effects. Also there is more incidence of glaucoma as well, so need to use caution when using this agent.
-Use caution in urinary retention, prostatic enlargement, cardiac insufficiency, liver or kidney dysfunction.

- ***ADVERSE EFFECTS:***

Confusion, blurred vision, (avoid performing hazardous activities until full effect of the medication is known); depression, psychotic reactions, constipation (patient should increase fluid intake), abdominal distension, urinary retention, dry skin, fever (specially children), dry mouth, difficulty in swallowing, palpitation, bradycardia.

- ***INTERACTIONS:***

Overview of Hyocine N-butyl Bromide Drug-Drug Interaction	
Drug	**Interaction**
Alcohol and *other* ***CNS depressants***	These have additive sedative effects if used with antispasmodics. Caution use.
Antacids	These will decrease absorption from the GI tract; allow 2 h interval between the two medications.
Antihistamines, ***Anticholinergics***, ***Phenothiazine,*** and ***TCAs***	Concurrent use results in additive anticholinergic side effects. Avoid concurrent administration.
Digoxin	Increased digoxin level and toxicity have been noted. Do not administer together.

- ***OVERDOSE:***

Symptoms are exaggerated adverse effects.

Treatment includes inducing emesis or performing gastric lavage. May administer activated charcoal after emesis. Use supportive and symptomatic therapy as needed in hospital setting.

- ***BRANDS:***

Scobutyl (JePharm), Scopal (BPC).

C) ANTIEMETICS

Vomiting (emesis) is an important defense mechanism by which the body attempts to get rid of a variety of toxins and poisons. Travelling (motion sickness) or pregnancy can also cause vomiting.

Antiemetics are useful in limited situations, but should always be used with caution because of the potential danger of masking the symptoms of more severe disease; i.e. acute viral gastroenteritis, head trauma, toxic ingestion, CNS infection, and GI obstruction, specially in children. They are also harmful in cases such as diabetic ketoacidosis, or in excessive digoxin or antiepileptic dosage.

Therapy should start by identifying and removing the cause if possible, replacing fluids and electrolytes, counseling if there is a problem like bulimia, then starting drug therapy. Some medications that can be used include: prochlorperazine and haloperidol in severe cases, lorazepam to relieve anxiety related nausea and vomiting, antihistamines like promethazine and meclizine, and metoclopramide. The choice of which medication to use depends on the cause and the patient's health.

Nausea and vomiting in pregnancy are common in the first trimester. It is recommended to use non-pharmacological approaches to the pregnant women before starting any medication. Eating small, frequent meals, lower the fat content of meals, ingesting crackers before arising in the morning, lying down, can all help to alleviate symptoms.

If nausea and/or vomiting continue despite such measures or are severe, then an antihistamine like meclizine can be prescribed. If symptoms have not settled in 24 to 48 hours, then a specialist's opinion should be sought.

1) Metoclopramide WHO,P

- ***DRUG SUMMARY:***

Metoclopramide (MTP) is a potent central dopamine receptor antagonist, classified as an autonomic nervous system agent; direct-acting cholinergic, antiemetic and GI agent. Exact mechanism of action is not clear. It has a spectrum of activity similar to phenothiazines, but has less peripheral action on the gut in addition to its central effect. Therefore, it may be superior to the phenothiazines in the emesis associated with gastroduodenal, hepatic and biliary disease. It does not stimulate gastric, or pancreatic secretions.

- ***INDICATIONS:***

Management of diabetic gastric stasis (gastroparesis), to prevent nausea and vomiting due to different etiologies; mainly in cancer chemotherapy, and in gastro-esophageal reflux, short term (4-12 weeks).

[For patients under 20 years; use is restricted to severe intractable vomiting of known cause, vomiting after radiotherapy and cytotoxics, and aid to gastrointestinal intubation, pre-medication: BNF, 2001].

- ***CONTRAINDICATIONS:***

Sensitivity or intolerance to MTP, allergy to sulfiting agents, history of seizure disorders (epilepsy), concurrent use of drugs that can cause extrapyramidal symptoms, mechanical GI obstruction or perforation, history of breast cancer; pheochromocytoma to avoid hypertensive crisis.

- ***DOSAGE FORMS:***

Tablets, syrup.

- ***RECOMMENDED DOSAGE:***

Adult: 10-15 mg PO q.i.d.; a.c. and h.s.
Young adult (15-19 yrs under 60 kg):
10 mg PO t.i.d., a.c.
Child (6-14 y): 2.5-5 mg PO t.i.d., a.c.;
max. dose for young adult and children 500 *u*g/kg/d.
Directions: Take medication 30 min. a.c.
*Need to report any involuntary movement of eyes, face or limbs. Might need to discontinue MTP therapy.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly needed and benefit outweighs potential risk. MTP crosses the placenta, however there are no adequate studies in pregnant woman (Category B), and reports on safety are conflicting.
Lactation- Exercise caution. MTP is excreted into breast milk. There appears to be no serious risk to the nursing infant, but side effects may include intestinal discomfort and possible CNS effects.
Children- Use caution, due to increased risk in children and young adults of extra-pyramidal side effects (involuntary movements of limbs or facial muscles). *Limit use to severe or persistent vomiting of known etiology.*
Renal Disease- Reduce dose, and use with caution. MTP is excreted in urine mainly.
Liver Disease- Use with caution. The drug is minimally metabolized in the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Depression has occurred in patients with and without prior history of depression. Use only if the expected benefits outweigh the potential risks.
-Carcinogenesis evidence has not been conclusive with MTP use. Elevated prolactin levels persist during therapy, and approximately 1/3 of human breast cancers are prolactin-dependent. Evaluate patient history carefully before prescribing.

- ***ADVERSE EFFECTS:***

These are usually mild, transient and reversible upon drug withdrawal. Sedation, fatigue, restlessness, agitation, insomnia, extrapyramidal symptoms (especially in children/young adults), hypotension, nausea, diarrhea, sometimes constipation, dry mouth, galactorrhea, amenorrhea, impotence, methemoglobinemia, and altered drug absorption have been reported.

- ***INTERACTIONS:***

Overview of Metoclopramide Drug-Drug Interaction	
Drug	**Interaction**
Alcohol	***Alcohol*** rate of absorption is increased by MTP, increasing side effects. Discourage patient from alcohol intake.
Analgesics, and ***anti-cholinergics***	These may antagonize effect of MTP on GI motility, and enhance effect of aspirin and paracetamol.
Cyclosporine	An increase in the immuno-suppressive and toxic effects may result. Avoid use of MTP.
Digoxin	Plasma levels of digoxin may be decreased, decreasing its therapeutic effect. Monitor patients, the dose of digoxin may need to be increased.
Pheno-thiazines	Extrapyramidal symptoms may occur. Do not administer concurrently.

- ***OVERDOSE:***

Symptoms: drowsiness, disorientation, and extrapyramidal reactions which are self limiting and usually disappear within 24 h. Muscle hypertonia, irritability and agitation are common.
Treatment: an anticholinergic or anti-parkinson drug to help control extrapyramidal reaction. Refer to hospital for management.

- ***BRANDS:***

Emestop (BPC), Novomit (JePharm), Pramin (Rekah), Reglan (Robins).

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2) Meclozine/Meclizine

- ***DRUG SUMMARY:***

A long-acting piperazine antihistamine. Classified as a H_1-receptor antagonist, GI agent, antihistamine and antiemetic agent.

- ***INDICATIONS:***

Prevention and treatment of nausea, vomiting and dizziness (also in pregnancy) and/or motion sickness. Can also be used for the management of vertigo associated with diseases affecting the vestibular system.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the medication.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: ★*For Motion Sickness;*
25-50 mg PO 1 h. before travel, may repeat q. 24 h. if necessary for duration of journey.
★*For Vertigo Problems;*
25-100 mg/d in divided doses (b.i.d.).
Child: Not recommended for children under 12 years.

Directions: Meclizine can be given without regard to meals. Onset of action takes 1 h., while duration is for 12-24 h.
*Pyridoxine (vitamin B_6) has been shown to be effective in treatment of nausea and vomiting associated with pregnancy. So you might find it in some formulations as a combination with meclizine.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly needed. Meclizine presents the lowest risk of teratogenicity, and is the drug of choice in treating nausea and vomiting during pregnancy (Category B). Large-scale human studies have not demonstrated teratogenic effects.
Lactation- Safety for use in nursing mothers has not been established. There is no available data.
Children- Safety and efficacy for use in children have not been established. Not recommended for use in children < 12 years *(Drug Facts & Comparisons, 2000)*.
Renal + Liver Disease- Use with caution. Safety has not been established.

- ***PRECAUTIONS AND WARNINGS:***

-Due to possible anticholinergic effects, use caution in patients with glaucoma, obstructive disease of the GI or GU, and in elderly males with possible prostatic hypertrophy.

- ***ADVERSE EFFECTS:***

Drowsiness, dry mouth, blurred vision, and fatigue. (*Warn patient against performing hazardous activities like driving or operating machinery until the full effect of the medication is known*.)

- ***INTERACTIONS:***

Alcohol and other *CNS depressants* will enhance side effects. Avoid concomitant use.

- ***OVERDOSE:***

Symptoms: Moderate overdose may cause hyperexcitability alternating with drowsiness. Massive overdose may cause convulsions, hallucinations and respiratory paralysis.
Treatment: Inducing emesis, and performing gastric lavage. Take to hospital, do not use morphine or other respiratory depressants.

- ***BRANDS:***

Ancozine (BPC), Antivert (Roerig), Bonine (Leeming), Paravomine (JCL).

D) DRUGS USED IN DIARRHEA

Diarrhea is a symptom that is characterized by an increased frequency or consistency of stools during a limited time period. Epidemiological studies define it as the passage of three or more loose or watery stools in a 24 hour period, a loose stool being that would take the shape of a container. Variability in the causes of diarrhea makes identification of the pathophysiologic mechanism difficult. The

etiology may be psychogenic, neurogenic, surgical, endocrine, irritant, dietary, allergic, malabsortpive, infectious or inflammatory.

Simple and effective treatment measures are available that can markedly reduce the number of deaths caused by diarrhea, make admission to the hospital unnecessary in most cases and prevent the adverse effects of diarrhea on nutritional status. Practical preventive measures can also be taken that substantially reduce the incidence and severity of diarrheal episodes.

It is important to know that passing several loose stools daily or with every feeding in breast-fed infants is normal provided that the infant is steadily gaining weight. Mothers should be reassured that the infant doesn't need treatment, and should continue breast-feeding.

Causes of Diarrhea:

1. ***Food-borne diarrhea:*** Table-3.3 summarizes the most common pathogenic bacteria. Infectious diarrhea may be treated with fluid and electrolytes, since it is self-limiting. Only in certain cases initiation of antimicrobial therapy may be necessary; i.e. doxycycline, trimethoprim/ sulfamethoxazole, or a fluoroquinolone.
2. **Remember** that antimicrobial drugs are not indicated for the routine treatment of acute diarrhea. Their indiscriminate use must be discouraged, not only because they are often of no therapeutic value, but also they are needlessly expensive and can be harmful.
3. ***Food intolerance:*** It may be caused by a food allergy, or by ingestion of foods that are excessively fatty or spicy that contain high amount of roughage or many seeds. Need to advise patient to monitor the cause, and to avoid. Lactose deficiency in infants or adults who develop intolerance to whole milk or milk-based products, can reduce/ eliminate their problem by intake of lactase enzyme.
4. ***Viral diarrhea*** is a common problem in infants and young children. Children aged 6-24 months are most susceptible to viral gastro-enteritis. Respiratory illness such as otitis media or tonsillitis may occur concurrently.

During the 12-24 hour incubation period vomiting, watery diarrhea and low-grade fever may occur. The illness tends to be self-limiting, lasting 5-8 days, and treatment should be restricted to symptomatic therapy, mainly to prevent dehydration complications.

5. ***Protozoal diarrhea***, table-3.4 summarizes the main protazoal organisms. Effective therapy consists of metronidazole, after the confirmation of the causing agent by stool analysis.
6. ***Drug-induced diarrhea*** can occur with administration of medication. Commonly prescribed antibiotics that have a broad spectrum of activity; i.e. ampicillin, clindamycin, erythromycin, tetracycline, and fluoroquinolones can produce diarrhea as a side effect. Other drugs that may cause diarrhea and cramping include; stimulant cathartics, anticancer agents, colchicine, antacid containing magnesium, methyldopa and metoclopramide. If diarrhea does not subside within few days of starting any medication, reduction of the dose might be necessary.

Table- 3.3: Summary of the Most Common Pathogenic Bacteria [#]				
Type	**History**	**Symptoms**	**Treatment**	**Prognosis**
Salmonella spp.	Ingestion of improperly cooked or refrigerated poultry products, immuno-compromised host.	Onset of 24-28 h, diarrhea, fever, and chills	Fluid and electrolytes; no antibiotics needed	Self-limiting
Shigella spp.	Ingestion of contaminated vegetables or water, immunocompromised host.	Onset of 24-48 h, nausea, vomiting, diarrhea	Fluid and electrolytes; antibiotics (cotrimoxazole, ampicillin, ciprofloxacin)	Self-limiting
Enterotoxigenic Escberichea coli (Travelers' diarrhea)	Ingestion of contaminated food or water, recent travel outside the country.	Onset of 8-72 h, watery diarrhea, fever, abdominal cramps	Fluid and electrolytes; in moderate or severe cases, antibiotics; (fluoroquinolones)	Self-limiting
Campylobacter jejuni	Ingestion of contaminated water, fecal-oral route, immunocompromised host.	Nausea, vomiting, headache, malaise, fever, watery diarrhea	Fluid and electrolytes; in severe or persistent diarrhea, antibiotics (erythromycin, fluoroquinolones)	Self-limiting
Clostridium difficile	Antibiotic-associated diarrhea.	Watery or mucoid diarrhea, high fever, cramping	Water and electrolytes; discontinuation of offending agent; oral vancomycin, oral metronidazole, bacitracin, cholestyramine	Good, if treated
Staphylococcus aureus	Ingestion of improperly cooked or stored food.	Nausea, vomiting, watery diarrhea	Fluid and electrolyte; no antibiotics	Self-limiting

[#] *Handbook of Nonprescription Drugs, 10th ed., 1993: p. 204-5.*

Table-3.4: Summary of Protozoa Organisms that Cause Diarrhoea #				
Type	**History**	**Symptoms**	**Treatment**	**Prognosis**
Giardia lamblia	Ingestion of water contaminated with human or animal feces, immuno-compromised host	Chronic watery diarrhea, abdominal distension	Metronidazole, furazolidone	Good, if treated
Cryptosporidia	Contaminated water, AIDS, immunocomp-romised host	Chronic watery diarrhea	Fluid and electrolytes	Self-limiting, except in AIDS or other immunocomp-romised patients
Entamoeba histolytica	Fecal soiled food or water, immunocomp-romised host	Chronic watery diarrhea, blood mucous, abdominal cramps, maybe fever	Fluid and electrolytes; metronidazole; iodoquinol	Need stool culture to confirm. Good, except for immunocomp-romised patients

[#] *Handbook of Nonprescription Drugs, 10th ed., 1993: p. 204-5.*

1) Oral Rehydrating Salts [WHO,P] (ORS)

- ***DRUG SUMMARY:***

Oral Rehydrating Salt (ORS) solutions are the first line treatment in acute diarrhea, especially in infants and in frail/elderly patients. They are a simple and effective way to markedly reduce the number of deaths caused by diarrhea. ORS are balanced mixtures of glucose and electrolytes. Intestinal absorption of sodium and water is enhanced by glucose, to replace what has been lost through diarrhea, and restore acid-base balance.

The WHO criteria for an oral replacement fluid contains (per liter)

*Total substance concentration (including that contributed by glucose) should be within the range of 200-310 mmol/l.

* The individual substance concentration:

- Glucose - should at least equal that of Na but should not exceed 111 mmol/l
- Sodium - should be within the range of 60-90 mEq/l
- Potassium - should be within the range of 15-25 mEq/l
- Citrate - should be within the range of 8-12 mmol/l
- Chloride - should be within the range of 50-80 mEq/l.

No commercial product currently available strictly fulfils WHO recommendation. Still, available products are more convenient and seem to be potentially safer because they are premixed and there is less chance of error in preparation.

- ***INDICATIONS:***

To prevent dehydration in cases of electrolyte and water depletion as in diarrhea or vomiting. Severe cases need hospitalization and require parenteral therapy.

- ***CONTRAINDICATIONS:***

None; see warnings.

- ***DOSAGE FORMS:***

Packages to be dissolved in certain amount of water as directed.

- ***RECOMMENDED DOSAGE:***

✶*Mild/Moderate Diarrhea* (not more than one stool q. 2 h. or longer):
100 ml/kg body weight per day until diarrhea stops.

✶*Severe Diarrhea* (more than one stool q. 2 h.): 10-15 ml/kg body weight per hour, until diarrhea stops.

Directions: Need to dissolve package in required amount of water. Do not add sugar or boil after mixing. The prepared solution should be discarded after 24 hours, and replaced with a fresh one to avoid spoilage.
*Drink slowly, small amount initially especially if vomiting is present.
*Administering fluid without electrolytes is potentially dangerous because of the risk of inducing hyponatremia.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use caution, might need to refer to hospital for monitoring.
Lactation- Safe if taken for short period of time as directed.
Children- Safe when used according to directions and under supervision as indicated for use.
Renal Disease- Warning. Special care is needed during usage because electrolyte or fluid imbalances might be aggravated if kidney is malfunctioning.
Liver Disease- Use with caution.

- ***PRECAUTIONS AND WARNINGS:***

-Severe continuing diarrhea or other critical fluid loss such as intractable vomiting, prolonged shock, should be referred to hospital, and will require parenteral therapy.
-Use caution in patients with diabetes, cardiac failure, hypertension (specially patients on low sodium diet), impaired renal function and in peripheral or pulmonary edema. Such solutions will aggravate their condition.

- ***ADVERSE EFFECTS*:**

Dizziness, nausea, or skin rash may occur. Vomiting may occur if the solution is given too rapidly or forcefully to the infant.

- ***INTERACTIONS:***

Electrolytes affect a lot of medications when given concomitantly. It is advisable not to take any medication the same time as the preparation, unless clearly needed and under direct supervision of doctor.

- ***OVERDOSE:***

Serious electrolyte disturbances will occur if there is an ingestion of large amount of preparation; due to the electrolytes (Na & K) included. Cardiac and respiratory functions could be serious. Refer to hospital for symptomatic and supportive care.

- ***BRANDS:***

Electrosubs (BPC), Hydran 60 (Teva), Orset L.S. (Ciba), ORS (UNICEF), Rehidrat (Searle).

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2) Antidiarrheal Agent - Loperamide [P]

- ***DRUG SUMMARY:***

Loperamide is a synthetic piperidine derivative, chemically related to diphenoxylate and to meperidine, but possesses a more favorable side effects profile than the opiate and opiate-like agents. Classified as a GI, antidiarrheal agent. It slows intestinal motility and affects water and electrolyte movement through the bowel. It inhibits peristalsis, prolongs transit time of intestinal contents, increases consistency of stools, and reduces fluid and electrolyte loss. Tolerance to the antidiarrheal effect has not been observed.

- ***INDICATIONS:***

Acute non-specific diarrhea, chronic diarrhea associated with inflammatory bowel disease, and to reduce fecal volume from ileostomies.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug, in patients who must avoid constipation, severe colitis, acute diarrhea caused by broad spectrum antibiotics or associated with micro-organisms, body temperature > 38.3 °C, and bloody diarrhea, in children < 4 years.

- ***DOSAGE FORMS:***

Capsules, drops.

- ***RECOMMENDED DOSAGE:***

Adult: ★*For Acute Diarrhea;*
4 mg followed by 2 mg after each loose stool, for not more than 5 days,
usual dose 6-8 mg/d, max. 16 mg daily.
★*For Chronic Diarrhea;*
4 mg PO followed by 2 mg after each loose stool until diarrhea is controlled. Continue administration if diarrhea cannot be controlled with diet or specific treatment.
Child: Do not use for children < 4 y old.
If oral rehydration solutions fail, can administer 0.1 mg/kg after each loose stool, usually 1 mg for acute diarrhea, for not more than 2 days.
Directions: Loperamide is administered after each unformed stool, up to a maximum of 16 mg/d for adults.
*Include appropriate fluid and electrolyte therapy to prevent dehydration and further complications. Advise patient to drink plenty of fluids.
*In acute diarrhea, loperamide should be discontinued if there is no improvement after 48 hrs. of therapy.
*The doctor should be notified if abdominal pain or distention, or fever occurs. Discontinuation of the medication may be needed.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use of Loperamide. No available well controlled studies on pregnant women. Safety has not been established (Category B).
Lactation- It is not known if loperamide is excreted in breast milk. Safety has not been established.
Children- Not to be used in children < 4 yrs. Use special care if you have to use for young children (6-12 yrs). Rehydration is usually sufficient.

Renal Disease- The drug is primarily excreted in feces. Small amounts are excreted by the kidneys, thus use caution.

Liver Disease- Warning. Patients with hepatic dysfunction have reported increased CNS toxicity because of large first-pass bio-transformation. Avoid use unless clearly needed.

- ***PRECAUTIONS AND WARNINGS:***

-Antiperistaltic agents should not be used in acute diarrhea associated with organisms that penetrate the intestinal mucus (tissue invasive); entroinvasive *E-coli*, *salmonella*, or *shigella*; or in pseudomembranous colitis associated with broad-spectrum antibiotics.

-If clinical improvement of acute diarrhea is not observed in 48 hours, or abdominal distension occurs, discontinue the medication. Recommended dosage should not be exceeded.

- ***ADVERSE EFFECTS:***

Adverse experiences are generally minor and self-limiting. Drowsiness, fatigue dizziness are reported, therefore; need to caution patient while driving or performing hazardous jobs. Abdominal discomfort or pain, bloating, constipation, nausea, anorexia, dry mouth can also occur; patient should drink plenty of fluids to help prevent dehydration. May cause skin rash. In severe cases toxic megacolon (mainly in patients with ulcerative colitis) may occur.

- ***INTERACTIONS:***

No major drug-drug interactions reported.

- ***OVERDOSE:***

Symptoms: usually include constipation, CNS depression and GI irritation. Nausea and vomiting may occur.

Treatment: activated charcoal administered promptly after ingestion can reduce amount of drug absorbed into systemic circulation. Take to hospital for supportive, symptomatic management.

- ***BRANDS:***

Diacare (Pharmacare), Imodium (Janssen), Lipastop (Eastern Chem.), Loperid (Vitamid), Stopit (Rafa).

E) LAXATIVES

Constipation is generally defined as a decrease in the frequency of fecal elimination and is characterized by the difficult passage of hard, dry stools. (In other words incomplete evacuation or feeling of it.) It usually results from the abnormally slow movement of feces through the colon with a resultant accumulation in the descending colon, and increased water resorption. In elderly persons, constipation occurs due to inappropriate diet, lack of exercise, medication use, or lack of muscle tone in the colon. Constipation in pregnancy is also common, due to increasing size of uterus, or intake of mineral supplements that contain iron and calcium that tend to be constipating.

Patients should be counseled about non-pharmacological methods before a drug is prescribed; proper diet, adequate fluid intake (6-8 glasses/day) and reasonable exercise to alleviate or prevent this problem. If the patient is still constipated, and the constipation is not secondary to an underlying undiagnosed complaint, a laxative may be used. The laxative facilitates the passage and the elimination of feces from the colon and rectum. In children, the introduction of fruit and vegetable puree into the diet may be sufficient to regulate bowel action. Persistent constipation should be fully investigated.

Abuse of laxatives may lead to hypokalemia and an atonic non-functioning colon. It is important to recognize that the improved mobility and the provision of time and privacy for going to the toilet may be all that is required.

Laxatives are classified into different categories. Table-3.5 indicates the properties of each type:

Table-3.5: Classification and Properties of Laxatives[1]					
Laxatives		**Onset of Action (hrs)**	**Site of Action**	**Systemic Absorption**	**Use in Pregnancy**
Saline	Magnesium citrate Magnesium-OH Magnesium SO_4 [3] ---------- Na-biphosphate	0.5 - 3 2-4 ---------- 0.03 - 0.25 [2]	Small & large intestine ---------- Colon	Yes	Avoid, possible dangerous electrolyte imbalances.
Irritant/stimulant	Cascara Senna Phenolphthalein Biscodyl tabs. ---------- Biscodyl supp. ---------- Castor oil	6 - 10 ---------- 0.25 - 1 ---------- 2 - 6	Colon ---------- Small intestines	Yes ---------- Yes	Avoid, unless under direct M.D. supervision. ---------- Avoid, premature labor.
Bulk-forming	Bran Methylcellulose Polycarbophil Psyllium	12-24 (up to 72)	Small & large intestine	No	Safe
Lubricant	Mineral oil (Liquid parafin)	6 - 8	Colon	Yes, minimal amount	Do not use for long time, loss of vitamin absorption.
Surfactant	Docusate	24 - 72	Small & large intestine	Yes	OK. Best in anorectal painful-conditions.
Misc.	Glycerin supp. ---------- Lactulose	0.25 - 0.5 ---------- 24 - 48	Colon	? ---------- ↓ amount	Caution use.

-[1] Reference: Drug Facts and Comparisons. 2000, p. 1166.
-[2] 2-15 minutes.
-[3] Magnesium sulphate (Epsom salt) is available in packs. Dissolve in water and use before breakfast.
-Stimulant laxatives should not be used regularly. If obstruction is suspected, do not use laxative.

1) Bisacodyl [P]

- ***DRUG SUMMARY:***

A stimulant laxative, GI agent. Induces peristaltic contractions by direct stimulation of sensory nerve endings in the colonic walls. It also expands intraluminal fluid volume by increasing epithelial permeability.

- ***INDICATIONS:***

Temporary relief of acute constipation and for evacuation of colon before surgery, or radiological examinations. Also used to empty colon before delivery and to relieve constipation in patients with spinal cord injury.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug. Acute surgical abdomen, nausea, vomiting, abdominal cramps, intestinal obstruction, fecal impaction, ulcerative lesions of the colon. Use of rectal suppository in presence of anal or rectal fissures, or ulcerated hemorrhoids.

- ***DOSAGE FORMS:***

Tablets, suppositories.

- ***RECOMMENDED DOSAGE:***

Adult: 5-15 mg PO p.r.n. up to 30 mg for special procedures.
10 mg PR once daily p.r.n.
Child (6 to 12 y): 5 mg PO or PR p.r.n.
Directions: Administer PO drug in the evening or before breakfast. Suppository may be inserted at time bowel movement is desired.
*Tablets are enteric coated, therefore, to avoid gastric irritation, they should be swallowed whole, and not cut, crushed or chewed. They are preferably taken with a full glass of water or other liquid.
*Advise patient not to take medication within 1 hour of antacids or milk administration. These substances may cause premature dissolution of the enteric coating, resulting in gastric irritation.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use (Category C). Bulk forming or surfactant laxatives are a better choice.
Lactation- Better to avoid. Excreted in small amounts in breast milk.
Children- Avoid use in children < 6 years old. Safety has not been established. Other agents may be safer for use.
Renal Disease- Use with caution. Drug is excreted in urine.
Liver Disease- Use with caution. Drug is metabolized in the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Abuse/dependency; chronic use of stimulant laxatives such as bisacodyl, may lead to laxative dependence, which in turn may result in fluid and electrolyte imbalances, osteomalacia, vitamin and mineral deficiencies. Use not recommended for long term (> 1 week).

- ***ADVERSE EFFECTS:***

Systemic effects not reported. Rarely: mild cramping, nausea, vertigo, diarrhea, fluid and electrolyte disturbances; especially potassium and calcium. Suppositories may cause proctitis (inflammation of rectum).

- ***INTERACTIONS:***

Milk and *Antacids* cause early dissolution of enteric-coated tablets, resulting in abdominal cramping. Do not use within 1 h of antacid intake.

- ***OVERDOSE:***

There is no specific antidote, however, supportive care may be required to prevent dehydration or electrolyte imbalances.

- ***BRANDS:***

Bisalax (JCL), Laxadin (Teva).

---

2) Castor Oil

- ***DRUG SUMMARY:***

Castor oil is also a stimulant laxative GI agent. Indicated for constipation; bowel evacuation before radiological procedures, endoscopy or surgery. It is one of the

widely abused laxatives, and should be seldom used routinely for constipation.
It is contraindicated in abdominal pain, intestinal obstruction, nausea or vomiting. Should be avoided during pregnancy, since it provokes premature labor. It should not be used for more than one week of regular therapy. Chronic abuse may lead to "cathartic colon", a poorly functioning colon.
Misuse may lead to severe cramping, enteric loss of protein, excess loss of fluid and electrolytes, and inhibition or absorption of fat-soluble vitamins.
Dose ranges for adults: 15-60 ml/day.
Children (2-12): 5-15 ml/day.
It is most effective when given on empty stomach, and produces evacuation within 2-6 hours after ingestion. It should not be given at bedtime. Can be given with fruit juice to mask the unpleasant taste.

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3) Glycerin P

- ***DRUG SUMMARY:***

A GI agent; hyperosomotic laxative. It produces an irritant effect, and by absorbing water from tissues it creates more mass, therefore stimulates peristalsis.

- ***INDICATIONS:***

To relieve constipation.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Adult and pediatric suppositories.

- ***RECOMMENDED DOSAGE:***

Adult: *For Constipation*;
1 supp. when needed, inserted high into the rectum.
Child: 1 supp. when needed.
Directions: Insert suppository high into the rectum and retain 15 minutes. Onset requires 15-30 minutes.
*Store in cool place, preferably the refrigerator.

- ***SPECIAL CASES:***

Pregnancy- Use with caution. Only use if under medical supervision. It is safer to use bulk forming agents or surfactants when needed.
Lactation- It is not known whether glycerin used rectally is excreted into breast milk. Safety not established, since there is no available data.
Children- Glycerin suppositories are used in children and infants often to initiate defecation. Adverse effects are minimal.

- ***PRECAUTIONS AND WARNINGS:***

-Laxative use should only be used temporarily.

- ***ADVERSE EFFECTS:***

Abdominal cramps, rectal discomfort.

- ***INTERACTIONS:***

No drug-drug interactions have been reported.

- ***BRANDS:***

Glycerol (various).

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4) Psyllium

- ***DRUG SUMMARY:***

A bulk-forming laxative, GI agent. Usually seen as a highly refined colloid of blond psyllium seed with equal amount of dextrose added as dispersing agent. On contact with water, produces bland, lubricating gelatinous bulk that promotes peristalsis and natural elimination. Reportedly, chronic use may reduce plasma cholesterol, possibly by interfering with reabsorption of bile acids.

- ***INDICATIONS:***

Orally as self-treatment of constipation. For atonic or spastic constipation and constipation associated with rectal disorders of anorectal surgery, irritable bowel disease and hemorrhoids.

- ***CONTRAINDICATIONS:***

In nausea, vomiting, undiagnosed abdominal pain, intestinal obstruction, appendicitis, ulceration or stenosis, and diarrhea.

- ***DOSAGE FORMS:***

Powder.

- ***RECOMMENDED DOSAGE:***

Adult: 1-2 rounded tsp. or 1 packet 1-3 times/d.

Child (≥ 6 y): 1 tsp. in water h.s.

Directions: Need to stir dose into a full glass (240 ml) of water, fruit juice or other liquid, and drink.

*Additional fluids should be taken during the day, fecal impaction can occur if fluid intake by mouth is insufficient.

*Drug may reduce appetite if it is taken before meals.

*Laxative effect generally occurs in 12-24 hours, however some patients may require 2-3 days of medication; inform patient.

**NOTE:* if there is discomfort or abdominal fullness, patients should take smaller doses.

- ***USE IN SPECIAL CASES:***

Pregnancy- Bulk-forming laxatives seem to be the safest laxatives to use during pregnancy. There are no well-controlled studies in pregnant women.

Lactation- Generally safe.

Children- Laxative use in children should not be encouraged. Psyllium preparations might not be acceptable by children due to taste or form. Increasing both fluid and bulk contents of the child's diet are usually sufficient to improve bowel habits. High fiber cereal, vegetables and fruits should be enough. Unbuttered popcorn is a good bulk-containing snack for children.

Renal or Liver Disease- Safe when used properly without abuse.

- ***PRECAUTIONS AND WARNINGS:***

-Impaction or obstruction may be caused by bulk-forming agents, if patient does not drink sufficient fluids, or has an obstructive problem in the GI passage.

-Rectal bleeding or failure to respond to therapy may indicate a serious condition that requires further medical attention.

- ***ADVERSE EFFECTS:***

Diarrhea, nausea, fecal impaction, esophageal obstruction.

- ***INTERACTIONS:***

None has been reported.

- ***OVERDOSE:***

No reported cases. Need supportive care to prevent obstruction or impaction.

- ***BRANDS:***

Metamucil (Searle).

F) ANTI-HEMORRHOIDAL

Hemorrhoids (also known as piles) are abnormally large bulging, symptomatic conglomerates of veins, supporting tissue, and overlying mucous membranes or skin of the anorectal area. They are classified as external (occur below the anorectal line) or internal (occur above the anorectal line).

Many factors have been implicated in the etiology of hemorrhoidal disease, such as: heredity, erect posture, pregnancy, prolonged standing, lack of dietary bulk, heavy lifting, constipation, portal hypertension, pelvic tumors and anal infections.

Symptoms include burning sensation, pain, itching, inflammation, irritation, swelling in the anorectal region and general discomfort. Some potentially serious anorectal disorders, including fissures, fistulas, inflammatory bowel disease and tumors may present hemorrhoidal like symptoms and should be taken seriously by the physician.

Pharmacological agents recommended to relieve symptoms of anorectal disease include;

1) Local Anesthetics: Temporarily relieve pain, burning, itching, and irritation by preventing transmission of nerve impulses. Examples; Benzocaine 5-20 %, benzyl alcohol 5-20 %, dibucaine 0.25-1 %, and lidocaine 2-5 %.

2) Vasoconstrictors: They cause constriction of arterioles, shrink swollen hemorrhoidal tissue a little, as well as relieve some itching. [*These need to be avoided in patients with diabetes, hyperthyroidism,*

hypertension, prostatic enlargement, cardiovascular disease, and patients taking MAO Inhibitors]. Examples; aqueous solution of ephedrine sulfate, epinephrine, phenylephrine and epinephrine base.

3) Protectants: These prevent irritation of the anorectal area, and water loss from the stratum corneum. Examples; Aluminium hydroxide gel, cocoa butter, glycerine in aqueous solution, mineral oil, white petrolatum.

4) Astringents: They provide relief from local anorectal irritation and inflammation. Examples; Calamine and zinc oxide in concentrations of 5-25 %.

5) Hydrocortisone: Reduce itching, inflammation, and discomfort by producing vasoconstriction, lysosomal membrane stabilization and antimiotic activity. Topical hydrocortisone-containing products are indicated for temporary relief of minor external anal itching due to minor irritation or rash.

6) Other agents that may be used include: counter irritants (camphor, menthol), wound healers (Peruvian balsam, vitamin A, vitamin D), antiseptics (boric acid, phenol, sodium salicylic acid) and bulk forming laxatives (to relief constipation contributing to hemorrhoids). These agents have not been proven to be safe or effective for hemorrhoidal preparations.

For intra-rectal use, the only approved ingredients are protectants, vaso-constrictors, and astringents.

As a general rule, products containing the least number of recommended ingredients are the best, since you minimize undesirable interactions and maximize effectiveness. Scented or tinted products used, (whether preparations or toilet paper) should be avoided, since they can cause allergic reactions.

The importance of maintaining normal bowel function by eating properly, drinking adequate amount of fluids, avoiding excessive laxative use, as well as proper anal hygiene should be emphasized as a way of preventing anorectal disease.

1) Anusol (or other equivalent preparation WHO,P)

- ***DRUG SUMMARY:***

This antihemorrhoidal preparation contains an astringent (Phenylephrine HCl 0.25%), a protector (vegetable oil base) in suppository form. Ointment contains; an anesthetic (pramoxine HCl 1%), astringents (zinc oxide 12.5% + balsam nicaragua 3.0%), as well as mineral oil. Anusol helps to relieve pain, itching and discomfort arising from irritated anorectal tissue.

- ***INDICATIONS*:**

Hemorrhoids.

- ***CONTRAINDICATIONS:***

History of hypersensitivity to product.

- ***DOSAGE FORMS:***

Suppository, ointment.

- ***RECOMMENDED DOSAGE:***

Adults: Apply small amount of ointment at night and morning, and after defecation.
Insert suppository up the anus after defecation and at bedtime.

Directions: For maximum effect, anorectal products should be used after, rather than before defecation.

*Before the product is applied, the anorectal area should be washed with mild soap and warm water, rinsed thoroughly, and gently dried by patting or blotting with toilet tissue or a soft cloth. Proper anal hygiene is very important to emphasize to patients.

*Suppository should be inserted into rectum, while ointments should only be used externally and applied sparingly.

*If hypersensitivity reactions occur, seepage, bleeding, severe pain resulting from the medication, or symptoms worsen or do not improve after 7 days of treatment, discontinue use. May need further evaluation or a different product.

- ***USE IN SPECIAL CASES:***

Pregnant + **Lactating women-** only use products for external use.

Children- Safety and efficacy has not been established. Children with hemorrhoids or other anorectal disease should be evaluated for cause, and treated accordingly. Use of local anesthetic should be only for short time (no longer than 3-4 days), since may cause sensitization of the anal skin.

- ***PRECAUTIONS AND WARNINGS:***

-Approved ingredients for intra-rectal use are vasoconstrictors, protectant and astringents. Other ingredients might cause irritation to the inner mucosa.

-Vasoconstrictors should be avoided in patients who have diabetes, hyperthyroidism, hypertension, difficulty in urination due to prostate enlargement, cardiovascular diseases, and in those patients who are taking monoamine oxidase inhibitors. Topical anorectal products containing ephedrine sulphate may cause nervousness, tremor, sleeplessness, nausea, and loss of appetite.

-In case of local infection, treat with an appropriate antibiotic.

- ***ADVERSE EFFECTS:***

Hypersensitivity reactions manifested by local redness, skin irritation, and rash.

- ***BRANDS:***

Anusol (Park Davis), Hemoral H.C. (JCL), Procyoxylene (BCP).

Chapter 4: RESPIRATORY DRUGS

A) ANTIHISTAMINES
1. **Chlorpheniramine Maleate**
2. **Astemizole**

B) NASAL DECONGESTANTS
1. **Oxymetazoline**
2. **Pseudoephedrine**

C) EXPECTORANTS
1. **Ammonium Chloride**
2. **Guaifenesin**

D) ANTITUSSIVES/ COUGH DEPRESSANTS
1. **Codeine**
2. **Dextromethorphan**

E) MUCOLYTICS
1. **Acetylcysteine**
2. **Bromhexine**

F) BRONCHODILATORS AND ASTHMA MEDICATION
1. **Theophylline**
2. **Salbutamol/ Albuterol**
3. **Cromolyn/ Cromoglycate**
4. **Beclomethasone Dipropionate**
5. **Prednisolone**

RESPIRATORY DISORDERS

Diseases of the respiratory tract may be due to viruses, bacterial infections, allergens … etc. causing common cold, allergic rhinitis, upper respiratory tract infections and asthma. For the proper diagnosis, the doctor should be able to differentiate between these disorders (bacterial vs. viral infections, or allergy vs. asthma) so that the minor self-limiting conditions can be managed differently from the potentially serious ones that need immediate action.

The common cold is one of the most common causes for which patient seek medication. The course of the symptoms is 5-7 days, if no complications occur, and the disease is self-limiting since there are no curative remedies. Influenza A may also mimic a cold and needs to be treated promptly.

Whereas the common cold and influenza are caused by viruses, allergic rhinitis is caused by pollen and mold spores. Weather conditions as well as temperature and rainfall cause the seasonal pattern of occurrence. Allergic rhinitis and asthmatic attacks may be precipitated by the same agents. If symptoms of allergic rhinitis are prolonged, persistent cough, asthmatic wheezing or a feeling of constriction in the chest may follow. These are dangerous signals, or a warning of possible asthma onset.

Patients with allergic rhinitis may develop complications of chronic nasal inflammation, including recurrent otitis media with hearing loss, sinusitis, and loss of epithelial cilia. These are more prominent in children.

For the symptomatic treatment of the runny nose, cough, congestion and pain due to the mentioned disorders, there are various OTC medications available. Misuse or overuse of these products can lead to complications. Anti-infective medications should be limited to the bacterial infections.

Single-agent therapy offers the ability to design a specific regimen directed at each symptom. However, many products contain multiple medications. These combination products may be effective and provide a convenient dosage form when the patient has multiple symptoms. However, combination products are usually more expensive, are limited by fixed doses in the preparation, and may have additive adverse effects.

There is no evidence that show that incorporating secondary agents or other ingredients of the same pharmacological classes in a sub-therapeutic dose provide more relief or even as much relief as one agent at its full therapeutic dose. *Two or more antihistamines do not increase efficacy of product.* A decongestant may be added to an antihistamine in a product for allergic rhinitis, it may provide additional relief of symptoms, and counter act some drowsiness produced by the antihistamine.

Combination products containing analgesic and antipyretics should not be generally recommended since they carry the risk of masking a fever that might indicate bacterial infections.

In this chapter, the most common agents used in the respiratory system are discussed, noting some of the agents that are misused as well.

Notes concerning certain agents:

1) Sodium chloride 0.9% (normal saline) given as nasal drops may relieve nasal congestion by helping to liquefy mucous secretions.

2) Inhalations of warm moist air is useful in the treatment of symptoms of acute infective conditions, and the use of compounds containing volatile substances such as menthol and eucalyptus may encourage their use.

3) There is no evidence that nasal preparations containing antihistamines in

combination with anti-infective agents have any therapeutic effect.
4) Douching the nose with salt and water is not recommended.
5) There is no evidence that topical anti-infective nasal preparations have any therapeutic value. Elimination of organisms such as staphylococci from the nasal vestibule can be achieved by the use of a cream containing ***chlorhexidine*** *and* ***neomycin****, but re-colonization frequently occurs. A nasal ointment containing* ***mupirocin*** *is also available; but it should be kept in reserve for resistant cases.*
6) Chronic use of topical decongestants which produce after-congestion may aggravate chronic rhinitis (rhinitis medicamentose) if used continuously.
7) Sodium cromoglycate is the first choice in children with allergic rhinitis.

A) ANTIHISTAMINES

Antihistamines are chemical agents that exert their effect in the body primarily by competitively blocking the action of histamine at H_1-receptor sites. They do not prevent histamine release. **These have no therapeutic effect on the common cold**. Their continued popularity stems from their drying effect. Differences in antihistamines may be seen in table-4.1.

1) Chlorpheniramine WHO,P

- ***DRUG SUMMARY:***

Chlorpheniramine maleate will be used as the prototype of commonly used anti-histamines. It is a H_1-receptor antagonist, that generally produces less drowsiness than other antihistamines, but side effects involving CNS stimulation may be more common. It also has some antitussive, anticholinergic and local anesthetic action, but no antiemetic properties.

- ***INDICATIONS:***

Symptomatic relief of various allergic conditions, hay fever, urticaria, insect stings, conjunctivitis, angioedema, as well as adjunct in the emergency treatment of anaphylactic shock and severe angioedema.

- ***CONTRAINDICATIONS:***

Hypersensitivity to antihistamines, pre-mature or newborn infants, nursing mothers, narrow-angle glaucoma, obstructive prostatic hypertrophy or other bladder neck obstruction, GI obstruction/stenosis, asthmatic attack, and during or within 14 days of MAO inhibitor therapy.

- ***DOSAGE FORMS:***

Tablets, drops, syrups, capsules.

- ***RECOMMENDED DOSAGE:***

Adult: 2-4 mg PO t.i.d. or q.i.d., or
8-12 mg b.i.d or t.i.d.; max. 24 mg/24 hrs.
[*For anaphylaxis: can be given by slow SC or IM injection over 1 min., 10-20 mg repeated if required (max 40 mg/24hrs).*]
Child (6-12 y): 2 mg q. 4-6 h., max. 12 mg/d.
(2-6 y): 1 mg q. 4-6 h., max. 6 mg/d.

Directions: If GI upset occurs, can take with food and a full glass of water.
*Peak action occurs in 2-6 h., about 45% of dose reaches systemic circulation.
*Driving and other potentially hazardous activities should be avoided until drug response has been determined.
*Antihistamines have additive effects with alcohol or other CNS depressants. Caution your patient about this.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use chlorpheniramine only when clearly needed, and avoid during the third trimester (Category B). Safety during pregnancy has not been established. Several associations with malformation have been found with the use of some antihistamines, but significance is unknown.

Table – 4.1: Comparison of Selected Antihistamines						
Antihistamine	**Adult Single Dose (mg)**	**Dosing Interval (hour)**	**Sedative Effects**	**Anti-histaminic Activity**	**Anti-cholinergic Activity**	**Antiemetic Effects**
Ethanolamines						
Clemastine	1	12	+ +	+ to + +	+ + +	++ to +++
Diphenhydramine	25 - 50	6 - 8	+ + +	+ to + +	+ + +	++ to +++
Ethylenediamines						
Pyrilamine	25 - 50	6 - 8	+	+ to + +	±	-
Tripelennamine	25 - 50	4 - 6	+ +	+ to + +	±	-
Alkylamines						
Brompheniramine	4	4 - 6	+	+ + +	+ +	-
Chlorpheniramine	4	4 - 6	+	+ +	+ +	-
Dexchlorpheniramine	2	4 - 6	+	+ + +	+ +	-
Triprolidine	2.5	4 - 6	+	++ to +++	+ +	-
Phenothiazines						
Promethazine	12.5 - 25	6 - 24	+ + +	+ + +	+ + +	+ + + +
Trimeprazine	2.5	6	+ +	++ to +++	+ + +	+ + + +
Piperidines						
Azatadine	1 - 2	12	+ +	+ +	+ +	-
Cyproheptadine	4	8	+ +	+ +	+ +	-
Phenindamine	25	4 - 6	-	+ +	+ +	-
Miscellaneous						
Acrivistine	8	8	±	++ to +++	±	-
Astemizole #	10	24	±	++ to +++	±	-
Loratadine	10	24	±	++ to +++	±	-
Terfenadine §	60	12	±	++ to +++	±	-

++++ = very high, +++ = high, ++ = moderate, + = low, ± = low to none, - = none.

** Drug Facts and Comparisons 1997; 1135.*

Withdrawn from USA market 1999 voluntarily by the brand manufacturer Janssen since alternative available medications have less risk, § Withdrawn from USA and other European markets in 1998.

Lactation- Avoid use, unless clearly needed. Antihistamines in general are excreted in breast milk. Also can reduce milk flow.

Children- Use of chlorpheniramine in children < 2 years should be avoided. Use caution in children, they may experience paradoxical excitation.

Renal Disease- Use caution in simple cases, reduce dose if patient can't tolerate. Avoid in patients with urinary retention or severe renal disease.

Liver Disease- Avoid use. Some antihistamines have been reported to precipitate coma in hepatic dysfunction.

- ***PRECAUTIONS AND WARNINGS:***

-In elderly (> 60 yrs.), antihistamines are more likely to cause dizziness, excessive sedation, toxic confusional states and hypotension. Dosage reduction may be required.

-Use caution in patients with convulsive disorders, increased intraocular pressure, hyperthyroidism, diabetes, cardiovascular disease, hypertension, G6PD deficiency.

- ***ADVERSE EFFECTS:***

Chlorpheniramine has a low incidence of side effects. Possible side effects include: Drowsiness, headache, tinnitus, disturbed coordination, nervousness, restlessness, mild hypotension, tachycardia, dryness of

mouth, nose and throat, blurred vision, diplopia, epigastric distress, nausea, constipation or diarrhea, or urinary retention.

- ***INTERACTIONS:***

Overview of Chlorpheniramine Drug-Drug Interaction	
Drug	**Interaction**
Alcohol and other ***CNS depressants***	These potentiate the side effects of the medication. Caution patients.
MAO inhibitors	Intensify and prolong the anticholinergic effects of the antihistamines. May cause severe hypotension and extra-pyramidal reactions. Avoid use of antihistamines within 14 days of MAO inhibitor therapy.

- ***OVERDOSE:***

Symptoms may vary from mild CNS depression (sedation, diminished mental alertness, tinnitus) and cardiovascular collapse, to stimulation (insomnia, hallucinations, convulsions, severe hypotension) and respiratory depression leading to coma, especially in children and geriatric patients. Death may occur.

Treatment: Induce emesis even if emesis has occurred spontaneously, using syrup of ipecac. Following emesis administer activated charcoal as a slurry with water and a cathartic to minimize absorption. Do not induce emesis in unconscious patients. Continue with supportive and symptomatic treatments as needed.

- ***BRANDS:***

Ahiston (Teva), Allergon (JCL), Anaphyl (Sam-On), Artix (Megapharm) Cloroyate (Pharmacare), Disoramin (Dexxon).

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2) Astemizole

- ***DRUG SUMMARY:***

(Astemizole and Terfenadine have been withdrawn from some countries due to the risks of death of irregular heart rhythms when taken with certain other drugs and when used at higher than recommended doses).

Astemizole is a long acting selective histamine H_1-receptor antagonist. It binds preferentially to peripheral rather than central H_1-receptors. It does not block histamine release, antibody production or antigen-antibody interactions. Has little or no anticholinergic and sedative effects compared with diphenhyramine. Astemizole has a slow onset of action and is more appropriate for use on a regular basis than when symptoms occur.

Good choice for people who cannot tolerate the sedative or anticholinergic effects of other antihistamines that are indicated for rhinitis, as well as having the benefit of once a day dose. The downside to its use, is the high cost, potential rare but possible adverse cardiac events including death, as well as the serious side effects that can result from drug-drug interactions.

- ***INDICATIONS:***

Relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria.

- ***CONTRAINDICATIONS:***

Same as chlorphineramine.

Also in patients with significant hepatic dysfunction, concomitant erythromycin, ketoconazole or itraconazole therapy, patients with hypokalemia and other electrolyte imbalances.

- ***DOSAGE FORMS:***

Tablets, syrup.

- ***RECOMMENDED DOSAGE:***

Adult and child > 12 yrs: 10 mg PO q.d.
Child 6-12 yrs: 5 mg daily.
Child < 6 yrs: Not recommended.

Directions: **DO NOT EXCEED RECOMMENDED DOSE.**

*Should be taken on empty stomach, since absorption is 60% decreased with food. Take at least 2 hrs. after a meal. Have no food for 1 h. after taking the drug.

*If syncope occurs, astemizole should be discontinued and patient evaluated for potential arrhythmias.

- ***USE IN SPECIAL CASES:***

Pregnancy- Safety and efficacy have not established. Toxicity has been reported in animal studies, manufacturers advise that women of child-bearing potential should use contraception while taking astemizole and for several weeks after stopping (owing to its long $t_{½}$), to avoid any potential risks to the fetus (Category C).

Lactation- Avoid use, due to the increased risk or adverse effects in infants in general.

Children- safety of use in children < 6 yrs. old has not been established.

Renal Disease- Use caution, this drug has a long half-life, 20-24 hours, metabolites 12-20 days, and is 25-50% excreted in urine.

Liver Disease- Astemizole is contra-indicated in patients with significant hepatic dysfunction or liver cirrhosis.

- ***PRECAUTIONS AND WARNINGS:***

-Cardiovascular effects; QT interval prolongation/ventricular arrhythmias, including death, cardiac arrest, *torsade de pointes* have all been observed in clinical setting.

-Severe arrhythmias have been preceded by episodes of syncope. Syncope in patients receiving astemizole (or terfenadine) should lead to discontinuation of treatment and evaluation of potential arrhythmias.

- ***ADVERSE EFFECTS:***

These may include; headaches, dizziness, appetite increase, weight gain, nervousness, depression, nausea, diarrhea, abdominal pain, angioedema, arrhythmias, photo-sensitivity, or rash.

- ***INTERACTIONS:***

Overview of Astemizole Drug-Drug Interaction	
Drug	**Interaction**
Anti-arrhythmic	Do not prescribe at the same time. Medication use increases the risk of ventricular arrhythmias if astemizole is added.
Azole antifungals (Fluconazole, itraconazole, ketoconazole, & miconazole)	**Use is contraindicated.** These increase astemizole (and terfenadine) plasma levels, which may lead to serious cardiovascular effects. [see warnings].
Fluvoxamine	**Use is contraindicated.** Increased concentration of the astemizole/ terfenadine increasing its cardiotoxicity.
Macrolide antibiotics	**Use is contraindicated.** Erythromycin coadministration increases risk of cardiac toxicity. Other macrolides may have the same risk. Loratidine antihistamine may be a safe alternative.
Tricyclic anti-depressants	Increased antimuscarinic and ventricular arrhythmia risks. Avoid use if possible.

- ***OVERDOSE:***

Symptoms: Serious ventricular arrhythmias have occurred following astemizole doses of > 200 mg, including severe forms of side effects.

Treatment: Need to induce emesis even if it has occurred spontaneously, using syrup of ipecac. Followed with activated charcoal as a slurry with water, and a cathartic to minimize absorption. Follow with supportive and symptomatic care.

- ***BRANDS:***

Hismanal (Janssen), Hismal (Eastern Chem.), Lahistan (BPC).

B) NASAL DECONGESTANTS

Decongestants are sympathomimetic amines administered directly to swollen membranes (e.g. via spray or drops), or systematically via the oral route. Oral agents are not as effective as topical products especially on an immediate basis, but generally have a longer duration of action, cause less local irritation and are not associated with rebound congestion as do topical products *(see table 4.2 & 4.3 for summary of topical and oral nasal congestion agents)*.

Treatment of nasal congestion not only relieves the discomfort, but also prevents excessive blowing, which may further irritate mucous membranes and nostrils. Topical decongestants are used to relieve nasal stuffiness in colds and allergies. It is very important to tell patient to strictly follow the decongestant's directions regarding the frequency and duration of use. When these agents are misused or overused, a rebound phenomenon (**rhinitis medicamentosa**) may occur. The nasal mucosa

becomes more congested and edematous as the drugs vasoconstrictor effect subsides.

Table – 4.2: Topical Nasal Decongestant Dosages (Drops or Sprays)

Drug	Concentration (%)	Adult dosage	Children 6-12 y	Children 2 to < 6 y
Ephedrine	0.5	2-3 (≥ 4 h.)	1-2 (≥ 4 h.)	-
Naphazoline Hydrochloride	0.05	2 (≥ 4-6 h.)	Not recommended	-
	0.025	-	1-2 (≥ 6 h.)	-
Oxymetazoline Hydrochloride	0.05	2-3 (morning and evening)	Same as adult	-
	0.025	-	-	2-3 (morning and evening)
Phenylephrine Hydrochloride	1.0, 0.5	1-2 (≥ 4 h.)	Not recommended (refer to 0.25%)	Not recommended (refer to 0.125%)
	0.25, 0.2	1-2 (≥ 4 h.)	1-2 (≥ 4 h.)	Not recommended (refer to 0.125%)
	0.125	-	-	1 drop (≥ 4 h.)
Xylometazoline Hydrochloride	0.1	2-3 (8-10 h.)	Not recommended (refer to 0.05)	Not recommended (refer to 0.05%)
	0.05	-	2-3 (8-10 h.)	2-3 (8-10 h.)

(-): There is no recommended dosage for children, except under direct supervision of physician. Only drops should be used in children under 2 to 6 years of age.

Table – 4.3. Oral Nasal Decongestant Dosages (maximum/24 hours):

Drug	Adult	Children 6 to 12 y	Children 2 to < 6 y
Phenylephrine	10 mg q. 4 h. (60 mg)	5 g q. 4 h. (30 mg)	2.5 mg q. 4 h. (15 mg)
Phenylpropanolamine	25 mg q. 4 h. (150 mg)	12.5 mg q. 4 h. (75 mg)	6.25 mg q. 4 h. (37.5 mg)
Pseudoephedrine	60 mg q. 6 h. (240 mg)	30 mg q. 6 h. (120 mg)	15 mg q. 6 h. (60 mg)

There is no recommended dosage for children under 2 years old, unless under direct medical supervision.

1) Oxymetazoline

- ***DRUG SUMMARY:***

Oxymetazoline is an imidazoline-derivative sympathomimetic agent, an autonomic nervous system, alpha-adrenergic agonist. Oxymetazoline is a longer acting topical nasal decongestant, with an effect that may last 5-6 hours or longer, with a gradual decline thereafter. It can be used twice a day. (Xylometazoline is a similar nasal decongestant).

- ***INDICATIONS:***

Relief of congestion of the upper respiratory tract. As adjunctive therapy of middle ear infections, to decrease congestion around the Eustachian ostia.

- ***CONTRAINDICATIONS:***

Hypersensitivity, and use with MAO inhibitor therapy or within 14 days of therapy.

- ***DOSAGE FORMS:***

Drops or sprays.

- ***RECOMMENDED DOSAGE:***

Adults and children > 6 yrs: 2-3 drops or 2-3 sprays of 0.05% solution into each nostril b.i.d. (q. 12 h.) for up to 3-5 days.

Children 2-5 yrs: 2-3 drops of 0.025% solution into each nostril b.i.d. for up to 3-5 days.

Directions: Administer in the morning and at bedtime. Effects appear within 30 minutes and last about 6-7 hours.

*Nasal spray is delivered with patient in upright position. Instruct patient to place spray nozzle in nostril without occluding it, and to bend head slightly forward and sniff briskly during administration.

*Lateral, head-low position is recommended for instillation of nose drops.

*Instruct patient to rinse dropper or spray tip in hot water after each use to prevent contamination of solution by nasal secretion.

*Wash hands after use, and avoid rubbing eyes with contaminated fingers, can develop anisocoria (inequality of pupil size and blurred vision).

- ***USE IN SPECIAL CASES:***

Pregnancy- Use oxymetazoline if clearly needed (Category C). It is not known if topical agents cause fetal harm.

Lactation- Exercise caution. It is not known if topical agents are secreted in breast milk.

Children- Can use the 0.025% concentration solution in children 2-6 yrs of age for **not more than 3-5 days**. There is no recommended dosage for children ≤ 2 yrs. Direct supervision of a physician is required if it is decided that it is necessary to use this medication, to monitor for any toxicity.

Renal + Liver Diseases- Use caution. There should be no hazards, if used as directed in these patients.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution with hypertensive patients as they might experience a change in blood pressure because of the added vasoconstriction.

-Use caution in special risk population, patients with hyperthyroidism, cardio-vascular disease, coronary artery disease, increased intraocular pressure. Sympatho-mimetics may cause CNS stimulation or hypotension.

- ***ADVERSE EFFECTS:***

Burning, stinging, dryness of nasal mucosa, and sneezing are common. With excessive use: headaches, light-headedness, drow-siness, insomnia, palpitations, and rebound congestion. Stop use of medication immediately if severe effects occur.

- ***INTERACTIONS:***

Overview of Oxymetazoline Drug-Drug Interaction	
Drug	**Interaction**
MAO inhibitors	Concurrent use may result in severe headache, hyper-tension, hyperpyrexia, and possibly a hypertensive crisis. Avoid use concurrently or within 14 days of MAOI therapy.

- ***OVERDOSE:***

Hypertension or rebound hypotension may occur, heart palpitations, headache and dizziness. Treat symptomatically.

- ***BRANDS:***

Alrin (Teva), Nasivin (Merck), Nosacare (Pharmacare), Rhinoclir (Agis)

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2) Pseudoephedrine

- ***DRUG SUMMARY:***

An autonomic nervous system agent, α-adrenergic and β-adrenergic agonist, sympathomimetic decongestant amine. Unlike ephedrine, it acts directly on smooth muscle, has fewer side effects, less presser action, and longer duration of action. It produces little, if any, rebound congestion or irritation that occur with nasal sprays and solutions.

- ***INDICATIONS:***

Symptomatic relief of nasal congestion associated with rhinitis, coryza, sinusitis and Eustachian tube congestion.

- ***CONTRAINDICATIONS:***

Hypersensitivity to sympathomimetic amines, severe hypertension or coronary artery disease, use within 14 days of MAO inhibitors, glaucoma, hyperthyroidism, prostatic hypertrophy. The use of sustained release tablets in children < 12 years old is also contraindicated.

- ***DOSAGE FORMS:***

Tablets, syrup (in combination with other agents).

- ***RECOMMENDED DOSAGE:***

Adult: 60 mg PO q. 4-6 h. (or 120 mg SR q. 12 h.); max. 240 mg/24h.

Child (6-12y): 30 mg q. 4-6 h.; max. 120 mg/24h.

Child: (2-6y): 15 mg q. 4-6 h.; max. 60 mg/24h.

Directions: May take with food if GI upset occurs.

*Do not exceed recommended doses, higher doses may cause nervousness, dizziness, and sleeplessness.

*The drug acts as a stimulant, advise the patient to avoid taking it within 2 hours of bedtime.

- ***USE IN SPECIAL CASES:***

Pregnancy- Give only when clearly needed (Category C). It is not known whether these agents can cause fetal harm.

Lactation- Oral pseudoephedrine has been detected in breast milk, avoid use to eliminate possible side effects to the nursing infant. No reports of side effects have been found.

Children- Safe if used as recommended.

Renal + Liver Disease- Use with caution. The medication is metabolized in the liver, and excreted in the urine, but there have been no reported risks when used as recommended.

- ***PRECAUTIONS AND WARNINGS:***

-Special populations; administer with caution to patients with hyperthyroidism, diabetes mellitus, cardiovascular disease, coronary artery disease, ischemic heart disease, prostatic hypertrophy, and increased intraocular pressure. Sympathomimetics may cause CNS stimulation and convulsions or cardiovascular collapse

-Use caution with hypertensive patients as they might experience a change in blood pressure because of the added vasoconstriction.

-Elderly (≥ 60 yrs) are more likely to experience adverse reactions to sympathomimetics. Hallucinations, convulsions, CNS depression and death have been noted. Short acting sympathomimetics may be safer than the sustained release formulation in this population.

- ***ADVERSE EFFECTS:***

Transient stimulation, tremors, anxiety, difficulty in voiding, arrhythmia, palpitation, tachycardia, nervousness, headache, dizziness, insomnia, sweating, anorexia, dry mouth, nausea or vomiting, photophobia have all been reported.

- ***INTERACTIONS:***

Same as oxymetazoline.

- ***OVERDOSE:***

Symptoms include: somnolence, sedation accompanied by profused sweating, hypotension or shock.

Treatment: For accidental overdose, refer to hospital for supportive and symptomatic care.

- ***BRANDS:***

Pseudoephedrine is mostly available in combination with other antihistamines, antitussives, analgesics or expectorants. (*Refer to price list in Appendix.*)

C) EXPECTORANTS

Expectorants are periphery-acting anti-tussives that produce their effect by increasing the volume and reducing the viscosity of bronchial secretions, thus facilitating their removal by productive cough. Use of expectorants in **clinical practice is controversial because of doubts regarding their therapeutic efficacy.** There is a lack of strong, supportive, objective data showing that an expectorant truly decreases sputum viscosity or eases expectoration. Increasing fluid intake (6-8 glasses) and maintaining adequate humidity of the inspired air are important for the production and expectoration of respiratory tract fluid mucus.

1) Ammonium Chloride

Ammonium chloride is primarily used as an acidifying agent. Allegedly, it increases the removal of respiratory tract secretions by reflex stimulation of bronchial mucous glands that result from irritation of the gastric mucosa, which makes it a common ingredient in cough mixtures. But it has questionable efficacy. In the presence of renal, hepatic or chronic heart diseases, Ammonium Cl doses of 5 gm have caused severe poisoning. Symptoms of toxicity including nausea, vomiting, thirst, rash, headache, bradycardia, mental confusion, hyperventilation, hyper-reflexia and electroencephalogram abnormalities. A relative contraindication for use in patients with hepatic, renal or pulmonary insufficiency exists. Use in diabetics should also be avoided. Doses larger than those recommended may predispose the patient to hyperammonemia and metabolic acidosis. **[Need to warn such patients who are predisposed to toxicity.]** Since ammonium Cl acidifies the urine, it may also affect the excretion of other drugs when given in large doses; (i.e. amphetamines, methadone, ephedrine, pseudoephedrine, sulfonylureas and salicylates).

The expectorant safe dosing recommen-dation to be used are;

Adults: 300 mg q. 2-4 h.

Child (6-12 y): 150 mg q. 2-4 h.,

Child (2 to < 6 y): 75 mg q. 2-4 h.

Most companies include ammonium Cl in their cough products, and list it as a non-active ingredient. Use caution in susceptible patients.

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2) Guaifenesin

- ***DRUG SUMMARY:***

Guaifenesin (glyceryl guaiacolate) is claimed to enhance the output of respiratory tract fluid by reducing adhesiveness and surface tension facilitating the removal of viscous mucus. As a result nonproductive cough becomes more productive and less frequent. There is a lack of convincing studies to document efficacy just like any other expectorant.

- ***INDICATIONS:***

For the symptomatic relief of respiratory conditions characterized by dry, non-productive cough, and in the presence of mucus in the respiratory tract.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the product, no other absolute contraindications to its use.

- ***DOSAGE FORMS:***

Syrup 100 mg/5 ml.

- ***RECOMMENDED DOSAGE:***

Adults and children (≥ 12 y): 200-400 mg PO q. 4 h.
Do not exceed 2400 mg/24h.
Child (6-12 y): 100-200 mg q. 4 h. Do not exceed 1200 mg/24h.
Child (2-5 y): 50-100 mg q. 4 h. Do not exceed 600 mg/24h.

Directions: Drug is most effective if taken q. 4 h. around the clock or during waking hours. May take dose with a full glass of water if needed.

- ***USE IN SPECIAL CASES:***

Pregnancy- No sufficient data is available. Use if clearly needed (Category C).
Lactation- Exercise caution. Use only when clearly needed.

- ***PRECAUTIONS AND WARNINGS:***

-Do not use for persistent cough such as cough that occurs with smoking, asthma or emphysema, or where cough is accompanied by excessive secretions.

- ***ADVERSE EFFECTS:***

These are uncommon, but may include: nausea, vomiting, headache, and rash.

- ***INTERACTIONS:***

Guaifenesin may increase risk of hemorrhage in patients receiving heparin therapy.

- ***OVERDOSE:***

Symptoms: Overdosage may cause nausea and vomiting.
Treatment: Induce vomiting if it has not occurred already. Use supportive and symptomatic care.

- ***BRANDS:***

Resyl (Ciba-Geigy), Robutussin (Robins Consumer).

D) ANTITUSSIVES/ COUGH SUPPRESSANTS

Cough suppressants are centrally acting antitussives, suppressing the medullary cough center. The drawbacks of prescribing cough suppressants are really outweighed by the benefits of treatments and only occasionally are useful, for example if sleep is disturbed by dry cough. Cough suppressants may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis. The use of cough suppressants containing codeine or similar opioid analgesics are **not generally recommended in children** and should be avoided altogether in those under 1 year of age.

1) Codeine

- ***DRUG SUMMARY:***

An opium derivative made by methylation of morphine. It is classified as a CNS, narcotic agent, analgesic, and antitussive. The dose required to suppress cough is lower than the doses required for analgesia.

- ***INDICATIONS:***

For suppression of cough induced by chemical or mechanical respiratory tract irritation. Also for relief mild to moderate pain since it is a narcotic analgesic.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug, acute asthma, acute alcoholism, premature infants or during labor when delivery of a premature infant is anticipated.

- ***DOSAGE FORMS:***

Tablets. Syrup in combination products.

- ***RECOMMENDED DOSAGE:***

Adult: 10-20 mg PO q. 4-6 h.; max. 120 mg/24h.
Child (6-12 y): 5-10 mg q. 4-6 h.; max. 60 mg/24h.
Child (2-6 y): 2.5-5 mg q. 4-6 h.; max. 30 mg/24h.

Not to be used in premature infants. Safety and efficacy in newborn infants have not been established.

Directions: Take with food or milk to reduce possibility of GI distress.

*****Not to be administered to patients with persistent or chronic cough; as occurs with smoking, asthma or emphysema, or where cough is accompanied by excessive secretion.

Treatment is directed toward decreasing frequency and intensity of cough, without abolishing protective cough reflex that serves the important function of removing bronchial secretions.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use (Category C). Dependence has been reported in newborns whose mothers took opiates during pregnancy. Signs such as irritability, excessive crying, tremors, fever, vomiting and diarrhea, usually appear during the first few days of life. Use only if potential benefits outweigh the potential hazards to the fetus. Also codeine may prolong labor; avoid use especially if a premature infant is anticipated.

Lactation- Exercise caution. Use when clearly indicated. Studies have reported detectable amounts of codeine in breast milk, but no adverse effects were reported with the recommended doses for cough.

Children- Do not use opiates, including codeine, in premature infants. Opiates cross the immature BBB, producing respiratory depression. Codeine should be given to infants and small children only with great caution since safety and efficacy have not been established.

Renal Disease- Use with caution. Antitussive doses are not reported to be hazardous.

Liver Disease- Use caution. The drug is metabolized in the liver, may need to reduce dose if patient can not tolerate the recommended dose.

- ***PRECAUTIONS AND WARNINGS:***

-Head injury and increased intracranial pressure; the respiratory depressant effects of codeine and their capacity to elevate cerebrospinal fluid pressure may be markedly increased in the presence of such cases. Exercise caution.

-Should not be given to patients with or at risk of developing respiratory failure.

-Drug abuse and dependence; potential of abuse is less than that of heroin or morphine, but use caution in patients with a history of drug abuse. Psychological and physical dependence, and tolerance may occur. Be alert to over-prescribing.

- ***ADVERSE EFFECTS:***

In usual oral antitussive doses, codeine has mild side effect. Nausea, vomiting, sedation, dizziness, constipation are most common. Other effects may include: CNS depression, respiratory depression, biliary tract spasms, tachycardia, palpitation, faintness, orthostatic hypotension, urinary retention, antidiuretic effect, hallucination, disorientation, lightheadedness, euphoria, weakness, convulsions, as well as allergic reactions have been reported.

Warn patients against performing tasks that require full alertness and coordination (i.e. driving or operating machines) until the full effect of the medication is known.

Instruct patients to make position changes slowly, particularly from recumbent to upright posture, and to lie down immediately if light-headedness/dizziness occur, especially in elderly patients, to avoid falling down.

- ***INTERACTIONS:***

Overview of Codeine Drug-Drug Interaction	
Drug	**Interaction**
CNS depressants, and *alcohol*	Including other opiates, general anesthetics, phenothiazines, tricyclic anti-depressants, tranquilizers; all have additive effects when given concomitantly with codeine. Avoid, or use extreme caution.

- ***OVERDOSE:***

The lethal oral dose of codeine in an adult is in the range of 0.5 to 1 g. Infants, children, and elderly are more sensitive, and comparatively intolerant.

Symptoms include CNS depression, miosis, and respiratory depression.

Treatment: Transfer immediately to the emergency room for supportive and symptomatic care. Naloxone is the antagonist of choice in narcotic agonist overdoses.

- ***BRANDS:***

Codical (Sam-On), Codeine Phosphate (Trima).

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2) Dextromethorphan HBr WHO

- ***DRUG SUMMARY:***

Dextromethorphan is a non-narcotic derivative of levorphanol classified as an antitussive. Chemically related to morphine but without the capacity to cause tolerance or addiction. It controls cough spasms by depressing the cough center in the medulla. It does not depress respiration or inhibit cilliary action. Antitussive activity comparable to that of codeine, but it is less likely to cause constipation, drowsiness, or GI disturbances.

- ***INDICATIONS:***

Temporary relief of cough spasms in non-productive coughs due to colds, pertussis (whooping cough), and influenza.

- ***CONTRAINDICATIONS:***

Hypersensitivity to dextromethorphan, or any component of the product.

- ***DOSAGE FORMS:***

Tablets, syrup.

- ***RECOMMENDED DOSAGE:***

Adult: 10-20 mg PO q. 4 h. or 30 mg q. 6-8 h.; max. 120 mg/24h.

Child (6 - 12 y); 5-10 mg q. 4 h. or 15 mg q. 6-8 h.; max. 60 mg/24h.

Child (2 - 6 y); 2.5 mg q. 4 h. or 7.5 mg q. 6-8 h.; max. 30 mg/24h.

Directions: Drink some water after administration. If GI upset occurs, the medicine may be taken with food.

*Unnecessary cough may be lessened by avoiding irritants such as smoking, dust, fumes, and other air pollutants. Humidification of air may provide some relief.

*Increasing the dose does not increase the antitussive effect, but may extend its duration of action.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use if clearly needed (Category C). No sufficient data is available.

Lactation- It is advisable to avoid the medication, unless clearly needed.

Children- Not recommended for children < 2 years of age, unless under direct medical supervision (administered in hospital or clinic).

Renal Disease- Use with caution.

Liver Disease- Use with caution.

- ***PRECAUTIONS AND WARNINGS:***

-Should not be used for persistent or chronic cough, e.g. asthma, smoking emphysema, or where cough is accompanied by excessive secretions, or to patients with risk of developing respiratory failure.

-Cases of abuse of dextromethorphan-containing cough/cold products have been reported, but there is no sufficient data to prove potential dependency on this drug.

- ***ADVERSE EFFECTS:***

Side effects are rare, but may include; dizziness, drowsiness, CNS depression, GI upset, constipation and abdominal discomfort.

- ***INTERACTIONS:***

Overview of Dextromethorphan Drug-Drug Interaction	
Drug	**Interaction**
MAO inhibitors	Dextromethorphan should not be given to patients taking MAOI. Patient may develop hypotension, nausea, myo-clonic leg jerks or coma following co-administration. Do not co-administer.

- ***OVERDOSE:***

Symptoms: Children may experience ataxia, respiratory depression and convulsion with accidental overdose. Adults symptoms include altered sensory perception, ataxia, slurred speech, and dysphoria.
Treatment: There is rapid recovery after emesis with activated charcoal.

- ***BRANDS:***

Dextromethorphan is mostly available in combination with other antihistamines, decongestants, analgesics or expectorants. *Refer to price list for products.*

E) MUCOLYTICS

Mucolytics are often prescribed to facilitate expectoration, since they reduce the viscosity of the bronchial secretions by breaking down their structure. They supposedly reduce sputum viscosity in chronic asthma and bronchitis. Experts have suggested that "**mucolytics are probably no more effective than steam inhalation** . . . A productive cough may be helped by a warm drink and/or steam inhalation" specially in the case of cough and cold medications. Available mucolytics include: acetylcysteine, carbocysteine, methyl-cysteine, and bromhexine.

1) Acetylcysteine

- ***DRUG SUMMARY:***

Acetylcysteine is a derivative of the naturally occurring amino acid L-cysteine. It is used as adjunct therapy in patients with abnormal viscid, or inspissated mucous secretions, and in pulmonary complications of cystic fibrosis, surgery, and atelectasis. Also used in acute paracetamol (acetaminophen) overdoses or toxicity. It is found in various cough/ expectorant preparations. It can be administered by mouth or by inhalation. It should be avoided in patients with hypersensitivity, or risk of gastric hemorrhage. (No contraindications if used as an antidote for poisoning cases). Safe use in pregnancy (Category B) and lactation is not established. Use extreme caution in patients with asthma (if bronchospasm progresses, the doctor needs to discontinue medication immediately). Most common side effects include nausea, vomiting, bronchospasm, rhinorrhea, and burning sensation when given as inhalation.

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2) Bromhexine

- ***DRUG SUMMARY:***

A mucolytic agent used in the treatment of respiratory disorders associated with excessive mucus. It is usually given by mouth in a dose of 4-16 mg three times a day. Safety of use in pregnancy or lactation is not established. Do not administer to patients with history of peptic ulcer disease.

F) BRONCHODILATORS & ASTHMA MEDICATION

There has been an increase in morbidity and mortality from asthma worldwide in the last decade. This has been a major concern. Expert panels were established to provide guidelines for the diagnosis and management of asthma. **Asthma is defined as an inflammatory airway obstruction that is reversible** (but not completely in some patients). It is a familial disease, inherited like other allergic disorders. It is episodic in nature, were an episode may last from a few minutes to several days. Patients with chronic bronchitis and emphysema are often described as having irreversible airway obstruction, and should be treated differently by a specialist.

Therapy is directed at preventing severe attacks and normalizing an asthma patient's lifestyle. Severe asthma can be fatal. It is characterized by persistent dyspnea poorly relieved by bronchodilators, exhaustion, a high pulse rate (usually over 110/min.), and a very low forced expiratory volume (FEV_1 or PEF < 60% predicted, and PEF variability > 30%).

The respiration is so shallow that wheezing may be absent. Such patients should be immediately taken to the emergency rooms for prompt therapy with oxygen and corticosteroids.

Treatment of asthma has been undergoing major changes in recent years with the unrevealing of specific causes at the cellular level, and production of new classes of drugs such as the leukotriene modifiers.

This chapter will discuss an overview of available products only at the primary level, and give summary of classification and updated treatment of asthma.

National Asthma Education and Prevention program has adopted a classification of Asthma severity and treatment, this classification is as follows:

-**Severe persistent:** continual daytime symptoms, frequent night symptoms, FEV1/PEF<60%.
-**Moderate persistent:** daily daytime symptoms, > 5 nights/month with symptoms, FEV1/PEF = 60-80%.
-**Mild persistent:** 3-6 days/week with symptoms, 3-4 nights/month with symptoms, FEV1/PEF > 80%.
-Mild intermittent: < 2 days/week with symptoms, < 2 nights/month with symptoms, FEV1/PEF > 80%.

Patient is classified according to the worst symptomatology that he has, and he can be moved from one scale to another depending on his symptomatology. A summary of classification of asthma is presented in table-4.4.

Pregnancy and Breast-Feeding: It is particularly important that asthma be well-controlled during pregnancy. Inhalation has particular advantage as means of drug administration during pregnancy because the therapeutic action can be achieved without the need for plasma concentrations liable to have a pharmacological effect on the fetus. Severe exacerbation of asthma can have adverse effects on pregnancy and should be treated promptly with conventional therapy, including oral or parenteral administration of corticosteroids (Prednisolone preferred) and a selective β_2-agonist. Although theophylline has been given without adverse effects during pregnancy or breast-feeding, there have been occasional reports of toxicity in the fetus and neonate.

Table 4.4: Summary of Treatment of the Different Classes of Asthma in Adults		
Classification	**Long Term Control**	**Quick Relief**
Mild intermittent	No daily medication	Inhaled β-2 agonist
Mild persistent	One daily medication • **Either inhaled corticosteroids (low dose) or cromolyn** • Sustained release theophylline: not a preferred alternative.	Inhaled β-2 agonist
Moderate persistent	Daily medication • **inhaled corticosteroid (medium dose)** or • **inhaled corticosteroid (low-medium dose)** and add either **long acting inhaled β-2 agonist,** sustained release theophylline or long acting β-2 agonists tablets especially for nighttime symptoms if needed medium-high dose inhaled corticosteroids can be used	Inhaled β-2 agonist
Severe persistent	Daily medication • **inhaled corticosteroids (high dose) and** • **either long acting inhaled β-2 agonist,** sustained release theophylline or long acting β-2 agonist tablets and • Corticosteroid tablets or syrup long term (2mg/kg/d)	Inhaled β-2 agonist

Summary of Treatment of the Different Classes of Asthma in Children		
Classification	**Long Term Control**	**Quick Relief**
Mild intermittent	No daily medication is needed	Bronchodilator either: -inhaled short acting β-2 agonist by nebulizer or spacer or chamber -oral β-2 agonist
Mild persistent	-cromolyn (nebulizer is preferred or MDI) or nedocromil (MDI only) (infants and young children usually begin with cromolyn or nedocromil) or low dose inhaled corticosteroids with spacer or aerochamber.	Bronchodilator as needed
Moderate persistent	-medium dose inhaled corticosteroid with spacer or aerochamber.	Bronchodilator as needed for symptoms up to 3 times a day
Severe persistent	-high dose inhaled corticosteroid with spacer or aerochamber -if needed add systemic corticosteroids (2 mg/kg/day) and reduce to the lowest daily or alternate–day dose.	Bronchodilator as needed for symptoms up to 3 times a day

-Adapted from: National Asthma Education and Prevention Program, National Heart, Lung and Blood Institute, Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. NIH publication No. 97-4051, July 1997, updated 2002).

1) Theophylline [WHO,P] (or soluble salt derivatives)

- ***DRUG SUMMARY:***

Theophylline is a methyl-xanthine derivative. It is classified as a broncho-dilator, respiratory and cerebral stimulant, xanthine. Unlike sympathomimetic agents, tolerance to bronchodilator effects of theophylline derivative rarely develops. Theophylline inhibits the enzyme phospho-diesterase, resulting in the relaxation of the smooth muscle of the bronchi that are constricted, thus relieving the difficulty in breathing. Because of differing theophylline content, the various salts and derivatives are not equivalent on a weight basis (refer to dosage). Theophylline is considered third line therapy because of its narrow therapeutic window. It is reserved for patients who are unresponsive to β_2-agonists or steroids.

- ***INDICATIONS:***

Prophylaxis and symptomatic relief of bronchial asthma, as well as bronchospasm associated with chronic bronchitis and emphysema. (Also used for emergency treatment of paroxysmal cardiac dyspnea and edema of CHF.)

- ***CONTRAINDICATIONS:***

Hypersensitivity to xanthines or any derivatives (caffeine), coronary artery disease or angina pectoris when myocardial stimulation might be harmful, severe renal or liver impairment.

- ***DOSAGE FORMS:***

Tablets, syrup, capsules, suppository (adults and infants).

- ***RECOMMENDED DOSAGE:***

All doses are individualized, based on lean body weight. Dosages are based and adjusted on clinical response and improvement in pulmonary function with careful monitoring of serum levels.

Monitoring of serum levels should be done during chronic therapy at 6-12 months intervals or when toxicity is suspected, it should be measured 1-2 hours after administration of immediate release products and 5-9 hours after the morning dose for sustained release formulations. Therapeutic range of **10-20 mcg/ml** (narrow therapeutic range) plasma theophylline concentration should be maintained to avoid toxicity.

(see table- 4.5,6,7 for equivalent doses, guidelines for dosing).

*Better to take **before meals**, but if GI upset occurs, can take with food, and full glass of water. Take at same time each day, and adhere to the proper intervals between doses.

*A low-carbohydrate, high-protein diet increases theophylline elimination, and a high-carbohydrate, low-protein diet decreases it. Charcoal-broiled foods may increase elimination and reduce the half-life as much as 50%.

*Do not chew or crush enteric coated or sustained release tablets or capsules, unless specific product information identifies that capsule may be opened.

*Avoid large amounts of caffeine-containing beverages; i.e. tea, coffee, cocoa, cola or large amounts of chocolate, which may increase side effects.

Table – 4.5: Theophylline Content and Equivalent Dose of Various Theophylline Salts		
Theophylline salt	**Theophylline %**	**Equivalent Dose**
Theophylline anhydrous	100	100 mg
Theophylline monohydrate	91	110 mg
Aminophylline anhydrous	86	116 mg
Aminophylline dihydrate	79	127 mg

**Drug Facts & Comparisons 2000, p. 655.*

Table – 4.6: Dosage Guidelines for Rapid Theophyllinization* (patients not receiving theophylline)			
Patient Group	**Oral Loading Dose**	**Maintenance Dose**	**Maximum Daily Dose**
Children 1 to 9 years	5 mg/kg	4 mg/kg q.6h.	24 mg/kg/d
Children 9 to 16, and young adult smokers	5 mg/kg	3 mg/kg q.6h.	20 mg/kg/d
Otherwise healthy non-smoking adults	5 mg/kg	3 mg/kg q.8h.	13 mg/kg/d not to exceed dose, or 900 mg, whichever less.
Older patients, patients with corpulmonale	5 mg/kg	2 mg/kg q.8h.	
Patients with congestive heart failure	5 mg/kg	1-2 mg/kg q.12h.	

** Drug Facts & Comparisons 2000, p. 654. European countries may use different dosing regimens.*

Table – 4.7: Dosage Adjustment After Serum Theophylline Measurement		
If serum theophylline is:		**Directions**
Too low	5 to 10 mcg/ml	Increase dose by about 25% at 3 day intervals until either the desired clinical response or serum concentration is achieved.
Within desired range	10 to 20 mcg/ml	Maintain dosage if tolerated. Re-check serum concentration at 6-12 days.
Too high	20 to 25 mcg/ml	Decrease doses by about 10%. Re-check doses after 3 days.
	25 to 30 mcg/ml	Skip next dose and decrease subsequent doses by 25%. Recheck level after 3 days.
	> 30 mcg/ml	Skip next 2 doses and decrease subsequent doses by 50%. Recheck levels after 3 days.

- ***USE IN SPECIAL CASES:***

Pregnancy- Risk-benefit evaluation, use only if clearly needed (Category C). Theophylline seems to cross the placental barrier, but is not known if it can cause fetal harm. Neonatal irritability and apnea have been reported.

Lactation- Theophylline distributes readily into breast milk. May cause irritability and other signs of toxicity in nursing infants. It might be advisable to nurse the infant just before the mother takes the drug. If side effects are apparent, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Children- Use only when necessary. Infants < 1 year of age have not been studied sufficiently, need to use extreme caution. Exercise caution in young children who cannot complain of minor side effects, and may experience toxicity. There has been some concern about the impact of theophylline on learning, attention and cognitive functions, but studies have not proven any real problems.

Renal Disease- Use with caution, drug metabolites are excreted by the kidneys.

Liver Disease- Need to use reduced doses for hepatic disease. The drug is extensively metabolized in the liver, and plasma clearance is reduced with hepatic function impairments leading to toxicity.

- ***PRECAUTIONS AND WARNINGS:***

-Status asthmaticus is a medical emergency and is not rapidly responsive to usual doses of medication. Need intensive care setting.

-Cardiac effects: Theophylline may cause dysrhythmias or worsen pre-existing arrhythmias. Any significant changes in cardiac rate or rhythm should be monitored. Use extreme caution in patients with cardiac disease.

-Use caution in patients with hypoxemia, hepatic disease, peptic ulcer disease, hypertension, alcoholism, heavy smokers, the elderly (particularly males) due to decreased plasma clearance of medication, and neonates. All are candidates for toxicity effects.

- ***ADVERSE EFFECTS:***

CNS stimulation; irritability, restlessness, insomnia, headache, tremor, palpitations, tachycardia, flushing, hypotension, nausea, vomiting, anorexia, epigastric or abdominal pain, diarrhea, activation of peptic ulcer, transient urinary frequency, kidney irritation, fever, dehydration, and in severe cases drug-induced seizures, circulatory failure or respiratory arrest.

- ***INTERACTIONS:***

Drug effects on Theophylline levels;

Agents that Decrease Level	
β-agonist sympathomimetics	
Barbiturates	Benzodiazepines
Hydantoins	Ketoconazole
Rifampin	
Smoking (cigarettes or marijuana)	
May Increase or Decrease	
Carbamazepine	
Influenza virus vaccine	
Isoniazid	Loop diuretics
Agents that Increase Level	
Allopurinol	Ca channel blockers
Cimetidine	Corticosteroids
Macrolides	
Non-selective β-blockers	
Oral contraceptives	
Thyroid hormones	

Caution should be used when using these medications with theophylline, adjust dosage of theophylline accordingly.

- ***OVERDOSE:***

Symptoms include the adverse side effects, mainly: anorexia, nausea, vomiting nervousness, insomnia, irritability, tachy-cardia, tachypnea, tonic/clonic convulsions, life-threatening ventricular arrhythmia, respiratory arrest.

Overdose with sustained release prep-arations may cause a dramatic increase in serum theophylline concentrations with time (≥ 12 hrs.). Early treatment will help but will not prevent these delayed elevated levels.

Treatment: Transport to hospital as soon as possible. If seizure has not occurred induce vomiting, even if emesis has occurred spontaneously, ipecac syrup is preferred. Take precautions against aspirations especially in infants and children. If vomiting is unsuccessful or contraindicated (patient is unconscious), need to perform gastric lavage. If seizure occurs, establish an airway; administration of oxygen may be needed. Need to provide supportive measures as required and dialysis if needed.

- ***BRANDS:***

Asthma 'T' (Sam-On), Glyphillin (Teva), Somophyllin CRT (Fisons), Theo-dur (Key Pharmaceuticals), Theopharm (JePharm) Theotard (CTI), Theotrim (Trima).

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2) Salbutamol / Albuterol [WHO,P]

- ***DRUG SUMMARY:***

Salbutamol, also called albuterol, is a synthetic sympathomimetic amine and moderately selective β_2-adrenergic agonist with comparatively long action. Classified as an autonomic nervous system agent, β-adrenergic agonist and a bronchodilator (respiratory smooth muscle relaxant). It has minimal or no effects on α-adrenergic receptors. It is effective as isoproterenol and metaproterenol, but produces more prolonged bronchodilation with little direct cardiac stimulation.

- ***INDICATIONS:***

To relieve bronchospasm associated with acute bronchospasm or chronic asthma, bronchitis, or other reversible obstructive airway disease. Prophylaxis in exercise induced bronchospasm.

- ***CONTRAINDICATIONS:***

Hypersensitivity to any component (allergic reactions are rare), cardiac arrhythmias associated with tachycardia.

- ***DOSAGE FORMS:***

Tablets, syrup, aerosol, solution for nebulizer.

- ***RECOMMENDED DOSAGE:***

Adults ≥ 12 y: *PO:* 2-4 mg t.i.d. or q.i.d. May increase, max. 32 mg/24h.
Inhaled: 1-2 inhalations q. 4-6 h.
Nebulized: 2.5-5mg q.i.d.
Children 6-12 y: *PO:* 2 mg t.i.d. or q.i.d., may increase; max. 24 mg/24h.
Inhaled: 1-2 inhalations q. 4-6 h.
Nebulized: 2.5mg q.i.d
Children < 6 y: *PO:* 0.1 mg/kg t.i.d. may be increased to 0.2 mg/kg t.i.d.,
max. 12 mg/24h.
Nebulized: 0.15 mg/kg q.i.d.

Directions: Give explicit directions for use of inhaler to the patient. Periodically check the adequacy of patient's technique and compliance, especially if no improvement is observed.

Proper nebulizer use: Dilute the dose of solution for nebulizer in sterile normal saline to a total volume of 3 ml and administer over 5-10 minutes period.

Metered dose inhaler: shake the inhaler with canister in place for 5-10 seconds, breathe out to the end of a normal breath, hold the inhaler system upright, place the mouth piece into the mouth, close the lips tightly or position the mouth piece 2-3 fingers width from the open mouth and tilt head slightly backwards. While activating the inhaler, take a slow deep breath for 3-5 seconds, hold breath for 10 sec and exhale slowly. Allow 1 min between inhalation.

*If the required effective dose fails to provide relief, it could be a sign for seriously worsening asthma, which requires reassessment of therapy. Patient should not increase the number or frequency of inhalations without medical advice.

*If the patient is to receive beclomethasone inhalation treatment, salbutamol should be administered 20-30 minutes before.

For infants and young children, inhaled medications can be delivered through aerochamber or babyhaler and to older children through spacer.

- ***USE IN SPECIAL CASES:***

Pregnancy- There are no adequate studies in pregnant women (Category C). Salbutamol may cross the placental barrier. Use if potential benefit outweighs potential risk to the fetus. Oral salbutamol has delayed pre-term labor, avoid use.

Lactation- It is not known whether salbutamol is excreted in breast milk. Use only when benefit outweighs the potential risk on the nursing infant.

Children- This drug has been used in young children even though its safety and efficacy has not been established for children < 2 yrs. old for syrup and nebulizer, 6 yrs. for tablets. Note that children appear to be more

susceptible to experience CNS stimulation; hyperactivity, excitement, and insomnia.

Renal Disease- Use with caution. The drug is eliminated in the urine in 3 days.

Liver Disease- Use with caution. Salbutamol is metabolized in the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Special risk patients; use caution with patients with diabetes mellitus, hyper-thyroidism, and severe cardiovascular disease.

-A common adverse effect associated with the oral form of drug is fine tremor in fingers, which may interfere with precision handwork. Keep informed of any unusual symptoms.

- ***ADVERSE EFFECTS:***

Tremor of the hands, anxiety, nervousness, headache, palpitation, hypertension or hypotension, dilated pupils, hoarseness, nausea, muscle cramps, and possible hypersensitivity reactions such as rash (rarely with inhaled salbutamol). The patient should be warned about such things. In severe cases can cause convulsions and reflex tachycardia.

- ***INTERACTIONS:***

Overview of Salbutamol Drug-Drug Interaction	
Drug	**Interaction**
Epinephrine*, or *other sympatho-mimetic *broncho-dilators*	An additive effect when administered with *these* might occur. Patients should be advised to avoid OTC drugs, such as cold remedies, without consulting a doctor or pharmacist.
Beta-adrenergic blockers	These antagonize the effects of sympathomimetics. Do not administer both medications together.
Tricyclic anti-depressants	May potentiate the action of sympathomimetics on the vascular system, use caution.

- ***OVERDOSE:***

Symptoms due to inhalation include an exaggeration of the side effects listed in adverse effects. Seizures, hypokalemia and hypertension may result.

Treatment includes general supportive measures. Sedatives (barbiturates) may be given for restlessness. Use of a cardio-selective β-receptor blocker (i.e. metoprolol) is suggested, bearing in mind the danger of inducing an asthmatic attack. Dialysis is not appropriate.

Symptoms due to oral absorption; palpitation, tachycardia, heart block, delirium, chills, nausea and vomiting, as well as the above symptoms can occur.

Treatment: Emesis, gastric lavage or charcoal may be useful following overdose with the oral agent. Need to use supportive measures.

- ***BRANDS:***

Aerolin (3M), Asmalin (Agis), Fedral (Eastern Chem.), Salbuvent (Leiras), Ventocare (Pharmacare), Ventolin/ Volmax (Glaxo), Ventomin (Megapharm).

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3) Cromolyn [WHO,P] (Cromoglycate) Sodium

- ***DRUG SUMMARY:***

Cromolyn sodium, also known as cromoglycate, is a synthetic antiasthmatic, antiallergic, mast cell membrane stabilizer. It has no antichlolinergic, antiinflam-matory, or vasoconstrictor activity. **It is of no value in the treatment of an acute attack/quick relief**. Regular inhalation can reduce the incidence of asthma attacks, and allow dosage reduction of bronchodilators and oral corticosteroids, and is best used for the prevention of exercise induced asthma especially in children.

- ***INDICATIONS:***

Primarily used for prophylaxis of mild to moderate seasonal and perennial bronchial asthma and allergic rhinitis. Also used for prevention of exercise related broncho-spasm (prevent bronchoconstriction), prevention of acute bronchospasm induced by known pollutants or antigens. Used as

ophthalmic preparations for allergic ocular disorders.

- ***CONTRAINDICATIONS:***

Hypersensitivity to cromoyln or any of its components.

- ***DOSAGE FORMS:***

Inhalation, syrup.

- ***RECOMMENDED DOSAGE:***

See table-4.8.

Directions: It is important to inform the patient that **effectiveness of therapy depends upon administration at regular time intervals.**

*Onset of action requires 1 week for full effectiveness. Duration of effect lasts 4-6 hrs., and may last as long as 2 weeks.

*A trial of 8-12 wks. should be conducted before determining that cromolyn is ineffective.

*Treatment with cromolyn 15 minutes before doing protracted exercises, it reportedly blunts the effects of vigorous exercise as well as cold air.

*Advise patient to clear as much mucus as possible before inhalation treatments.

*Inform patient that throat irritation, cough, hoarseness can be minimized by gargling with water. Drinking a few swallows of water will help.

*Cromolyn does not eliminate the continued need for therapy with bronchodilators, expectorants, antibiotics, or corticosteroids, but the amount and frequency of use of these medications may be reduced.

Table - 4.8: Recommended Doses of Cromolyn

(Aerosol inhaler)	**Asthma**	**Bronchospasm‡**
Adults and children ≥ 5 y	2 puffs inhaled, 4 times a day	2 sprays inhaled 10-15 min before exposure to the precipitating factor
Children ≤ 4y	Safety and efficacy has not been established (Ketotifen may be used under a specialist's supervision)	
Nebulizer solution & Inhalation capsules via spinhaler	**Asthma**	**Bronchospasm‡**
Adults and children (> 5 y for capsules, and ≥ 2 y for nebulizer solution)	20 mg (1 amp. or 1 cap.) 4 times a day at regular intervals	20 mg (1 amp. or 1 cap.) No more than 1 hour before exposure to the precipitating factor.

‡ *Bronchospasm due to exercise or environmental agents.*

** Drug Facts & Comparisons 2000, p. 681.*

- ***USE IN SPECIAL CASES:***

Pregnancy- Use Cromolyn only when benefit outweighs potential risk. Safe use during pregnancy has not been established. Animal studies have demonstrated adverse fetal effects (Category B).

Lactation- Use caution. Safety for use in nursing mothers has not been established.

Children- Safety and efficacy have not been established for aerosol in children < 5 y. and for nebulizer in < 2 y. Oral use should be cautiously used in children < 2 y. under direct pediatrician's supervision.

Renal + Liver Disease- Decrease of dose or discontinuation may be advisable in severe cases of renal or hepatic impairment.

- ***PRECAUTIONS AND WARNINGS:***

-Cromolyn has no role in the treatment of acute asthma, make sure to inform the patient about this.

- ***ADVERSE EFFECTS:***

Dizziness, headache, lacrimation, rash, joint pain and swelling, nausea, nasal itching or burning, sneezing, dry or irritated throat, urinary frequency, and cough have all been reported.

- ***INTERACTIONS:***

No interactions have been reported.

- ***OVERDOSE:***

Stop administration of medication. In accidental overdose, no action other than medical observation should be necessary.

- ***BRANDS:***

Cromunal Inhaler (Agis), Lomudal Spin Capsules (Fison), Lomudal Nebuliser Solution (Fisons), Nalcrom Oral Capsules (Fisons), Vicrom Inhaler (Fisons).

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4) Beclomethasone Dipropionate WHO,P

- ***DRUG SUMMARY:***

A synthetic corticosteroid structurally related to hydrocortisone, with potent glucocorticoid (anti-inflammatory) and weak mineralocorticoid activity. Unlike hydrocortisone, therapeutic doses do not suppress the hypothalamic-pituitary-adrenocortical function or produce other systemic effects. Because asthma is predominantly an inflammatory disease, inhaled corticosteroids are becoming important in chronic asthma therapy. **They are not to be used during an acute asthma attack** because they don't give fast relief like salbutamol. They are not to be used for chronic bronchitis or emphysema either.

- ***INDICATIONS:***

Oral inhalation to treat chronic asthma adjunctively with other therapy (sympatho-mimetics, xanthines), when these are insufficient in controlling asthma. Relief of symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment. Allergic and vasomotor rhinitis.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug or any component of the product.

Untreated localized infections involving the nasal mucosa (i.e. fungal infections of *Candida albicans*), and status asthmaticus.

- ***DOSAGE FORMS:***

Aerosol (50 mcg/metered dose: 1-inhalation), nasal spray, inhalation caps.

- ***RECOMMENDED DOSAGE:***

Refer to table 4.4.

★For inhalation for asthma;

Adults:

Low dose: 200-500 mcg/day (4-10 puffs) in 2-4 divided doses

Medium dose: 500-800 mcg/day (10-16 puff) in 2-4 divided doses

High dose: > 800 mcg/day (16 puffs) in 2-4 divided doses

Max. 20 inhalations/24 h.

Children (<12 yrs):

Low dose: 100-300 mcg/day (2-6 puffs) in 2-4 divided doses.

Medium dose: 300-600 mcg/day (6-12 puffs) in 2-4 divided doses.

High dose: > 600 mcg (> 12 puffs)

(200 mcg/dose is not indicated for children).

★ ***For allergic Rhinitis;***

Adults: 1 spray in each nostril b.i.d. to q.i.d.
Children (6-12 yrs): 1 spray in each nostril 3 times a day
(< 6 yrs): no recommended dosage since no sufficient data is available.

Directions: Clear nasal passages of secretions prior to use. If nasal passages are blocked, use a decongestant before administration to ensure adequate penetration of the spray.
*Use the bronchodilator (salbutamol) several minutes before inhaling the corticosteroid, to enhance penetration of the steroid into the bronchial tree.
*Effects are not immediate and benefit requires regular use and usually occurs within 1-4 weeks.

- ***USE IN SPECIAL CASES:***

Pregnancy- Topical administration of recommended dosage is unlikely to achieve significant systemic levels; however, use these agents during pregnancy only if the potential benefits outweigh the potential hazards to the fetus (Category C).
Lactation- Use caution when administering to nursing women. It is not known whether these inhaled drugs are excreted in breast milk.
Children- the most recent guidelines issued by the National Asthma Education & Prevention Program use this drug in children < 6 yrs., even though there is no safety and efficacy reports for use; therefore the drug should be used with caution. Growth retardation does not seem to be a problem associated with inhalation administration in recommended doses. Spacer devices may improved delivery in this age group, and reduce possible adverse effects of the inhaled corticosteroid.

- ***PRECAUTIONS AND WARNINGS:***

-Localized fungal infections with *Candida albicans* or *Aspergillus niger* have occurred in mouth, pharynx and occasionally in the larynx. Decrease or discontinue aerosol steroid treatment and use appropriate antifungal therapy.

- ***ADVERSE EFFECTS:***

Sneezing after administration; rarely dryness and irritation of nose and throat, and epistaxis. Hoarseness and oral candidiasis may occur, these effects may be minimized by using a spacer device or by rinsing the mouth after each usage.

- ***INTERACTIONS:***

No major interactions have been reported when using the inhalation in the recommended doses.

- ***OVERDOSE:***

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hyper-cortisolism may occur, including, very rarely, menstrual irregularities, acneiform lesions and cushingoid features. If such changes occur, discontinue slowly, consistent with accepted procedures for discontinuing oral steroids.

- ***BRANDS:***

Bacloforte Inhaler (Glaxo), Beconase Nasal Aerosol (Glaxo), Becotide Inhaler (Glaxo), Viarex Inhaler (Schering USA).

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5) Prednisolone [WHO,P]

Refer to the Endocrine chapter under prednisone for further details.

Acute attack of asthma should be treated with short course of oral corticosteroid
Dose in acute asthma: 1-2 mg/kg/day PO in 2-3 divided doses for 5-7 days. No need to taper it if it is used less than 1 week. Some schools recommend a short course of 3-5 days, given once in the morning with no tapering (Nelson, 2001).
Alternate day administration has not been successful in the management of asthma because control tends to diminish during the second 24 hours. Dosage should always be titrated to the lowest dose that control symptoms.

Patients who have been taking long-term oral corticosteroids can be transferred to an inhaled product, but the transfer should be done slowly with gradual reduction in the oral dose, at a time when the asthma is well controlled.

Chapter 5: ANTI-INFECTIVE DRUGS

A) ANTI-BACTERIALS
1. **Penicillins**
2. **Cephalosporins**
3. **Tetracyclines**
4. **Macrolides**
5. **Sulphonamides and Trimethoprim**
6. **Nitrofurantoin (UTI)**
7. **Nalidixic Acid (UTI)**
8. **Fluoroquinolones (UTI)**

B) ANTI-TUBERCULOSIS
1. **Isoniazid**
2. **Rifampicin**
3. **Pyrazinamide**
4. **Ethambutol**

C) ANTI-PARASITICS
1. **Metronidazole**
2. **Diloxanide Furoate**
3. **Mebendazole**
4. **Niclosamide**
5. **Albendazole (hydatid disease)**

D) ANTI-FUNGALS
1. **Nystatin**
2. **Miconazole**
3. **Griseofulvin**

C) ANTI-VIRALS
1. **Acyclovir**

ANTI-INFECTIVES

Anti-infectives are those agents that are used for the treatment of infections by suppressing or destroying the causative microorganisms (bacteria, mycobacteria, fungi, protozoa, or viruses).

Anti-infective agents should be used only when:
a. A significant infection has been diagnosed or is strongly suspected.
b. An established indication for prophylactic therapy exists.

Abuse of these agents causes superinfections, cross-sensitivity and cross-resistance, resulting in inappropriate treatment and in consequent advserve reaction in adition to wastage of money.

DEFINITIONS:

◊ ***Bacteriostatic agents:*** Agents that inhibit the growth of the microorganisms by producing reversible changes. This delay in the growth will give the immune system the chance to get rid of the microorganism.

◊ ***Bactericidal agents:*** Agents that kill the microorganism.

(Being a bactericidal or a bacteriostatic agent depends on the mechanism of action of the antibacterial agent and on its concentration.)

◊ ***Narrow spectrum:*** The range of activity for agents that kill the micro-organism is small. It affects 1-2 classes of micro-organisms only. For example, Penicillin-G affects G+ve organisms and *Neisseriae*.

◊ ***Broad spectrum:*** The range of activity extends to many micro-organisms. For example, Tetracyclines depress G+ve, G-ve, Rickettsiae and Chlamydiae.

Separation between narrow and broad-spectrum activity is not clear due to the emergence of many resistant strains due to the overuse of these antibiotics. *Broad-spectrum antibiotics should be restricted to treatment of specific infections caused by a few organisms or even a single species of organism.* The property of broad specification should not be confused with a free license for broad-nonspecific use.

◊ ***Superinfection (suprainfection):*** Is the appearance of both microbiological and clinical evidence of a new infection with pathogenic microorganisms or fungi not sensitive to the used drugs during antimicrobial treatment of a primary disease. The body's natural resistance is compromised, making it more susceptible to secondary infections by more dangerous strains.

◊ ***Auto-infection:*** Infection by an organism existing within the body or transferred from one part of the body to another.

ABUSE OF ANTIMICROBIAL AGENTS:

Antibacterials are valuable drugs if used appropriately. They are very effective in treating infections if used in appropriate doses, at appropriate intervals and for the appropriate period of time against sensitive microorganisms.

They **should not** be used in the following cases:
1. To treat all infections (e.g. viral infections or nonspecific inflammation).
2. For minor infections (e.g. superficial bruises).
3. Just because it is a new agent on the market, while there is already another effective and cheaper alternative in use.

BACTERIAL RESISTANCE:

Antimicrobial agents are loosing their effectiveness because of the spread of drug-resistant strains. Therefore, there might come a time when such agents are no longer useful to combat diseases.

The problem of ***microbial resistance*** is global and is the result of widespread and indiscriminate use of antimicrobial drugs in man, animal and agriculture. Some bacteria are naturally resistant to certain antibiotics (e.g. S*taphylococcus*), but often resistance is acquired. Bacteria can become resistant by incorporating a "resistance factor" into their genes to render the antibiotic ineffective. This can pass quickly to other bacteria and this is called **cross-resistance**. **Multiple resistance**, where bacteria are resistant to several antibiotics, can also be transferred from one species to another (i.e. *Mycobacteria*).

Emerging bacterial resistance is increasing world wide. For example, methicillin resistant S*taph. aureous* (MRSA), vancomycine resistant staphylococcus, and S*trep.* pneumonia resistant to penicillins. Culture analysis is required to identify proper treatment in these cases.

Antibiotics given concurrently are useful in very specific circumstances (e.g., as part of a mixed drug treatment in tuberculosis). Fixed-ratio combinations of antibiotics (other than co-trimoxazole) have few indications. The US FDA has withdrawn almost all fixed dose combinations. There is only one drug kept (co-trimoxazole) on the WHO list of essential drugs. According to the WHO, *"Special mention must be made of the use of preparations containing two or more antibiotics in fixed ratio. Their spectrum of activity is often so wide that they have undesirable effects on the body, few of them have notable therapeutic advantages and they are generally costly."*

SELECTING AN ANTI-INFECTIVE AGENT:

When you want to choose an anti-infective agent, you should take into consideration the following parameters:

a. ***The spectrum of activity*** of the anti-infective agent: It should be active against the causative pathogen. This can be known by carrying the susceptibility tests or by a good clinical experience in treating a given syndrome that will help in suggesting a potential effective agent.

b. ***Patient factors*****:** These factors play a very important role in the selection of a specific anti-infective agent, determination of the appropriate drug dosage and route of administration,...etc. Those factors include:

1. History of drug allergy or adverse reactions. Anaphylaxis or reactions due to immunoglobulin E (IgE) may be life threatening when taking penicillins.

2. Age: A drug's pharmacokinetic properties vary widely in patients of different age groups.

3. Underlying disease:

-A pre-existing kidney and liver disease.
-CNS disorder.
-Neuromuscular disorders.

4. Immunological status: Patients with impaired immune system require a bactericidal agent rather than a bacteriostatic one.

5. Pregnancy and lactation.

6. Genetic traits.

7. Presence of a foreign body: It has been found that the presence of prosthetic joints or valves, cardiac pacemakers, and various internal shunts may reduce the effectiveness of many anti-infective agents.

DURATION OF ANTI-INFECTIVE THERAPY:

Acute cases: Treatment of acute uncomplicated infections generally should continue until the patient has been afebrile and asymptomatic for at least 72 hours (minimum 5 days in most cases). Other cases as in Strep. throat (*Streptococcal* pharyngitis) should be treated for 7-10 days. Some infections require a proof of eradication by culture.

Chronic cases: Treatment of chronic infections (e.g., endocarditis, osteomyelitis) may require a longer duration (4 to 6 weeks), with a follow-up culture analysis afterwards.

LACK OF THERAPEUTIC EFFECT-IVENESS:
This problem arises due to one or more of the following reasons:

a. **Misdiagnosis (inappropriate indication):** Either a doctor's or a lab's error of identified organism (the causative agent of the specific infection).
b. **Improper drug regimen:** Either the dose or the route of administration, or dosing frequency, or the duration of therapy is inappropriate.
c. **Inappropriate choice of antibiotic agent:** Occurs when the patient's factors and the agent's spectrum, or the agent's pharmacological properties, are not taken into consideration or when another agent might be more suitable for the case.
d. **Using a combination of bacteriostatic and bactericidal agents:** Each one will eliminate the effect of the other. Bactericidal agents need the microorganism to be active in order to kill it while a bacteriostatic agent inhibits the growth of the microorganisms.
e. **Microbial resistance.**
f. **Unrealistic expectations:** For example, fever should not be treated by antibiotics since it may occur due to other non-infectious causes. In cases where surgical drainage is required or renal calculi are present, antibiotic failure is expected.
g. **Infection by two or more micro-organisms** (mixed infection).
h. **Improper formulation** of the final dosage form, the raw materials quality and storage, or improper manufacturing procedures; such as compression and coating, that will interfere with the bioavailability of the final product.
i. **Patient compliance:** Patients frequently discontinue antibiotic therapy when they feel better. Unfortunately these individuals may then self-prescribe the remaining antibiotic for themselves or for others at some other time. On the other hand patients might forget to take all of the scheduled doses or find it difficult to wake up for a dose. All of these problems with patient compliance might lead to lack of therapeutic effectiveness.
j. **Unpleasant side effects** that the patient cannot handle for example diarrhea, constipation, stomach upset ...etc.

STORAGE OF THE ANTI-INFECTIVE AGENTS:
Generally, antibiotics should be stored in a cool dry place and protected from sunlight as they undergo degradation in high temperatures. Most suspended forms should be kept in the refrigerator after being mixed with water (check individual packages).

EXPIRATION DATE OF THE ANTI-INFECTIVE AGENTS:
Tablets, capsules: As indicated on the box.
Dry suspensions: The expiry date that is indicated on the box is for the dry powder before suspending or diluting with purified water.
After dilution: ***Normally, the bottle of medication should be used within 5-7 days. Refer to the label on the bottle. If the diluted suspension lasted for more than the assigned time duration, this might be an indication of misuse or wrong dilution. The suspension left should not be used after 7-14 days from the day of dilution (always check the manufactures label).***

A) ANTI-BACTERIALS

Antibacterials are divided into subgroups, and are presented as such: Penicillins, cephalosporins, tetracyclines, macrolides, sulphonamides and trimethoprim, and antibiotics used in urinary tract infection (UTI).

1) Penicillins (β-Lactam)

Agents of this group are characterized by the presence of a β–lactam ring in their structure. This ring is the one responsible for their activity.

Penicillins are the drugs of choice for the treatment of a wide variety of infections caused by various susceptible micro-organisms. The three major groups of penicillins are:

a. Benzylpenicillin & phenoxymethyl-penicillin (natural penicillin)
b. Cloxacillin & flucloxacillin (penicillinase resistant penicillin)
c. Ampicillin & Amoxicillin (amino-penicillin)

Penicillins are bactericidal agents that produce their antibacterial activity via inhibiting the synthesis of the bacterial cell wall.

a) Benzylpenicillin WHOP & Phenoxymethyl penicillin WHOP

- ***DRUG SUMMARY:***

These two are known as the natural penicillins. They are the first two penicillins that were discovered and are still in use. Natural penicillins are narrow spectrum antibiotics and are only active against facultative gram-positive cocci, rods and gram-negative cocci. Several anaerobic gram-negative rods are sensitive to penicillin, with the notable exception of *Bacteroides fragilis*.

Benzylpenicillin (Pen. G) is the drug of choice in streptococcal, pneumococcal, gonococcal, and meningococcal infections. It is also used in anthrax, diphtheria, gas-gangrene, leptospirosis, syphilis, tetanus, yaws, and in the treatment of lyme disease in children. It is inactivated by the gastric fluids, and absorption from the gut is low; therefore it is best given by injection. In addition to the use of Pen. G as sodium or potassium salts (soluble Pen. G), it is also available in two other salts that are commonly used. They are:

a- Procaine penicillin: a sparingly soluble salt of benzylpenicillin. It is used in intra-muscular depot preparations that provide therapeutic tissue concentrations for up to 24 hrs. It is the preferred choice for the treatment of syphilis, but neurosyphilis requires special consideration.

b- Benzathine penicillin: a benzylpenicillin salt with a very low solubility, giving a prolonged action after intramuscular injection. Its duration of action is 20 days.

Phenoxymethyl penicillin (Pen. V) has a similar antibacterial spectrum as Pen. G, but it is less active. It is gastric acid stable so it is suitable for oral administration. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations are variable.

- ***INDICATIONS:***

Benzylpenicillin is mainly indicated for the treatment of: throat infections, otitis media, streptococcal endocarditis, meningococcal and pneumococcal meningitis (if caused by susceptible microorganism), and as a prophylactic agent after limb amputation. Also it is used in combination with other agents if more than one organism are suspected.

Phenoxymethyl penicillin is indicated principally for respiratory tract infections in children, for Streptococcal tonsillitis and for continuing treatment after one or more injections of Pen. G when clinical response has begun. It should not be used for meningococcal or gonococcal infections. It is used prophylactically against rheumatic fever following streptococcal infections.

- ***CONTRAINDICATIONS:***

They are contraindicated in the case of hypersensitivity to any of the penicillins or cephalosporins. Procaine penicillin is also contraindicated in the case of hyper-sensitivity to procaine or any other "caine-type" local anesthetic.

- ***DOSAGE FORMS:***

Benzylpenicillin: vial.
Phenoxymethyl penicillin: tablet, suspension.

Directions: ***It is recommended that performance of a skin sensitivity test as well as taking a good history, before giving penicillins be done; adrenaline, dexa-methasone and aminophylline injections***

should readily be available for treatment in case of anaphylactic shock. *(Reported incidence of anaphylactic shock is between 0.015-0.04%.)*

Food increases the breakdown of such penicillins in the stomach. These agents are best taken on an empty stomach either one hour before meal or two hours after.

- ***USE IN SPECIAL CASES:***

Pregnancy- Natural penicillins cross the placenta with low concentrations, and in general are safe during pregnancy (Category B). Nevertheless, these agents should be used only when it is clearly indicated.

Lactation- Compatible. Penicillins are excreted in breast milk in low concentrations; use may cause diarrhea, candidiasis or allergic response in the nursing infant.

Liver diseases- Use with caution.

Kidney diseases- Cautious use, since the kidney excretes penicillins. Avoid benzyl-penicillins in renal failure.

- ***PRECAUTIONS AND WARNINGS:***

Caution should be taken in case of: history of or suspected allergy (asthma, eczema, hay fever, hives), myasthenia gravies, epilepsy, neonates, young infants.

If Pen. G Na is to be administered, take caution in patient with restricted Na intake.

Benzylpenicillins may cause convulsions after high doses by IV or in renal failure.

- ***ADVERSE EFFECTS:***

For most people it is one of the safest drugs.

Some side effects that have been reported: in the case of parenteral penicillin, injection site reactions might occur. Electrolyte disturbances might occur with penicillin-G Na and K salts due to accumulation of these salts in the body.

In the case of phenoxymethyl penicillin one might suffer from the following side effects: Nausea, vomiting, diarrhea, epigastric distress, hypersensitivity reactions (flushing, pruritus, urticaria or other skin eruptions, eosinophilia, anaphylaxis), hemolytic anemia, leukopenia, thrombo-cytopenia, neuropathy, superinfections.

- ***RECOMMENDED DOSAGE:***

Penicillin Derivative	Indication	Age	Route of administ-ration	Dose
Benzyl-penicillin (Pen. G)	Moderate to severe infections*	Adult	IV/IM	1.2-2.4 million IU divided q. 4-6 h.
		Child	IV/IM	25,000-300,000 IU/kg divided q. 4 h.
	If meningococcal disease is suspected GP are advised to give a single injection of benzyl-penicillin before sending the patient to the hospital	Adult	IV/IM	1.2 g
		> 10 y.	IV/IM	As for adults
		Child; 1-10 y.	IV/IM	600 mg
		Infants	IV/IM	300 mg
Benzathine penicillin	Mild to moderate infections * (including tonsillitis)	Adult	IM	1,200,000 IU once/d
		Child	IM	> 27 kg: 900,000 IU once/d. < 27 kg, or < 5 yrs: 300,000-600,000 IU single dose.
	Syphilis	Adult	IM	< 1 y duration: 2,400,000 IU as single dose. > 1 y duration: 2,400,000 IU/wk for 3 wk.
		Child	IM	Congenital: 50,000 IU/kg as single dose.
	Prophylactic for rheumatic fever	Adult	IM	1,200,000 IU every 4 weeks
		Child	IM	1,200,000 IU once for prevention, and every 3-4 weeks for prevention of recurrence.
Procaine penicillin	Moderate to severe infections *	Adult	IM	600,000-1,200,000 IU once/day for 10-14 days.
		Child	IM	300,000 IU (0.3 g) once/day
	Pneumococcal Pneumonia	Adult	IM	600,000 IU q. 12 h.
	Uncomplicated Gonorrhea (if sensitive to penicillins)	Adult	IM	4,800,000 IU divided between two different injection sites at one visit, preceded by 1 g of probenecid 30 min. before inj.
	Syphilis	Adult	IM	Primary, secondary, latent: 600,000 IU/day for 8 days. Late latent, tertiary, neurosyphilis: 600,000 IU /day for 10 to 15 days.
		Child	IM	500,000-1,000,000 IU/m^2, once/day.

Phenoxy-methyl penicillin (Pen. V)	Mild to moderate infections *	Adult	PO	125-500 mg q. 6 h.
		Child < 12 y	PO	15-50 mg/kg/d in 3-6 divided doses.
	Endocarditis Prophylactic	Adult	PO	2 g 30-60 min. before surgical procedure; then 500 mg q. 6 h. for 8 doses.
		Child	PO	< 30 kg; 1 g 30-60 min. before procedure; then 250 mg q. 6 h. for 8 doses.

** Moderate to severe infections include: Otitis media, Streptococcal throat infections, Meningococcal and Pneumococcal Meningitis, and Strep.Endocarditis.*

- ***INTERACTIONS:***

Overview of Penicillins Drug-Drug Interactions	
Drug	**Interaction**
Erythro-mycin	Coadministration effect of a penicillin and erythromycin is unpredictable. Some studies have shown antagonist effect, while others showed a synergistic effect when bactericidal effects are desirable. Use combination only when either drug alone has failed.
Oral contra-ceptive	Pen. G decreases the efficacy of these agents. Use additional methods (e.g. condoms).
Potassium sparing diuretics	May cause hyperkalemia with Pen. G potassium. Avoid concomitant use.
Probenecid	It decreases renal elimination of penicillins producing higher and more prolonged plasma concentration. This is beneficial in treatment of gonorrhea.

Large doses of penicillin may cause false positive test results with Benedict's solution, in urine glucose test; but not with glucose oxidase method.

- ***OVERDOSE:***

This may arise with the use of massive doses of IV penicillin (40 to 100 million units/day). Penicillins overdose can lead to neuromuscular hyper-excitability or convulsive seizures. It is more commonly to occur in patients with severe renal impairment.

Symptoms may include: agitation, confusion, hallucinations, stupor, coma, seizures, and encephalopathy. Hyper-kalemia is also possible.

Management is by symptomatic treatment. Hemodialysis may be used in severe cases.

- ***BRANDS:***

Bepen V.K. (BPC), Fenoxypen (Novo Nordisk), Mega (Rafa), Rafapen V-K (Rafa), Rafapen Oracillin (JePharm)

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b) Cloxacillin [WHO,P] & flucloxacillin

(Penicillinase resistant penicillins)

- ***DRUG SUMMARY:***

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases.

Cloxacillin and **flucloxacillin** are not affected by such enzymes, so they are effective in infections caused by penicillin resistant staphylococci, but they are less potent than Pen. G against penicillin sensitive microorganisms, and generally ineffective against G-ve bacteria and methicillin resistant staphylococci. The only difference between cloxacillin and flucloxacillin is that flucloxacillin has a higher bioavailability than cloxacillin after oral administration. Another two examples of this group are **Methicillin** and

Temocillin. However, only the first two will be discussed.

Notes: Sulbactam is another β-lactamase inhibitor that is used in combination with ampicillin. Two commonly used combinations in the market are **ampicillin** with **flucloxacillin** (Megacare, Magnicillin) and **amoxicillin** with **cloxacillin** (Clamoxin).

- ***INDICATIONS:***

Cloxacillin and flucloxacillin are indicated for the treatment of infections caused by penicillinase producing Staphylococci.

- ***CONTRAINDICATIONS:***

Hypersensitivity to penicillin.

- ***DOSAGE FORMS:***

Cloxacillin: Capsules and suspension.
Flucloxacillin: Not available in a separate formulation, but as combination with ampicilin in Capsules.

- ***RECOMMENDED DOSAGE:***

Mild to Moderate Upper Respiratory & Localized Skin and Soft Tissue Infections	
Adults and children (> 20 kg)	250 mg q. 6 h.
Children (< 20 kg)	50 mg/kg/day in equally divided doses q. 6 h.
Severe Infections (Lower Respiratory Tract or Disseminated Infections)	
Adult and children (> 20 kg)	500 mg q. 6 h.
Children (< 20 kg)	100 mg/kg/day in equal doses q. 6 h.

Another suggested cloxacillin dosage for infants and children is 50 to 100 mg/kg/day, up to a maximum of 4 g/d, divided q. 6 h.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly indicated (Category B).
Lactation- Use with caution; safety not established, but it is excreted in breast milk.
Neonates- Safety not established.
Liver diseases- Use with caution since they are metabolized in the liver.
Kidney diseases- Use with caution since they are primarily excreted in the urine.

- ***PRECAUTIONS AND WARNINGS:***

Cautious use in history of or suspected allergy (asthma, eczema, hives, hay-fever), renal or hepatic function impairment, history of allergy to cephalosporins.

- ***ADVERSE EFFECTS:***

GI: Nausea, vomiting, flatulence, diarrhea.
Hematologic: Eosinophilia, leukopenia, agranulocytosis.
Hypersensitivity: Pruritus, urticaria, rash, wheezing, sneezing, chills, drug fever, anaphylaxis.
Others: Super-infections.

- ***INTERACTIONS:***

Refer to penicillin drug-drug interactions.

- ***OVERDOSE:***

Refer to penicillin G.

- ***BRANDS:***

Cloxapen (Eastern Chem.), Loxavit (Vitamed), Orbenil (Teva).

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c) Ampicillin WHO,P & Amoxicillin WHO,P (aminopenicillins)

The commonly used penicillins are **ampicillin** and **amoxicillin.** In our community, amoxicillin is mostly used. An important drug in this group is Co-amoxiclav (combination of amoxicillin and clavulanate) which will be discussed later. Other examples of this group are **bacampicillin** and **pivampicillin**, which are esters of ampicillin.

- ***DRUG SUMMARY:***

Aminopenicillins are active against some G+ve and G-ve organisms but inactivated by penicillinases, including those produced by *Staphylococcus aureus,* and by common G-ve bacilli such as *Escherichia coli*. International studies indicate that all Staphylococci, 50% of *E. coli* strains and 15% of *Haemophilus influenzae* strains are now resistant.
Amoxicillin is a derivative of ampicillin that differs only by one hydroxyl group.

Unlike ampicillin it can be given 3 times daily without regard to food.

- ***INDICATIONS:***

They are principally indicated for the treatment of chronic bronchitis and mild ear infections, both of which are usually due to *Streptococcus pneumoniae* and *Haemophilus influenzae.* They are also indicated for: urinary-tract infections, otitis media, sinusitis, chronic bronchitis, invasive salmonellosis, and gonorrhea. Amoxicillin is also used for typhoid fever and endocarditis prophylaxis.

- ***CONTRAINDICATIONS:***

They are contraindicated in the case of hypersensitivity to penicillins.

- ***DOSAGE FORMS:***

Capsules, suspensions and injections.

- ***RECOMMENDED DOSAGE:***

These are shown in table-5.2.

Directions: Absorption of ampicillin is affected by the presence of food in the stomach, so it should be taken one hour before or two hours after the meal. But this is not the case of amoxicillin that is not affected by the presence of food, so it can be given without regard to food.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use if clearly needed, risk-benefit must be considered (Category B). Animal reproductive studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Penicillins in general have been considered safer than other antibiotics in pregnancy. Use lowest effective dose when needed.

Lactation- Compatible in general. They are excreted in breast milk, use may lead to sensitization of infants; therefore, risk-benefit must be considered.

Liver disease- It can be given safely.

Kidney disease- Caution use in the case of severely impaired renal function. Increase dosing interval to 12 hrs. if creatinine clearance < 10 ml/min.

- ***PRECAUTIONS AND WARNINGS:***

Avoid use in patients with a history of or suspected allergy (hives, eczema, hay fever, asthma), severely impaired renal function, and with history of cephalosporin allergy.

Table – 5.2: Recommended Doses of Ampicillin and Amoxicillin[#]

Ampicillin			
Systemic infections	Adult	PO	250-500 mg q. 6 h.
		IM/IV	250 mg - 2 g q. 6 h.
	Child	PO	25-50 mg/kg/d divided q. 6 h.
		IM/IV	25-100 mg/kg/d divided q. 6 h.
Meningitis	Adult	IV	150-200 mg/kg/d divided q. 4-6 h.
	Child	IV	Same as for adult
Gonorrhea	Adult	PO	3.5 g with 1 g probenecid x 1
		IM/IV	500 mg q. 8-12 h.
Amoxicillin			
Mild to moderate infections[↗]	Adult	PO	250-500 mg q. 8 h.
	Child	PO	20-40 mg/kg/d divided q. 8 h.
Gonorrhea	Adult	PO	3 g as single dose with 1 g probenecid.

[#] *Reference: Drug Facts & Comparisons 2000.*

[↗] Including infections of ear, nose, throat, GU, and lower RTI caused by S*trep.*, *penicillinase* & *non-penicillinase* producing *Staph.*, and *H. influenzae*.

- ***ADVERSE EFFECTS:***

Similar to other penicillins, including:
-GI: diarrhea, nausea, vomiting, pseudo-membranous colitis (rare).
-CNS: convulsive seizures.
-Skin: pruritus, urticaria, or other skin eruptions.
-Hematological: hemolytic anemia, thrombo-cytopenia, purpura, eosinophilia, leukopenia, agranulocytosis.
-Others: superinfections, cojunctival ecchymosis.

- ***INTERACTIONS:***

Overview of Aminopenicillins Drug-Drug Interactions	
Drug	**Interaction**
Tetracyc-lines	May inhibit activity of amoxicillin & ampicillin. Avoid concomitant administration.
Probenecid	Prolongs the activity of amoxicillin; may be beneficial in some cases.
Allopurinol	Increases incidence of rash with ampicillin. Avoid concomitant use.
Chloram-phenicol, erythro-mycin	May reduce the bactericidal effects of ampicillin, this interaction is significant primarily when low doses of ampicillin are used.
Oral contra-ceptives	Ampicillin reduces the oral contraceptive effectiveness. Female patients should be advised to consider nonhormonal contraception while on antibiotics.
β- blockers	Ampicillin may reduce the bioavailability of atenolol. Case reports indicate that β-blockers may potentiate anaphylactic reactions of penicillin.

- ***OVERDOSE:***

In the case of renal function impairment aminopenicillins can be removed by hemodialysis, but not peritoneal dialysis.

- ***BRANDS:***

Ampicillin: Ampicillin Balapharm (Ciba-Geigy), Ampitricine (JCL), Ampipharm (JePharm), Broadacillin (BPC), Penibrin (Teva), Pentrexyl (Bristol), Vitapen (Vitamed).
Amoxicillin: Amoxi (Genmedics), Amoxicare (Pharmacare), Amoxitid (BPC), Apomoxyn (Curex), Hiconcil (Mead Johnson), Moxypen (Teva), Moxepharm (JePharm), Moxyvit (Vitamed).

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d) Amoxicillin with Clavulanic Acid (Co-amoxiclav) [WHO,P]

- ***DRUG SUMMARY:***

Co-amoxiclav consists of amoxicillin and the β-lactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity, but by inactivating penicillinase, it makes the combination active against penicillinase-producing bacteria that are resistant to amoxicillin. These include *Staph. aureus*, *E. coli* strains, and of *H. influenzae* strains, as well as many *Bacteroides* and *Klebsiella spp*.

- ***INDICATIONS:***

Infections caused by **susceptible β-lactamase** producing organisms: lower respiratory tract infections, otitis media, sinusitis, skin and skin structure infections, and UTI.

- ***CONTRAINDICATIONS:***

Hypersensitivity to penicillins.
Infectious mononucleosis.

- ***DOSAGE FORMS:***

Tablets and suspension.

- ***RECOMENDED DOSAGE:***

See table-5.3.
Directions: May be taken without regards to meal.
*Reconstituted suspension should be refrigerated and discarded within 10 days.

Table – 5.3: Recommended Doses of Co-amoxiclav	
Patient	**Dosage**
Adult	250 mg or 500 mg tab. q. 8 h.
Children (< 40 kg)	Children's dose is based on the amoxicillin content. Usually 20 mg/kg/day, in divided doses q. 8 h. Because of the different amoxicillin to clavulanic acid ratios in the 250 mg (250/125) tabs. vs. 250 mg chewable tabs. (250/62.5), do not use 250 mg tab. until the child's weight ≥ 40 kg.
Children (≥40 kg)	Dose according to the adult recommendations.
Severe infections and respiratory tract infections (adult)	One 875 mg tab. q. 12 h. or one 500 mg tab. q. 8 h.
Otitis media*, sinusitis, lower respiratory infections and severe infections	Children (< 40 kg): 40 mg/kg/day, in divided doses q. 8 h.

*****Co-amoxiclav has been used for short-term treatment in otitis media, (400/75 mg suspension) twice daily for children 2 mon-12 yr. *(BNF 2001 Sep., p. 261).*

Note: **Since both the 250 and the 500 mg tablets contain the same amount of clavulanic acid (125 mg as potassium salt), two 250 mg tablets are not equivalent to one 500 mg tablet. Tablets containing 875 mg amoxicillin also contain 125 mg clavulanic acid.**

- ***USE IN SPECIAL CASES:***

Pregnancy- Co-amoxiclav should be used only when clearly indicated (Category B). It crosses the placenta in very small amounts. Use of a single agent penicillin may be safer.

Lactation- Cautious use; it is excreted in the breast milk in very small amounts.

Liver diseases- Dose with caution and monitor hepatic function at regular intervals, since the drug is metabolized in the liver.

Kidney diseases- Does not generally require a dose reduction unless impairment is severe. Severely impaired patient with a GFR of < 30 ml/min should not receive the 875 mg tablet. Patients with GFR between 10-30 ml/min should receive 500 or 250 mg tablet q. 12 h., depending on the severity of infection. Patients with GFR <10 ml/min should receive 500 or 250 mg tablet q. 24 h., depending on the severity of infection. Hemodialysis patients should receive 500 or 250 mg tablet q. 24 h., they should receive additional dose both during and at the end of the dialysis.

- ***PRECAUTIONS AND WARNINGS:***

Lactation and pregnancy. See amoxicillin.

- ***ADVERSE EFFECTS:***

GI: diarrhea, nausea, vomiting.

Skin: rash, urticaria.

Others: *candidal vaginitis*, moderate increase in serum ALT and AST, bone marrow depression (rare), and glomerulonephritis.

- ***INTERACTIONS:***

Similar to those of amoxicillin.

- ***OVERDOSE:***

Refer to benzylpenicillin.

- ***Brands:***

Augmentin (Smithkline Beecham), Curam (Biochemi), Ogmin (BPC).

2) Cephalosporins (β - Lactam)

These are broad-spectrum antibiotics. There are many cephalosporins where individual agents have slightly different activities against certain organisms. They have a similar mechanism of action as penicillins; they inhibit the bacterial cell wall synthesis, so they are bactericidal agents.

Cephalosporins are not first-line drugs. They should be used only to treat specific infections that are resistant to antimicrobials of primary use. For this purpose, they would be considered essential. For example, some are suitable for the treatment of *H. influenzae* type b meningitis where there is evidence that strains are resistant to chloramphenicol and benzyl penicillin.

Cephalosporins are divided into four groups called generations. This classification is based on the spectrum of activity of these agents. Only the first three generations will be discussed (See table-5.4).

Note: Each generation of cephalosporins has shifted toward increased G-ve activity but has lost activity toward G+ve organisms.

Cephalosporins are not considered as the first line of treatment because they are:

1. Broad spectrum.
2. Expensive.
3. Resistance will develop easily and rapidly for such agents (since they are broad spectrum). Most are not active orally, instead IV or IM routes should be used (this is the case for all third generation cephalosporins and second generation ones; except cefaclor and many first generation agents).

Cephalexin, Cefaclor, Cefadroxil are the three orally active ones & should be used as 2nd line therapy, due to the reasons mentioned above.

Cephalexin[P], Cefadroxil and Cefaclor

- ***DRUG SUMMARY:***

Cephalexin and cefadroxil are orally active first generation cephalosporins while cefaclor is an orally active 2nd-generation cephalosporin. For the spectrum of activity refer to the previous table. Cefaclor has a good activity against *Hemophilus influenzae*, but it is associated with protracted skin reactions especially in children. Cefadroxil has a longer duration of action than other cephalosporins but poor activity against *H. influenzae*.

Tables 5.4 & 5.5 give an overview and comparison of the three agents.

Table – 5.4: Summary of the Main Three Generations of Cephalosporins.			
Class	**First-generation**	**Second-generation**	**Third-generation**
Spectrum of activity	1. Most G+ve cocci (exept enterococci) 2. Enteric aerobic G-ve bacilli (*E. coli*, *K. pneumoniae*, and *Proteus mirabilis*).	1. The same organisms covered by 1st generation. 2. Extended G-ve coverage (including β-lactamase-producing strains of *Hemophilus influenzae.*	1. Wider activity against G-ve bacteria as: *Enterobacter, Citrobacter, Serratia, Providencia, Neisseria and Hemophilus spp*. (including β-lactamase producing organisms.)
Examples	Cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephradine.	Cefaclor, cefamandole, ceforanid, cefonicid, cefoxitin, cefuroxime.	Cefoperazone, cefotaxime, cefotetan, ceftazidime, ceftizoxime, ceftriaxone, moxalactam.
Indications	1. Serious *Klebsiella* infections & G+ve & some G-ve infections in patients with mild penicillin allergy. 2. Preoperative prophylaxis.	1. Urinary tract infections resulting from *E. coli* & gonococcal disease caused by organisms-resistant to other agents. 2. Cefaclor is useful in otitis media & sinusitis in patients allergic to aminopenicillins. 3. Cefoxitin can be used for mixed aerobic-anaerobic infections as in intra-abdominal infection. 4. Cefamandole & cefuroxime used in community-acquired pneumonia.	1. Since they penetrate the blood brain barrier they are used for the treatment of meningitis caused by microbes as *Meningococci*, *Pneumococci*, *H. influenzae*, and enteric G-ve bacilli. 2. To treat sepsis of unknown origin in immunosuppressed patients, or to treat fever in neutropenic immuno-suppressed patients (where it is used in combination with aminoglycosides) 3. As empiric therapy* for life-threatening infection in which resistant organisms are the most likely cause. 4. Initial therapy of mixed bacterial infections (e.g., sepsis).

** Empirical therapy: is the therapy given before the identification of the infecting organism in life-threatening conditions.*

Table – 5.5: Monograph Summary of Selected Oral Cephalosporins			
Drug	**Cephalexin**	**Cefadroxil**	**Cefaclor**
Indications	To treat infections caused by susceptible pathogens in the respiratory and urinary tracts, middle ear, skin, soft tissue, and bone.	Primarily in the treatment of urinary tract infections caused by *E. coli*, *Proteus mirabilis*, and *Klebsiella* spp.; infection of the skin and skin structures caused by S*taph.* and S*trepto-cocci*; and group *A β-hemolytic Streptococcal* pharyngitis and tonsillitis.	Treatment of otitis media and infections of upper and lower respiratory tract, urinary tract, and skin and skin structures caused by ampicillin-resistant *H. influenzae*, acute uncomplicated UTI.
Contra-indications	Hypersensitivity to cephalosporins and related antibiotics (i.e. penicillins).		
Dosage forms	Caps, susp.		
Pregnancy	Use if clearly needed as no well-controlled studies have been established (Category B). They are used for the treatment of urinary tract infections.		
Lactation	They are excreted in breast milk in small quantities, however, consider the following problems in the nursing infant: modification/alteration of bowel flora; pharmacological effects; interference with the interpretation of culture results if a fever/infection investigational testing is needed.		
Children	Consider the relative benefit to risk before using the drug. In neonates, accumulation of cephalosporin antibiotics has occurred.		
Liver disease	Safe in general.		
Kidney disease	Cephalosporins may be nephrotoxic; use with caution in the presence of markedly impaired renal function (Cr_{cl} < 50 ml/min/1.73 m^2). In elderly and in patients with known or suspected renal impairment, monitor carefully prior to and during therapy. If renal impairment is severe the dose of cephalexin should not exceed 500 mg/day and if renal impairment is moderate the dose of cefadroxil should be reduced.		
Precautions and warnings	Cautious use in history of hypersensitivity to penicillins or other drug allergy. Severely impaired renal function.		
Possible adverse effects	Diarrhea (generally mild), nausea, vomiting, anorexia, abdominal pain, dizziness, headache, fatigue, hypersensitivity reactions (rash, pruritis, . .), interference with blood clotting factors leading to bleeding tendency.		
Interactions	**Probenecid:* decreases renal elimination of cephalexin. **Aminoglycosides:* nephrotoxicity risk is increased when both drugs are used together. Avoid, or monitor renal function closely if needed. **Anticoagulants:* Bleeding complications may occur. Use caution.		
Overdose	It occurs mainly with parenteral administration of cephalosporins, particularly if the patient suffers from severe renal impairment. Seizures may occur. Treat accordingly.		

Table – 5.6: Recommended Doses of the Selected Cephalosporins				
Drug	**Indication**	**Age**	**Route**	**Dosage**
Cephalexin	Mild to moderate infections	Adult	PO	250-500 mg q. 6 h.
		Child	PO	25-50 mg/kg/d in 4 divided doses
	Skin/skin structure infections	Adult	PO	500 mg q. 12 h.
	Otitis media	Child	PO	75-100 mg/kg/d in 4 divided doses
Cefadroxil	Uncomplicated UTI	Adult	PO	1-2 g/d in 1-2 divided doses
		Child	PO	30 mg/kg/d in 2 divided doses
	Skin/skin structure infections, Streptococcal pharyngitis, tonsillitis	Adult	PO	1 g/d in 1-2 divided doses
		Child	PO	30 mg/kg/d in 2 divided doses
	Renal impairment (Cr_{cl} < 25 ml/min)	Adult	PO	1 g q. 24 h.
		Child	PO	15 mg/kg q. 24 h.
Cefaclor	Mild to moderate infections	Adult	PO	250-500 mg q. 8 h.
		Child	PO	20-40 mg/kg/d divided q. 8 h. (max. 1 g/d)
	Acute bacterial exacerbation of chronic bronchitis	Adult	PO	500 mg q. 12 h. (for 7 days).

Direction: It is important to inform the patient that the full course of therapy should be completed. Duration of therapy should be for a minimum of 48-72 hours after evidence of bacterial eradication has been obtained.

*If GI upset occurs, may take the oral preparation with food or milk.

- ***BRANDS:***

Cephalexin: Cefacare (Pharmacare), Cefalex (BPC), Ceforal (Teva), Cefovit (Vitamed), Keflex (Lilly), Jeflex (JePharm).
Cefaclor: Ceclor (Lilly).
Cefadroxil: Biodroxil (Biochemi), Cefadrox (BPC), Duracef (Mead-Johnson).

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3) Tetracyclines

Tetracyclines are broad-spectrum antibiotics whose values have decreased due to increasing bacterial resistance. There is a large number of tetracyclines in the market (i.e. doxycycline[WHO,P] minocycline, chlortetracycline). The tetracyclines have similar antimicrobial spectra, and cross-resistance is common. Tetracycline will be used as the prototype for this group.

Tetracycline (TC)

- ***DRUG SUMMARY:***

TC is a broad spectrum, bacteriostatic, antibiotic. It acts by interfering with the bacterial protein synthesis process. Its usefulness has decreased due to the widespread bacterial resistance. It remains however the drug of choice in some infections (see indication below). TC is one of the cheapest antibiotics.

- ***INDICATIONS:***

It is the drug of choice in the treatment of infections caused by chlamydia (trachoma, psittacosis, salpingitis, nongonococcal urethritis, inclusion conjunctivitis, and lymphogranuloma venereum), rickettsia (including Q-fever, Rocky Mountain spotted fever, typhus), mycoplasma e.g. *Mycoplasma pneumoniae* (respiratory and genital infections).

1. Spirochetal infections (relapsing fever - *Borrelia burgdorferi* - Lyme disease), leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin), Syphilis (in penicillin hypersensitivity patients).
2. Amebiasis.
3. G-ve bacterial infections (e.g., brucellosis, shigellosis, cholera, Gonorrhea [in penicillin hypersensitivity patients], granuloma inguinale, tularemia).
4. G+ve infections (e.g. tetanus).
5. Used orally and topically (solution) for inflammatory acne vulgaris.
6. Topical ointment used for superficial skin infections.
7. Ophthalmic use.
8. Exacerbation of chronic bronchitis (because of their activity against *Haemophilus influenzae*).
9. As a sclerosing agent for pleural effusions due to malignancy or cirrhosis.

- ***CONTRAINDICATIONS:***

Hypersensitivity to tetracyclines or to any ingredient in the formulation.
Severe renal or hepatic impairment, common bile duct obstruction, use during tooth development, during infancy and children < 8 yrs., pregnant and nursing women.
Safety of the use of tetracycline topically in children 8-11 yrs. has not been established.

- ***DOSAGE FORMS:***

Capsules, ointment.

- ***RECOMMENDED DOSAGE:***

Dosage of Tetracycline		
Systemic Infections		
Adult	PO	250-500 mg b.i.d. to q.i.d. (1-2 g/d).
Child	PO	> 8 yrs: 25-50 mg/kg/d in 2-4 divided doses.
Acne		
Adult and Child > 8 yrs	PO	500-1000 mg/d in 4 divided doses.
	Topical	Apply to cleansed areas twice daily.

<u>*Direction*</u>: The drug may be taken with food if GI upset occurs, with a full glass of water. Do not take with dairy products.
(Doxycycline's absorption is less likely to be affected by food or dairy products, but it has to be taken with plenty of fluid and an hour before lying down to sleep.)

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use during pregnancy (Category D). It readily crosses the placenta and can have toxic effects on the developing fetus especially early in pregnancy (retardation of skeletal development).
Lactation- It is excreted in breast milk. A dosage of 2 g/d for 3 days has achieved a milk plasma ratio of 0.6 to 0.8. Because of the potential for serious adverse reactions, decide whether to discontinue nursing or to discontinue the drug.
Children- It should not be used in children under 8 years of age, unless other drugs are not likely to be effective, or are contraindicated.
<u>*Teeth*</u>*:* The use of tetracycline during the period of tooth development (from the last half of pregnancy to the eighth year of life) may cause permanent discoloration (yellow-gray-brown) of deciduous and permanent teeth. This adverse reaction is more common during long-term use of the drug, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported.
<u>*Bone*</u>*:* Tetracycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg q 6 h. This reaction was reversible when the drug was discontinued.
Liver diseases- Avoid use. Dose related toxicity especially with IV administration.
Kidney diseases- Avoid use. One can use doxycycline or minocycline.

- ***PRECAUTIONS AND WARNINGS:***

Cautious use in the case of history of renal or hepatic dysfunction, myasthenia gravis, history of allergy, asthma, hay fever, urticaria, undernourished patients.

- ***ADVERSE EFFECTS:***

Gastrointestinal upset, glossitis, stomatitis, rashes, proctitis, and infections due to *Candida albicans, Proteus, Pseudomonas, or Staphylococci*. It is deposited in calcifying areas of bone, nails and teeth, resulting in irreversible damage. Photosensitization and hypersensitivity reactions including anaphylactic shock can occur. May have hepatotoxic and nephrotoxic effects. Erythema (discontinue treatment). Headache and visual disturbances that may indicate benign intracranial hypertension, and pseudo-membranous colitis.

- ***INTERACTIONS:***

Overview of Tetracyclines Drug-Drug Interactions	
Drug	**Interaction**
Antacids	Calcium, magnesium bind to tetracycline in the gut and decrease its absorption.
Anti-diarrheal agents	The ones with kaolin and pectin may decrease TC absorption.
Food	Dairy products and ***iron supplements*** decrease tetracycline absorption. Space administration within 2 hrs. of tetracycline intake.
Meth-oxyflurane	May produce fatal nephro-toxicity. Avoid concomitant use.
Oral antico-agulants	Coadministration may potentiate hypoprothrom-binemia.
Oral contra-ceptives	Effectiveness of OC decreases. Backup methods should be used.
Penicillin	Bacteriostatic drugs (e.g. tetracycline) may interfere with the bactericidal action of penicillins; avoid concomitant administration.

- ***BRANDS:***

Brimocyclin (BCP), Tetrapharm (JePharm), Tevacycline (Teva).

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4) Macrolides

Macrolide antibiotics include erythro-mycin, clarithromycin, azithromycin, dirithromycin and troleandomycin. These may be bacteriostatic or bactericidal depending on factors such as drug concentration. Macrolides are weak bases, their activity increases in alkaline pH. This is important when using for UTI. They enter pleural fluid, ascitic fluid, middle ear exudates and sputum. Erythromycin is the most commonly used macrolide.

a) Erythromycin [WHO,P]

- ***DRUG SUMMARY:***

Erythromycin has an antibacterial spectrum that is similar but not identical to that of penicillin; it is thus a good alternative to penicillin, in penicillin-allergic patients. It can be a bactericidal or a bacteriostatic agent depending on its concentration. It produces its antibacterial activity by inhibiting bacterial protein synthesis. Erythromycin is active against many G+ve organisms, including streptococci (e.g., *Streptococcus pneumoniae*), *Coryne-bacterium* and *Neisseria* species, some strains of *Mycoplasma*, *Legionella*, *Treponema*, and *Bordetella*. Some *S. aureus* strains that resist penicillin G, are susceptible to erythromycin.

- ***INDICATIONS*:**

a. Erythromycins are the preferred drugs for the treatment of *Mycoplasma pneumoniae* and *Campylobacter* infections, legionnaires disease, chlamydial infections, diphtheria, and pertussis. It is also used for the treatment of sinusitis, chronic prostatitis and acne vulgaris.

b. In patients with penicillin allergy, erythromycin is an important alternative in

the treatment of pneumococcal pneumonia, S. aureus infections, syphilis, and gonorrhea.

c. Erythromycin may be given prophylactically before dental procedures to prevent bacterial endocarditis.

d. It has activity against gut anaerobes and has been used with neomycin for prophylaxis before bowel surgery.

* (Clarithromycin is indicated as part of therapy for eradication of *Helicobacter pylori* -peptic ulcer- with other agents).

- ***CONTRAINDICATIONS:***

-Hypersensitivity to macrolide antibiotics.

-Porphyria.

-Erythromycin estolate is contraindicated in liver disease. It produces cholestatic jaundice.

- ***DOSAGE FORMS:***

Tablets and suspensions.

- ***RECOMMENDED DOSAGE:***

Adult: 250-500 mg q. 6 h. or 0.5-1 g q. 12 h. up to 4 g daily in severe infections.

Early syphilis: 500 mg q. 6 h. for 14 days.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage for children is 30-50 mg/kg/day in equally divided doses q. 6 h.

In mild to moderate infections the usual dosage of erythromycin base is as table-5.7 indicates.

Table-5.7: Erythromycin Base Dosages in Children

Body Weight	Total Daily Dose
Under 4.5 kg (under 10 lb.)	30-50 mg/kg/day
4.5 to 6.8 kg (10-15 lb.)	200 mg
7.0 to 11.5 kg (16-25 lb.)	400 mg
11.6 to 22.7 kg (26-50 lb.)	800 mg
22.8 to 45.5 kg (51-100 lb.)	1200 mg
Over 45.5 kg (over 100 lb.)	1600 mg

Directions: Erythromycin dose is doubled in severe infections.

*It should be given on an empty stomach (1 hour before or 2 hours after meals).

*If GI upset occurs may administer with food.

*There is no interaction between milk and erythromycin preparations.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly indicated (Category B). Only small amounts cross the placental barrier of erythromycin base. Side effects have only been reported when using erythromycin estolate. Do not use erythromycin estolate in pregnant women.

Lactation- Only small amount is excreted in breast milk and no infant adverse effects are reported. But problems that may occur in nursing infants include modification of bowel flora and interference with the interpretation of culture results if a fever work-up is required. The American Academy of Pediatrics considers erythromycin to be compatible with breast-feeding.

Renal Disease- If severe case, the maximum possible dose to be given is 1.5 g daily. Ototoxicity (hearing loss) or transient hearing loss has been reported in such cases. *(Refer to BNF42; 2001)*.

Liver Disease- Erythromycin is principally excreted by the liver. One must take caution during the administration of erythromycin to patients with impaired hepatic function. There have been reports of hepatic dysfunction with or without jaundice. Erythromycin estolate is contraindicated in liver disease.

- ***PRECAUTIONS AND WARNINGS:***

- Hepatic and renal impairment.
- Superinfections might occur.

- ***ADVERSE EFFECTS:***

Nausea, vomiting, abdominal discomfort, diarrhea after large doses, reversible hearing loss also reported after large doses. If given for more than 14 days it may occasionally cause cholestatic jaundice.

- ***INTERACTIONS:***

Overview of Erythromycin Drug-Drug Interactions	
Drug	**Interaction**
Astemazole and ***terfenadine***	Inhibit the metabolism of ***astemazole and terfenadine*** leading to cardiotoxicity. **Contraindicated use.**
Bromo-criptine	Serum level may be increased due to erythromycin inhibiting hepatic metabolism. Monitor patient, and adjust bromocriptine dose accordingly.
Carba-mazepine	Inhibit the metabolism of ***carbamazepine***, leading to an increase in its plasma level.
Cyclosporins	Inhibit the metabolism of ***cyclosporins***.
Digoxin	Enhance the effect of ***digoxin***. Use with caution.
Theophyline	Inhibit the metabolism of ***theophyline***, leading to an increase in its plasma level, use with caution.
Warfarin	Enhanced effect of ***warfarin.*** Monitor prothrombin (PT) levels and caution the patient.

- ***OVERDOSE:***

Symptoms may include nausea, vomiting, epigastric distress and diarrhea. Reversible pancreatitis, hearing loss with or without tinnitus and vertigo especially in patients with renal or hepatic insufficiency.

Treatment includes usual supportive measures. GI decontamination is not necessary unless five times the normal dose has been ingested. Hemodialysis and peritoneal dialysis are not particularly effective.

- ***BRANDS:***

Bristamycin (Bristol), E-Mycin (Upjohn), Eryc (Taro), Erytab (Abbot), Erythrocare (Pharmacare), Erythrocin Filmtab (Abbot), Erythroped (Abbot), Erythrolet (BPC), Erythropharm (JePharm), Erythroteva (Teva).

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5) Sulphonamides and Trimethoprim [P]

The importance of sulphonamides as chemotherapeutic agents has decreased due to the increase in bacterial resistance and their replacement by antibiotics which are generally more active and less toxic. Sulphamethoxazole is the most commonly used sulphonamide, it is used in combination with trimethoprim (TMP) for the treatment of some infections. Increasing bacterial resistance to sulphonamides and the high incidence of sulphonamide-related side effects, have limited the value of use of this drug alone. TMP has been used in combination because of the synergistic activity, leading to less bacterial resistance. The combination is indicated as first line treatment in many cases. This combination is called **co-trimoxazole (TMP-SMZ)**.

- ***DRUG SUMMARY:***

Co-trimoxazole combination contains five parts of SMZ and one part of TMP.

- ***INDICATIONS:***

1. Urinary tract infections and prostatitis (if sensitive organisms).
2. Bone and joint infections due to *Haemophilus influenzae*.
3. Invasive salmonellosis and typhoid fever.
4. Sinusitis and exacerbation of chronic bronchitis.
5. High doses of co-trimoxazole are used for *Pneumocustis carinii* infections.

It is no longer recommended for the treatment of gonorrhea.

Table – 5.8: Dosage of Co-trimoxazole in Systemic Infections *			
Adult	PO	UTI, Acute otitis media, Acute exacerbation of chronic bronchitis	160 mg TMP/800 mg SMZ (1 double strength [DS] tablet) q. 12 h. for 10-14 days.
		Shigellosis	160 TMP/800 SMZ q. 12 h. for 5 days
		Travelers diarrhea	160 TMP/800 SMZ q. 12 h. for 5 days
Child	PO	> 2 month, less 40 kg	8 mg/kg TMP/ 40 mg/kg SMZ divided q. 12 h. for 10 days
		> 40 kg	160 TMP/800 SMZ (1 DS tablet) q. 12 h.

** Reference: Drug Facts & Comparisons, 2000, p 1352-54.*

- ***CONTRAINDICATIONS:***

1. Hypersensitivity to TMP, SMZ, sulphonamides, or bisulfites.
2. Jaundice, blood disorders, porphyria, megaloblastic anemia (due to folate deficiency).
3. Infants 2 mon. (except in treatment or prophylaxis of pneumocystis pneumonia).
4. Renal and hepatic failure.

- ***DOSAGE FORMS:***

Tablets and suspension.

- ***RECOMMENDED DOSAGE:***

See the table-5.8.

Directions: Take each oral dose with a full glass of water. If GI distress occurs when taken on empty stomach, take with food or milk.

*Advise patient to maintain adequate fluid intake.

***Duration** of therapy should be 7-10 days for uncomplicated cases (i.e. acute cystitis). For moderate infections (i.e. pyelonephritis, bronchitis), duration should be 10-14 days.

*3 day regimens may be used in; 1st episode of UTI, non-diabetic, young patients. But relapse or recurrence may occur or an upper UTI may be missed. Evaluate your patient.

*Severe cases should be referred to hospital for IV treatment.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use (Category C). Cardiovascular defects have been reported when used in the first trimester. Use of aminopenicillins or cephalosporins is safer.

Lactation- Avoid use. Since there is a small risk of kernicterus in jaundiced infants and of hemolysis in G6PD deficient infants (due to the sulphamethoxazole ingredients).

Children- It is contraindicated in children under 2 months, since there is a risk of kernicterus in these infants.

There is limited data on safety of repeated use for OM in children < 2 yrs; not indicated for prophylactic use of prolonged administration (*Facts & Comparisons 2000; 1352*).

Renal Disease- If there is a moderate renal impairment, one should reduce the dose (Cl_{cr} 15-30 ml/min: ½ dose). Rashes (including Stevens-Johnson syndrome) and blood disorders may cause further deterioration of renal function. In the case of renal failure (or Cl_{cr} < 15 ml/min) it is contraindicated.

Liver Disease- Use is contraindicated in the case of hepatic failure.

- ***PRECAUTIONS AND WARNINGS:***

– Group A β-hemolytic *Streptococcal* pharyngitis: Avoid use of this combination for such cases, since there has been high incidence of bacteriologic failure than with penicillins.

– Special care should be taken in patients who may be folate deficient such as, old patients, chronic alcoholics, patients on anticonvulsant therapy and ones receiving prolonged treatment or high doses of the drug.

– It should be used with care in the elderly and preferably only if there is no acceptable alternative. Since there has been recent

reports of death in patients over 65 years old using co-trimoxazole.
– Special care should be taken in patients with G6PD deficiency.
– In patients receiving the drug for a long time, blood counts should be monitored
– One should stop treatment if rashes appear.

- ***ADVERSE EFFECTS:***

Most common are GI disturbances. Other rare but possible effects include: rash, Stevens-Johnson syndrome (erythema multiforme), eosinophilia, agranulocytosis, granulocytopenia, purpura, leucopenia, thrombocytopenia, aplastic or megaloblastic anemia due to trimethoprim, pseudomembranous colitis, jaundice and hepatic necrosis (rare but have been reported).

- ***INTERACTIONS:***

Overview of Co-trimoxazole Drug-Drug Interactions	
Drug	**Interaction**
Cyclosporin	The risk of nephrotoxicity increases if co-trimoxazole is given along with cyclosporin.
Phenytoin	Co-trimoxazole has been found to cause an increase in the plasma concentration of phenytoin. This might lead to toxic effects because of the narrow therapeutic index.
Sulphonyl-urea	The effect of sulphonylurea has been found to be enhanced by co-trimoxazole, i.e. may cause hypoglycemia.
Warfarin	The effect of warfarin has been found to be enhanced by co-trimoxazole, i.e. increase the anticoagulant effect. Monitor Prothrombin time (PT) and adjust dose accordingly.

- ***OVERDOSE:***

Symptoms:
Acute: Signs and symptoms observed with either TMP or SMZ alone includes: Anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness, unconsciousness, pyrexia, hematuria, crystalluria, depression, and confusion.
Chronic: High doses or use for extended periods may cause bone marrow depression manifested as thrombocytopenia, leukopenia or megaloblastic anemia. Leucovorin (Ca-Folinate); 5 to 15 mg/day has been recommended to treat this case.
Treatment includes usual supportive measures. Perform gastric lavage or emesis, force oral fluids and administer IV fluids if urine output is low and renal function is normal. Acidifying the urine will increase the renal elimination of TMP. Monitor patient with blood counts and appropriate blood chemistries, including electrolytes. If significant blood dyscrasia or jaundice occurs, institute specific therapy for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating co-trimoxazole.

- ***BRANDS:***

Bactrim (Roche), Diseptyl (Rekah), Pathoprim (BPC), Pharmaprim (Pharmacare), Resprim (Teva), Sulfatrim (Vitamed), Sulprim (JePharm).

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6) Nitrofurantoin [WHO,P]

- ***DRUG SUMMARY:***

Nitrofurantoin is a synthetic nitrofuran that is bacteriostatic in low concentrations (5-10 mcg/ml) and bactericidal in higher concentrations.
Most G-ve bacilli and G+ve cocci associated with urinary tract infections are susceptible. Some strains of *Enterobacter* and *Klebsiella* are resistant. Most strains of *Proteus* and *Serratia* species are resistant.

It has no activity against *Pseudomonous spp*. Susceptible strains do not develop resistance during therapy.

- ***INDICATIONS:***

Urinary tract infections due to susceptible strains of *E. coli, Enterococci, S. aureus* (not for treatment of pyelonephritis or perinephric abscesses) and certain strains of *Klebsiella* and *Enterobacter spp*.

- ***CONTRAINDICATIONS:***

-Renal function impairment if creatinine clearance < 60 ml/min. Anuria or oliguria as risk of toxicity might increase.
-Hypersensitivity to nitrofurantion.
-Pregnant patients at term, during labor and delivery, and in infants under 1 month.

- ***DOSAGE FORMS:***

Capsules.

- ***RECOMMENDED DOSAGE:***

Adult: 50-100 mg 4 times/day a.c. and h.s. For long-term suppressive therapy, reduce dosage: 50-100 mg at bedtime.
Child: 5-7 mg/kg/24 hrs. given in 4 divided doses. For long term suppressive therapy, doses as low as 1 mg/kg/24 hrs., given in single or in 2 divided doses, may be adequate.
Directions: Administration with food or milk decreases GI disturbances and enhances bioavailability.
*Duration: Continue for at least 1 week or 3 days after sterile urine analysis.
*It may cause brown-orange discoloration of the urine.
*There are no suspension preparations in the local market, which requires pharmacist to specially prepare it.

- ***USE IN SPECIAL CASES:***

Pregnancy- Safety for use in pregnant women has not been established, Category B; low incidence of minor malformation has been reported in mice. Contraindicated in pregnant women at term. Do not give to pregnant women with G6PD deficiency because of the risk of hemolysis.
Lactation- It is excreted into milk in very low concentrations. Infants with G6PD deficiency are adversely affected, and may develop hemolytic anemia upon exposure. Safety for use in nursing mothers has not been established.
Children- Contraindicated in infants < 1 mon. (< 3 mon.: *in BNF 2001*), due to risk of hemolytic anemia.
Renal Disease- Exercise caution. Refer to contraindications.

- ***PRECAUTIONS AND WARNINGS:***

-Culture and susceptibility testing should be performed prior to and during treatment.
-Peripheral neuropathy may occur and become severe or irreversible. Predisposing factors like renal impairment, anemia, diabetes, electrolyte imbalance, vitamin B deficiency and debilitating diseases may enhance these problems.
-Overuse may result in bacterial and fungal overgrowth and non-susceptibility that may cause super infections.
-Pulmonary reactions, acute, sub-acute or chronic, may occur (i.e. pulmonary fibrosis like symptoms).
-Hematological disorders may occur such as hemolytic anemia.

- ***ADVERSE EFFECTS:***

GI, hepatic and pulmonary disturbances may occur. Some lab tests abnormalities may be found, such as increased AST, ALT, decreased hemoglobin, increased serum phosphorus.

- ***INTERACTIONS:***

Overview of Nitrofurantoin Drug-Drug Interactions

Drug	Interaction
Anti-cholinergics	Nitrofurantoin bioavailability will increase; clinical interventions may not be necessary.
Magnesium salts	Nitrofurantoin absorption may be delayed or increased. Avoid concomitant use.
Uricosurics	Nitrofurantoin renal clearance will decrease and serum level increase- leading to toxic effects.

Drug/lab tests interactions: A false-positive glucose test in urine may occur

with Benedict`s and Fehling`s but not with the glucose enzymatic tests.

Drug/food interactions: food intake increases the drug bioavailability.

- ***OVERDOSE:***

Symptoms: no specific or serious symptoms have been reported except for vomiting.

Treatment: Induction of emesis and increase fluid intake to enhance excretion. The drug is dialyzable.

- ***BRANDS:***

Furadantin/Macrodantin (Proctor&Gamble), Macrofuran (BPC), Urantoin (Rafa).

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7) Nalidixic Acid WHO,P

- ***DRUG SUMMARY:***

Nalidixic acid is a bactericidal quinolone agent that interferes with DNA polymerization. It is effective against G-ve bacteria, i.e. *Proteus mirabilis, Proteus morganii, Proteus vulgaris, Providencia rettgeri, E. coli, Enterobacter and Klebsiella* species. *Pseudomonus* strains are generally resistant.

- ***INDICATIONS:***

Treatment of urinary tract infections caused by susceptible G-ve microorganisms, including the majority of *Proteus* strains, *Klebsiella* and *Enterobacter spp*. and *E. coli*, if the patient did not respond to, or is not sensitive to co-trimoxazole.

- ***CONTRAINDICATIONS:***

Hypersensitivity to nalidixic acid, history of convulsive disorders.

- ***DOSAGE FORMS:***

Tablets and suspension.

- ***RECOMMENDED DOSAGE:***

Adult: *Initial therapy:* 1.0 g 4 times daily (total of 4 g/d) for 1 or 2 weeks.

Prolonged therapy: may be reduced to 2 g/day after the initial treatment period.

*Under dosage (< 4 g/d) during initial therapy may predispose to emergence of bacterial resistance.

Child (3 mon. - 12 yrs. of age):

Initial therapy: 55 mg/kg/d in 4 equally divided doses.

Prolonged therapy: may be reduced to 33 mg/kg/day.

Do not administer to infants < 3 months of age.

Directions: Should be taken with food to prevent GI disturbances.

*May produce drowsiness or dizziness; caution the patient against hazardous activities such as driving till full effect of the medication is known.

- ***USE IN SPECIAL CASES:***

Pregnancy- Not recommended, since safety for use during the first trimester has not been established (Category B). No congenital defects have been reported. If benefit outweighs risks to the fetus, and the drug is used, need to discontinue the drug prior to delivery because of the theoretical risk that exposure *in utero* may lead to significant blood levels in the neonate immediately after birth.

Lactation- Data is little on nalidixic acid. Milk to plasma ratios are 0.08 to 0.13. Although small amounts, but hemolytic anemia was reported in one case.

Children- Use care in prepubertal children; as erosions of the cartilage in weight bearing joints in animals were reported.

Renal Disease- Exercise caution if Cl_{cr} is 2-8 ml/min.

Liver Disease- Exercise caution.

- ***PRECAUTIONS AND WARNINGS:***

-Periodic blood counts, renal and liver function tests should be performed if treatment is continued for > 2 weeks.

-Photosensitivity may occur, advise patient against prolonged exposure to sunlight.

-May produce drowsiness and dizziness; exercise caution while driving or operating dangerous machines.

-It might cause hemolytic anemia in patients with or without G6PD deficiency.

- ***ADVERSE EFFECTS:***

CNS disturbances (i.e. drowsiness, headache) and ophthalmic disturbances

might occur but are reversible upon discontinuation. GI disturbances (i.e. nausea, diarrhea) might occur.

- ***INTERACTIONS:***

The effects of ***anticoagulants*** may be enhanced by nalidixic acid, hemorrhage could occur. A decrease in dose of warfarin may be required.

Drug/Lab test interactions: The urinary metabolites of nalidixic acid liberate glucuronic acid and produce false-positive urinary glucose results with Benedict's or Fehling's or Clinitest's tests.

- ***OVERDOSE:***

Symptoms: Toxic psychosis, convulsions, increased intracranial pressure, metabolic acidosis, vomiting, nausea and lethargy may occur in patients taking more than the recommended dosage.

Treatment: Reactions are short lived (2-3 hrs.) because the drug is rapidly excreted. Gastric lavage is indicated if the overdosage was noticed early. If absorption has occurred, increase fluid administration and have supportive measures. Anti-convulsants may be indicated in severe cases.

- ***BRANDS:***

Granexin (Dexxon), NegGram (Sterling-winthrop), U-Gram (JePharm), Urigram (Trima).

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8) Fluoroquinolones

Fluoroquinolones are synthetic, broad-spectrum antibacterial agents related to the 1st generation quinolones; nalidixic acid and cinoxacin. Ciprofloxacin, is the main 2nd generation quinolone, others include enoxacin, lomefloxacin, norfloxacin, and ofloxacin. Newer 3rd generation quinolones include levofloxacin and sparfloxacin. Fluoroquinolone agents are bactericidal. They may not be indicated as essential or 1st line therapy drugs, but are of real value as reserve agents when other agents have failed.

Ciprofloxacin WHO,P

- ***DRUG SUMMARY:***

A fluoroquinolone antibacterial agent with a wide spectrum of activity, mainly for G-ve bacteria (i.e. *Salmonella spp., Shigella spp., Brucella melitensis* . . .), including *Enterobacteriaceae, Pseudo-monas aeruginosa, Heamophilus, Neisseria spp.*, *Staphylococci,* and some other G+ve bacteria. Most anaerobic organisms are not susceptible. (It may be used for infections that were resistant to other antibiotics including penicillins, cephalosporins and aminoglycosides).

- ***INDICATIONS:***

Mainly used for urinary tract infections due to G-ve and some G+ve susceptible bacteria.

May be used for lower respiratory infections, gonorrhea and chancroid, typhoid fever, salmonella, severe shigellosis, and hospital-acquired infections when other agents have failed.

- ***CONTRAINDICATIONS:***

Hypersensitivity to ciprofloxacin or other quinolones.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult (>18 yrs)**:** 250-500 mg b.i.d.

Child: Use not recommended in growing children < 18 yrs. (adolescents).

<u>*Directions*</u>: Should be administered for at least 3 days after signs and symptoms of infection have disappeared.

*Ensure adequate fluid intake (advise patient to drink fluids) to prevent crystaluria.

*Milk decreases the absorption of quinolones; space out interval between milk-product ingestion and quinolones intake as much as possible.

- ***USE IN SPECIAL CASES:***

Pregnancy- Not to be used in pregnant women (Category C). Animal studies have shown teratogenic effects.

Lactation- Use not recommended. It is excreted in milk, and the potential for arthropathy and other toxicities to occur in the nursing infant are high. Levels of this drug are undetectable after 36-48 hours, therefore if there is a clear indication for use, do not breast feed until 48 hours after the last dose of a fluoroquinolone.

Children- Avoid use in children < 18 yrs. and adolescents *[Some references use 12 yrs.]*. Reports of bone disorders in animal studies have been established.

Renal Disease- Dose should be reduced if creatinine clearance is < 20 ml/min.

Liver Disease- Exercise caution.

- ***PRECAUTIONS AND WARNINGS:***

-Avoid use in pregnancy, lactation and growing children.

-Exercise caution in patients with G6PD deficiency.

-Should be used with caution in patients with epilepsy or with history of CNS disturbances, and in patients with myasthenia gravis. Fluoroquinolones may induce convulsions in such patients.

-Rupture of the shoulder, hand and Achilles tendons that required surgical repair have been reported with use of fluoroquinolones. Treatment should be discontinued if the patient experiences pain, inflammation or rupture of the tendon.

- ***ADVERSE EFFECTS:***

GI, CNS disturbances and some dermatological reactions as well as photosensitivity reactions. Superinfections with organisms not very susceptible to ciprofloxacin may occur.

- ***INTERACTIONS:***

Overview of Fluoroquinolones Drug-Drug Interactions	
Drug	**Interaction**
Antacids	Quinolones pharmacological effect is decreased due to decreased absorption. If necessary antacids may be given at least 6 hrs. before or 2 hrs. after quinolone administration.
Didanosine	Quinolones effect may be decreased. If concurrent use cannot be avoided, give didanosine at least 6 hrs. before or 2 hrs. after the quinolone.
Iron & calcium salts	These reduce fluoroquinolones absorption; thus, ciprofloxacin should not be administered 4 hrs. within taking these preparations.
Sucralfate	It decreased absorption of quinolones. If needed, give sucralfate at least 6 hrs. after quinolone administration.
Warfarin	Enhanced anticoagulant effect may occur. Use with caution.

- ***BRANDS:***

Ciprocare (Pharmacare), Ciprogis (Agis), Ciproxin (Bayer), Floxin (JePharm).

B) ANTI-TUBERCULOSIS

Tuberculosis is one of the most serious infections that are showing a comeback. Control of this epidemic will require a number of initiatives on the part of clinicians and health care workers.

Because of the slow growth rate of mycobacteria and their intracellular location, drugs must be administered for a longer period of time than in other infectious diseases. The risk of adverse reactions must be a major consideration in drug selection. Furthermore, to prevent the emergence of resistant strains that occur

naturally at very low frequencies, it is vital to employ combined therapy with at least two agents to which the organism is susceptible.

Antituberculosis drugs are classified into first-line and second-line drugs, on the basis of their efficacy, activity, and risk of adverse reactions. The four first-line drugs are: Isoniazid (INH), Rifampin/rifampicin, Pyrazinamide (PZN) and Ethambutol *(see table-5.9 for standard dosing regimens)*. Second-line drugs are indicated only when the *Mycobacterium tuberculosis* organisms are resistant to the first-line agents. **In general the drugs with similar toxicities should not be used together**.

Table-5.9: Recommended dosage for standard unsupervised 6-month regimen	
Isoniazid (INH) *(for 6 months)*	Adult: 300 mg/d Child: 10 mg/kg/d (max. 300 mg).
Rifampicin *(for 6 months)*	Adult < 50 kg: 450 mg/d Adult ≥ 50 kg: 600 mg/d Child: 10 mg/kg/d
Pyrazinamide (PZN) *(for first 2 months only)*	Adult < 50 kg: 1.5 g /d Adult ≥ 50 kg: 2 g /d Child: 35 mg/kg/d

Tuberculosis is treated in two phases: an initial phase using at least three drugs and a continuation phase using two drugs. Treatment requires specialized knowledge, particularly where the disease involves resistant organisms or non-respiratory organs.

Initial phase: The concurrent use of at least three drugs during the initial phase is designed to reduce the population of viable bacteria as rapidly as possible and to prevent the emergence of drug resistant bacteria. Treatment of choice for the initial phase is the daily use of INH, rifampicin, and/or PZN; ethambutol is added if drug resistance is a problem.

Continuation phase: After the initial phase, treatment is continued with INH and rifampicin; longer treatment may be necessary for bone and joint infections, for meningitis, or for resistant organisms.

Pregnancy and breast feeding:
The standard regimen (table-5.9) may be used during pregnancy and breast-feeding; pyridoxine supplements are advisable. Monitor infant for possible toxicity and theoretical risk of convulsions and neuropathy. Prophylactic pyridoxine is advisable in mother and infant.

Children:
As for adults, children are given INH, rifampicin, and PZN for the first two months followed by isoniazid and rifampicin during the next 4 months. If PZN is omitted from the initial phase, then treatment with isoniazid and rifampicin should be given for 9 months. Except in exceptional circumstances (e.g. drug resistance). **Ethambutol should be avoided in young children because of the difficulty in testing eyesight and in obtaining reports of visual symptoms**.

Non-compliant patients:
Treatment needs to be fully supervised in patients who cannot be relied upon to comply with the treatment regimen. These patients are given INH, rifampicin, and PZN three times a week under supervision for the first two months followed by INH and rifampicin three times a week for a further four months.

Immunonocompromised patients:
Immunocompromised patients may develop tuberculosis owing to reactivation of previously latent disease or to new infection. Multi-resistant *Mycobacterium tuberculosis* may be present or the infection may be caused by other mycobacteria. Here a culture should be always carried out and the type of organism and its sensitivity should be confirmed. A minimum duration of treatment of 9 months is currently recommended.

1) Isoniazid (INH) [WHO,P]

- ***DRUG SUMMARY:***

INH is a bactericidal agent that is cheap and highly effective. It should always be included in any antituberculosis regimen unless there is a specific contraindication. Its only common side effect is peripheral neuropathy which is more likely to occur where there are pre-existing risk factors, such as diabetes, alcoholism, chronic renal failure, and malnutrition. In these circumstances pyridoxine 10 mg daily should be given prophylactically from the start of the treatment.

- ***INDICATIONS:***

-Treatment of all forms of active TB caused by susceptible organisms.
-Preventive therapy in high-risk persons (e.g., household members, persons with positive tuberculin skin test reactions).

- ***CONTRAINDICATIONS:***

History of INH-associated hypersensitivity reactions including: hepatic injury, acute liver damage of any etiology, and porphyria.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Treatment		
Adult	PO/IM	5 mg/kg up to 300 mg/day.
Child	PO/IM	10-20 mg/kg up to 300-500 mg/d.
Preventive Therapy		
Adult	PO	300 mg/day
Child	PO	10 mg/kg up to 300 mg/day or 15 mg/kg three times/wk.

Directions: It should be taken 1 hour before meals, since food decreases rate and extent of isoniazid absorption.

- ***USE IN SPECIAL CASES:***

Pregnancy- Category C. Refer to the introduction of antituberculosis drugs.
Lactation- Monitor infant for possible toxicity, theoretical risk of convulsions and neuropathy. Prophylactic pyridoxine is advisable in mother and infant. Refer to the introduction of antituberculosis drugs.
Children- Refer to the introduction of antituberculosis drugs.
Renal Disease- If severe renal impairment is present, the maximum dose to be given is 200 mg daily; since increase risk of peripheral neuropathy.
Liver Disease- Avoid. Idiosyncratic hepatotoxicity is more common.

- ***PRECAUTIONS AND WARNINGS:***

Caution should be taken in the case of: impaired liver and kidney function, epilepsy, history of psychosis, alcoholism, breast-feeding, and patients > 35 years old.

- ***ADVERSE EFFECTS:***

Nausea, vomiting, hypersensitivity reactions including rashes, peripheral neuritis (with high doses), convulsions, psychotic episodes, agranulocytosis; hepatitis (especially > 35 years); systemic lupus erythematosus-like syndrome.

- ***INTERACTIONS:***

Overview of Isoniazid Drug-Drug Interactions	
Drug	**Interaction**
Alcohol	Ingestion on a daily basis increases risk of hepatotoxicity.
Antacids and ***adsorbants***	Those reduce absorption of INH. INH should be administered 2 hrs. before administration of these.
Anti-epileptics	Metabolism of carbamazepine, ethosuximide, and phenytoin is inhibited leading to an increase in the plasma concentrations of such agents. Monitor liver functions with carbamazepine use. Use INH with caution.
Rifampicin	Coadministration may result in a higher rate of hepatotoxicity. If coadministration is necessary, monitor liver function tests. If alterations occur, consider discontinuation of one or both of the agents.

Theophyl-line	INH possibly increases plasma theophylline concentration. Use with caution.

- ***OVERDOSE:***

Symptoms of an overdosage occur within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision and visual hallucinations (including bright colors and strange designs) are among the early manifestations. With marked overdosage, respiratory distress and CNS depression will occur along with severe, intractable seizures.

Isoniazid overdosage can be fatal, but good response has been reported in most patients adequately treated within the first few hours after drug ingestion.

Treatment: Secure the airway and establish adequate respiratory exchange, gastric lavage is advised within the first 2 to 3 hrs., but do not attempt it until convulsions are under control. Supportive and symptomatic care should be implemented as needed.

- ***BRANDS:***

Isoniazid (Rekah).

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2) Rifampicin WHO,P

- ***DRUG SUMMARY:***

Rifampicin, a bactericidal agent, is a key component of any antituberculosis regimen. Like isoniazid it should always be included unless there is a specific contraindication. During the first two months of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common, but generally it does not require interruption of treatment.

Occasionally more serious liver toxicity requires a change of treatment particularly in those with pre-existing liver disease. Rifampicin is a potent hepatic enzyme inducer which accelerate the metabolism of several drugs.

- ***INDICATIONS:***

1. Tuberculosis.
2. Leprosy.
3. Brucellosis, legionnaires' disease, and serious staphylococcal infections.
4. Prophylaxis of *Meningococcal meningitis* and *Haemophilus influenzae* (type B) infections.

- ***CONTRAINDICATIONS:***

Jaundice and other obstructive biliary diseases. In patients with porphyria.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Pulmonary Tuberculosis		
Adult < 50 kg	PO	450 mg/day in conjunction with other antituberculous agents.
Adult ≥ 50 kg	PO	600 mg/day in conjunction with other antituberculous agents.
Child	PO	10-20 mg/kg daily (max 600 mg/day).
Meningococcal Carriers		
Adult	PO	600 mg b.i.d. for 2 consecutive days.
Child	PO	10-20 mg/kg twice daily for 2 consecutive days (max. 600 mg/day).
Prophylaxis for *H. influenzae* type B		
Adult	PO	600 mg/day for 4 days.
Child	PO	10-20 mg/kg/day for 4 days; max. 600 mg/day.
Dapsone-Sensitive Multibacillary Leprosy		
Adult	PO	600 mg once/month with clofazimine and dapsone for minimum of 2 years.

Directions: It could be taken with food to avoid gastric distress, but it is recommended to be taken 1 hour before or 2 hours after meal.

- ***USE IN SPECIAL CASES:***

Pregnancy- There are evidences of teratogenic effect, in animal studies, if it has been used during the first trimester. The risk of neonatal bleeding may be increased if rifampicin has been administered during the third trimester.

Lactation- Rifampicin is excreted in breast milk with a milk/plasma ratio of 0.2 to 0.6. Decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Children- Data is not available to determine dosage for children < 5 yrs. of age.

Renal Disease- No dosage adjustment is required in the case of renal failure.

Liver Disease- Avoid use or do not exceed 8 mg/kg daily because elimination might be reduced and the risk of hepatotoxicity might be increased.

- ***PRECAUTIONS AND WARNINGS:***

1. Reduce dose in hepatic impairment-look at special cases.
2. Carry out liver function tests and blood counts in the case of hepatic disorders and on prolonged therapy.
3. It discolors soft contact lenses.
4. Cautious use in the case of alcoholism or concomitant administration of another hepatotoxic agent.

- ***ADVERSE EFFECTS*:**

Heartburn, anorexia, nausea, vomiting, diarrhea, epigastric distress, flatulence, cramps, transient elevation in liver function tests (bilirubin, BSP, alkaline phosphatase, ALT, AST), thrombocytopenic purpura, flushing, urticaria and rashes, saliva and other body secretions will be colored orange-red.

- ***OVERDOSE:***

Signs and symptoms: Nausea, vomiting and increase lethargy will probably occur within a short time after ingestion; unconsciousness may occur with severe hepatic involvement. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears and feces is proportional to the amount ingested. Liver enlargement and jaundice may develop rapidly.

Treatment: Gastric lavage is probably preferable to induction of emesis. Activated charcoal slurry instilled into the stomach following evacuation of gastric contents can help absorb any remaining drug in the GI tract. Antiemetic medication may be required to control severe nausea and vomiting.

- ***INTERACTIONS***:

Overview of Rifampicin Drug-Drug Interactions	
Drug	**Interaction**
Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including: ***estrogens, corticosteroids, phenytoin, sulphonylurea, anticoagulants, antiarrhythmics, chloramphenicol, anti-depressants, antipsychotics, anxiolytics, hypnotics, β-blockers, Ca-channel blockers, cardiac glycosides, theophylline, thyroxine and cimetidine.*** Monitor patients and plasma levels when applicable, and adjust dosage regimens as needed.	
Oral contra-ceptives (OC)	The effectiveness of *OC* is reduced; alternative family planning method should be offered.
Antacids	They reduce absorption of rifampicin.
Alcohol, and ***isoniazid***	Coadministration of any one of these increases the risk of hepatotoxicity. Refer to INH.
Para-amino-salicylic acid	Effectiveness of rifampicin is reduced. If necessary to administer, give apart at an interval of 8-12 hrs.

- ***BRANDS:***

Mycobutin (Farmitalia/Agis), Rimactan (Ciba-Geigy).

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3) Pyrazinamide [WHO,P]

- ***DRUG SUMMARY:***

Pyrazinamide (PZN) is a bactericidal drug, only active against intracellular dividing forms of *Mycobacterium tuberculosis*; it exerts its main effect only in the first two to three months. It is particularly useful in tuberculous meningitis because of good meningeal penetration. It is not active against *M. bovis*.

- ***INDICATIONS:***

Tuberculosis in combination with other drugs.

- ***CONTRAINDICATIONS:***

Liver damage, porphyria.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult < 50 kg	PO	1.5 g daily
Adult ≥ 50 kg	PO	2 g daily
Child	PO	35 mg/kg daily.

- ***USE IN SPECIAL CASES:***

Pregnancy- Pyrazinamide should be used only if it is clearly indicated (Category C).

Lactation- It is found in small amounts in breast milk, therefore, one should take the risk-benefit ratio of this therapy into account.

Children- PZN regimens employed in adults are probably equally effective in children. PZN appears to be well tolerated in children.

Renal Disease- No dosage adjustment is required.

Liver Disease- Patients with preexisting liver disease should be followed up closely, and one should discontinue PZN if signs of hepatocellular damage appear.

- ***PRECAUTIONS AND WARNINGS:***

One should take caution in the case of: impaired renal function, diabetes, gout, or history of peptic ulcer.

- ***ADVERSE EFFECTS:***

Hepatotoxicity including: fever, anorexia, hepatomegaly, jaundice, or liver failure; nausea, vomiting, arthralgia, sideroblastic anemia, and urticaria.

- ***INTERACTIONS:***

It inhibits the renal secretion of urates. PZN antagonizes the effect of ***probenecid and sulphinpyrazone*** which are uricosuric agents.

- ***OVERDOSE:***

Overdose experience is limited.

- ***BRANDS:***

No brand names available in our market.

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4) Ethambutol [WHO,P]

- ***DRUG SUMMARY:***

Ethambutol, a bacteriostatic agent, is included in the treatment regimen of tuberculosis when resistance to other agents is suspected.

- ***INDICATIONS:***

Tuberculosis in combination with other drugs.

- ***CONTRAINDICATIONS:***

- Renal function impairment.
- Poor vision of optic neuritis.
- Children under 13 years old.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Directions: Absorption is not affected by food. Can be taken with food in order to minimize stomach upset.

Unsupervised Treatment with Ethambutol
25 mg/kg daily in the initial phase followed by 15 mg/kg daily in the continuation phase (or 15 mg/kg daily throughout).
Fully Supervised Intermittent Treatment
30 mg/kg three times a week or 45 mg/kg twice a week

- ***USE IN SPECIAL CASES:***

Pregnancy- It should be used only when clearly indicated (Category B).

Lactation- The amount excreted in breast milk is too small to be harmful to the nursing baby.
Children- It is contraindicated in children less than 13 years old.
Renal Disease- Dose should be reduced if the degree of impairment is mild.
Liver Disease- No dosage adjustment is required in the case of hepatic dysfunction.

- ***PRECAUTIONS AND WARNINGS:***

-Reduce dose in the case of renal impairment.
-Cautious use in the case of: gout, cataract, recurrent ocular inflammatory conditions, diabetic retinopathy, and the elderly.

- ***ADVERSE EFFECTS:***

-Visual disturbances.
-Optic neuritis, red/green color blindness, peripheral neuritis.

- ***INTERACTIONS:***

Aluminum salts may delay and reduce the absorption of ethambutol, so separate their administration by several hours.

- ***OVERDOSE:***

Experience with overdose is limited.

- ***BRANDS:***

Myambutol (Lederle).

C) ANTI-PARASITICS

Parasitic infections are a major world wide health problem, particularly in less developed countries (i.e., malaria, schistomsomes, amoebiasis . . . etc.). Different factors contribute to this increase such as population crowding, poor sanitation and lack of health education, inadequate control of parasite vectors, contaminated water supplies, increased world travel, population migrations, as well as development of resistance to agents used to treat these infections.

Antiparasitics or anthelmintics are drugs used to rid the body of worms known as helminths. The term anthelminitc applies to agents that act either locally to expel worms from the GI tract or systemically to eradicate species and developmental forms of helminths that invade organs and tissues.

The common antiparasitic drugs used in our community are discussed in this section.

1) Metronidazole [WHO,P]

- ***DRUG SUMMARY:***

Metronidazole is an antimicrobial drug with a high activity against anaerobic bacteria and protozoa. It is the drug of choice for acute invasive amoebic dysentery, since it is very effective against vegetative amoebae in ulcers at a dosage of: 800 mg every eight hours for five days. It is also effective against amoebae which may have migrated to the liver.

- ***INDICATIONS:***

-Anaerobic infections (including brain abscess).
-Protozoal infections including:
  a: Trichomoniasis.
  b: Amoebiasis (not for cystic form).
  c: Gardiasis (not for cystic form).
-Bacterial vaginosis (as *Gardnerella vaginalis* infections and *Trichomonas vaginalis)*.
-Surgical and gynecological sepsis in which its activity against colonic anaerobes, especially *Bacteroid fragilis*, is important.
-Treatment of pseudomembranous colitis (in a dose of 400 mg by mouth three times/day).
-Topical metronidazole reduces the odor produced by anaerobic bacteria in fungating tumors.

- ***CONTRAINDICATIONS:***

Blood dyscrasias, active CNS disease, first trimester of pregnancy, nursing mothers.

- ***DOSAGE FORMS:***

Tablets, suspension, gel or cream.

- ***RECOMMENDED DOSAGE:***

See table-5.10.

Directions: Administer oral preparations immediately before, with, or immediately after meals. If GI distress occurs, one can take the drug with food or with milk.

- ***USE IN SPECIAL CASES:***

Pregnancy- Metronidazole is contraindicated in first trimester. It should be used only when it is clearly indicated. If benefit outweighs risk for use, avoid high-doses regimens, or single doses (Category B).

Lactation- Stop lactation during treatment as significant amount of the administered drug appears in the breast milk and it may give a bitter taste to the milk. A nursing mother should discard any breast milk produced while she is on the drug, and resume nursing 24 to 48 hours after the drug is discontinued.

Children- Safety and efficacy in children have not been established, except for the treatment of amebiasis. There is a decrease in elimination in newborns.

Renal Disease- No dosage adjustment is required in the case of renal impairment.

Liver Disease- Reduce the dose in the case of severe liver dysfunction.

- ***PRECAUTIONS AND WARNINGS:***

-Metronidazole is carcinogenic in rodents after long term use; avoid unnecessary use.

-It causes disulfiram-like reaction if it is administered with alcohol.

-Cautious use in the case of liver impairment.

-Cautious use in the case of alcoholism and coexistent candidiasis.

- ***ADVERSE EFFECTS:***

Nausea, vomiting, unpleasant taste, GI disturbances, rashes, urticaria and angio-edema, drowsiness (rare), headache, dizziness, ataxia, and darkening of urine.

- ***INTERACTIONS:***

Overview of Metronidazole Drug-Drug Interactions	
Drug	**Interaction**
Alcohol	Disulfiram-like reaction. Warn patient against alcohol or alcohol containing product intake.
Disulfiram	Concomitant administration will cause acute psychosis
Phenobar-bitone and cimetidine	These inhibit the metabolism of metronidazole.
Phenytoin	Metronidazole inhibits the metabolism of phenytoin, this might lead to toxic effects.
Warfarin	Metronidazole enhances the anticoagulant effect. Use with caution.

- ***OVERDOSE:***

Symptoms: Nausea, vomiting, ataxia, and neurotoxic effects.

Treatment: No specific antidote for metro-nidazole is available. Treatment consists of usual supportive measures.

- ***BRANDS:***

Entogyl (JePharm), Flagy (Specia), Metrocare (Pharmacare), Metrogyl (Teva), Metrozole (BPC), Trichonazole (Vitamed), Zadstat (Lederle).

Table – 5.10: Recommended Doses of Metronidazole *			
Disease	**Age**	**Route**	**Dosage**
Anaerobic infections	Adult	PO	An initial dose of 800 mg followed by 400 mg q. 8 h. for 7 days.
	Child	PO	7.5 mg/kg q. 8 h. for 7 days.
Leg ulcers and pressure sores	Adult	PO	400 mg q. 8 h. for 7 days.
Bacterial vaginosis	Adult	PO	400-500 mg twice daily for 7 days or 2 g as a single dose.
Acute ulcerative gingivitis	Adult	PO	200 mg q. 8 h. for 3–7 days.
	Child (1- < 3 y)	PO	50 mg q. 8 h. for three days.
	Child (3- < 7 y)	PO	100 mg q 12 h for three days.
	Child (7- 10 y)	PO	100 mg q. 8 h. for three days.
Acute dental infections	Adult	PO	200 mg q. 8 h. for 3-7 days.
Invasive intestinal amoebiasis	Adult	PO	800 mg q. 8 h. for 5 days.
	Child (1- < 3 y)	PO	200 mg q. 8 h. for 5 days.
	Child (3- < 7 y)	PO	200 mg q. 6 h. for 5 days.
	Child (7- 10 y)	PO	400 mg q. 8 h. for 5 days.
Amoebiasis *(including liver abscess)*	Adult	PO	800 mg q. 8 h. for 7-10 days
	Child	PO	35-50 mg/kg/d given in 3 divided doses, q. 8 h. for 7-10 days.
Urogenital trichomoniasis	Adult	PO	400-500 mg q. 12 h. for 5-7 days
	Child	PO	15mg/kg/d given in 3 divided doses for 7 days.
Giardiasis	Adult	PO	2 g daily for 3 days and a further 2 g dose may be given if no clinical improvement, or 400 mg q. 8 h. for 5 days, or 500 mg q. 12 h. for 7-10 days.
	Child	PO	35-50 mg/kg/d given in 3 divided doses, q. 8 h. for 7-10 days.

**Reference: BNF 2001 (Sept), pp. 286,316.*

2) Diloxanide Furoate [WHO]

- ***DRUG SUMMARY:***

Diloxanide furoate, a dichloroacetamide derivative, is a luminal amoebicide acting principally in the bowel lumen and is used in the treatment of intestinal amoebiasis. It is given alone in the treatment of asymptomatic cyst-passers, and in conjunction with an amoebicide that acts in the tissues, in patients with invasive amoebiasis. Good choice for recurrent or chronic amoebae.

- ***INDICATIONS:***

Treatment of asymptomatic carriers (*E. histolytica* cyst-passers) in nonendemic areas *(metronidazole and tinidazole are relatively ineffective for such cases. Refer to BNF 2001:316)*. Eradication of residual amoebae in the colonic lumen following treatment of invasive disease with metronidazole or other amoebicides.

- ***CONTRAINDICATIONS:***

Hypersensitivity to diloxanide.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: 500 mg 3 times daily for 10 days.
Child: 20 mg/kg daily in 3 divided doses for 10 days.
Directions: If necessary a second course may be given immediately following the first.
*May be taken without regard to meals.

- ***SPECIAL CASES:***

Pregnancy- Use only if clearly indicated. Treatment is best deferred until after the first trimester.
Lactation- Use with caution. Safety has not been reported.
Children- It has been used safely in children.
Renal + Liver Disease- Use with caution. No special adjustments reported.

- ***PRECAUTIONS AND WARNINGS:***

It is not effective against hepatic amoebiasis.

- ***ADVERSE EFFECTS:***

Mild GI tract symptoms, particularly flatulence, may be troublesome. Vomiting, pruritus and urticaria have been reported.

- ***INTERACTIONS:***

None reported.

- ***OVERDOSE:***

Symptoms: Nausea and vomiting.
Treatment: Induces emesis if not already occurred. Gastric lavage may be used. Use supportive symptomatic care.

- ***BRANDS:***

Furamide (Knoll).

---

3) Mebendazole [WHO]

- ***DRUG SUMMARY:***

Mebendazole is effective in threadworm infections (the commonest one is the pinworm "*Enterobius vermicularis*"), but its use needs to be combined with hygienic measures to break the cycle of auto-infection. All members of the family require treatment. Mebendazole is the drug of choice for patients of all ages over two years. It is given as a single dose; as reinfection is very common, a second dose may be given after 2-3 weeks. Also, it is used in the treatment of infection caused by other types of helminths as roundworm (Ascaris), whipworm, and hookworm infections.

- ***INDICATIONS:***

Treatment of infections caused by threadworm, roundworm, whipworm, and hookworm.

- ***CONTRAINDICATIONS*:**

Hypersensitivity to mebendazole.

- ***DOSAGE FORMS:***

Tablets and suspension.

- ***RECOMMENDED DOSAGE:***

Doses are summarized in the table below.
Directions: It may be given without regard to food. The tablet may be chewed, crushed, or swallowed.

Recommended Doses of Mebendazole		
Threadworms' infection (*Enterobius vermicularis*)		
Adult & children over 2 years	PO	100 mg as a single dose; if reinfection occurs a second dose may be needed after 2-3 weeks.
Other infestations		
Adult & children over 2 years	PO	100 mg twice daily for 3 days. If no cure, another course may be given.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use not recommended for pregnant women (Category C); benefit-risk issue.

Lactation- Use not recommended. Safety in nursing mother has not been established.

Children- Not recommended for children under 2 years.

Renal Disease- Minimally absorbed from the GI tract, safely used in the case of renal disease, when used as directed.

Liver Disease- Minimally absorbed from the GI tract, can be used in the case of liver disease.

- ***ADVERSE EFFECTS:***

Abdominal pain and diarrhea which are rare.

- ***INTERACTIONS:***

****Carbamazepine*** and ***hydantoins*** may reduce the plasma level of mebendazole, leading to a decrease in its therapeutic effectiveness.

- ***OVERDOSE:***

GI complaints lasting to a few hours may occur. Induce vomiting and purging.

- ***BRANDS:***

Vermacare (Pharmacare), Vermazol (JePharm), Vermox (Abic), Wormex (Megapharm).

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4) Niclosamide

- ***DRUG SUMMARY:***

Niclosamide is a halogenated salicylanilide derivative anthelminitic. It is the most widely used drug for tapeworm infections. It is not effective against larval worms, and it affects the cestodes of the intestine only. The fact that fasting is not necessary, makes it more preferred by patients particularly in the treatment of children.

- ***INDICATIONS:***

Intestinal tapeworm (cestode) infections, example *Taenia saginata* (beef tapeworm), *Diphyllobothrium latum* (fish tapeworm), *Hymenolepis nana* (dwarf tapeworm), *Hymenolepis diminuta* (rat tapeworm), *Dipylidium caninum* (dog or cat tapeworm).

- ***CONTRAINDICATIONS:***

Hypersensitivity to niclosamide or any of its components.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Beef and Fish Tapeworm		
Adult	PO	2 g as a single dose
Child (> 34 kg)	PO	1.5 g as a single dose
Child (11-34 kg)	PO	1 g as a single dose
Dwarf Tapeworm		
Adult	PO	2 g/d as a single dose for 7 days
Child (>34 kg)	PO	1.5 g/d as a single dose for 6 days
Child (11-34 kg)	PO	1 g as a single dose on day 1, then 500 mg once/d for next 6 days.

<u>Directions</u>*:* It should be taken after a light meal. Instruct the patient to chew tablet thoroughly, then swallow with a little water.

*For young children, tablet may be crushed to a fine powder and mixed with sufficient water to form a paste for ease of ingestion.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use during pregnancy only when it is clearly indicated (Category B).
Lactation- Its use during lactation has not been established.
Children- Its use in children less than 2 years has not been established.
Renal Disease- Minimally absorbed from the GI tract, therefore, safely used in the case of renal disease.
Liver Disease- Minimally absorbed from the GI tract, may be used in the case of liver disease.

- ***ADVERSE EFFECTS:***

Occasional GI upset, light-headedness, and pruritus.

- ***OVERDOSE:***

In the events of the overdose, do not induce vomiting. Refer to the hospital and give a fast-acting laxative and enema.

- ***BRANDS:***

Yomesan (Bayer).

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5) Albendazole [WHO]
(hydatid disease)

Cysts caused by *Echinococcus granulosus* grow slowly and asymptomatic patients do not always require treatment. Surgical treatment remains the method of choice in many situations. **Albendazole** is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases.

Alveolar echinococcosis due to *E. multilocularis* is usually fatal if untreated. Surgical removal with albendazole use is the treatment of choice, when effective surgery is impossible, repeated cycles of albendazole (for a year or more) may help.

Careful monitoring of liver function is particularly important during drug treatment.

D) ANTI-FUNGALS

Fungal infections are frequently associated with a defect in host resistance which should, if possible, be corrected; otherwise drug therapy may fail. Treatment of dermatophyte infections may be unsuccessful until the animal source has been removed or controlled. Fungal infections are traditionally divided into two classes; superficial and systemic. The most common fungal infections are superficial and are treated with topical agents or with oral agents. Most current drugs (i.e. imidazoles and triazoles) may be used systemically or topically. Systemic mycotic infections are often found in debilitated or immunosuppressed patients.

(For topical use of antifungal agents refer to the dermatological section).

1) Nystatin [WHO,P]

- ***DRUG SUMMARY:***

It is not absorbed when it is given by mouth and is too toxic for parenteral use. It is active against a number of yeast and fungi but is principally used for *Candida albicans* infections of skin and mucous membranes. It is also used in the treatment of intestinal candidiasis.

- ***INDICATIONS:***

Candidiasis.

- ***CONTRAINDICATIONS:***

It is contraindicated in the case of hypersensitivity to nystatin, and in the case of vaginal infections caused by *Gardnerella vaginalis* or *Trichomonas spp*.

- ***DOSAGE FORMS:***

Tablets, suspension, vaginal tablets.

- ***RECOMMENDED DOSAGE:***

Refer to the following table:

Recommended Doses of Nystatin		
Candida Infections		
Adult	PO	50,000-1,000,000 IU three times daily. 1-4 troches 4-5 times/d. Suspension: 400,000-600,000 IU 4 times daily.
	Vagi-nal	1-2 tablets daily for 2 weeks.
Child	PO	Suspension: 400,000-600,000 IU 4 times daily.
Infants	PO	100,000-200,000 IU 4 times daily.

Directions: In the case of oral suspension: rinse the mouth with 1-2 tsp of nystatin oral susp., keep it in the mouth as long as possible then expectorate or swallow (better for children and infants). Avoid food and drink for at least 30 min. after administration.

*Avoid the direct contact of the drug with hands.

*Store vaginal suppositories in refrigerator below 15° C.

*Treatment of candidiasis should be continued for at least 48 hours after the disappearance of symptoms.

- ***USE IN SPECIAL CASES:***

Pregnancy- Category A. No adverse effects or complications have been attributed to nystatin in infants born to women treated by nystatin.

Lactation- It is poorly absorbed from the GI tract, therefore it should not have any adverse effects on the nursing infant.

Renal and liver Diseases- It is poorly absorbed from the GI tract, and passes unchaged in the stool, therefore no special precautions are recorded.

- ***ADVERSE EFFECTS:***

Nausea, vomiting, diarrhea at high doses.

- ***BRANDS*:**

Nystatin (Taro), Candistan (BPC).

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2) Miconazole [WHO,P]

- ***DRUG SUMMMARY:***

Miconazole is mainly used for local treatment and can be given by mouth for oral and intestinal infection; it can also be given parentally for systemic infections including aspergillosis, candidiasis, and cryptococcosis but the injection contains polyethoxylated caster oil which may give rise to hypersensitivity reactions.

- ***INDICATIONS:***

Mainly used to treat severe systemic fungal infections.

- ***CONTRAINDICATIONS:***

Hypersensitivity to miconazole.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Oral and Intestinal Fungal Infections		
By mouth as tablets	250 mg q. 6 h. for 10 days or up to two days after symptoms clear.	
By mouth as oral gel	Adult	5-10 ml in the mouth after food q. 6 h.; retain near lesions before swallowing.
	Child < 2 yrs.	2.5 ml b.i.d.
	Child 2-6 yrs.	5 ml b.i.d.
	Child > 6 yrs.	5 ml 4 times daily.
Vaginal Infections		
Intra-vaginal	Vaginal cream or vaginal supp.	1 applicator full of cream or one 100 mg supp. at bedtime for 7 days or one 200 mg supp. at h.s. for 3 days.

Directions: Oral preparations should be taken after food. In the case of oral gel, smear the affected area with a clean finger and hold it in the mouth for a while before swallowing.

- ***USE IN SPECIAL CASES:***

Pregnancy- Category B after the first trimester. It should be used only when clearly indicated.
Lactation- No available data on use. Avoid use, unless clearly indicated.
Children- Safety in children under 1 year of age has not been established.
Renal Disease- Cautious use in the case of renal impairment.
Liver Disease- Cautious use in the case of hepatic impairment.

- ***PRECAUTIONS AND WARNINGS:***

Hepatic and renal impairment.

- ***ADVERSE EFFECTS:***

Nausea, vomiting, pruritus, and rashes.

- ***INTERACTIONS:***

Overview of Miconazole Drug-Drug Interactions	
Drug	**Interaction**
Warfarin, sulphonyl-ureas and phenytoin	Miconazole enhances the effect of these. Monitor patients and adjust their doses as needed.
Ampho-tericin	Miconazole antagonizes its effect. Use with caution.

- ***BRANDS:***

Dakatrin Oral Gel (Abic), Daktazol Oral Gel (JePharm), Gyno-Daktarin (Abic), Gyno-Daktazol (JePharm), Gyno-Daktazol Ovules (JePharm).

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3) Griseofulvin [WHO,P]

- ***DRUG SUMMARY:***

May be produced by the growth of certain strains of *Penicillium griseofulvum* or by other means. It is selectively concentrated in keratin and is the drug of choice for widespread or intractable dermatophyte infections. It is well absorbed from the gut but is inactive when applied topically. It is more effective in skin than in nail infections and treatment must be continued for several weeks or even months. Side effects are uncommon.

- ***INDICATIONS:***

Dermatophyte infections of the skin, scalp, hair and nails, where topical therapy has failed or is inappropriate. It is effective against various species of *Epidermophyton*, *Microsporum*, and *Trichophyton* (has no effect on other fungi, including *Candida spp.*, bacteria, and yeast).

- ***CONTRAINDICATIONS:***

In porphyria, hepatic failure, and systemic lupus erythematosus.

- ***DOSAGE FORMS:***

Tablets

- ***RECOMMENDED DOSAGE:***

Tinea Corporis, Tinea Cruris, and Tinea Capitis		
Adult	PO	500 mg microsize or 330-375 mg ultramicrosize daily in single or divided doses.
Tinea Pedis, Tinea Unguium		
Adult	PO	0.75-1 g microsize or 660-750 mg ultramicrosize daily in single or divided doses; microsize dose should be decreased to 500 mg/d after response is noted.
Child	PO	11 mg/kg/d microsize or 7.3 mg/kg/d ultramicrosize in single or divided doses.

<u>*Directions*</u>: It should be taken with or after the meal. Continue taking the medication for entire course of therapy even if beneficial effects may not be noticeable.
*Duration of treatment depends on the thickness of the keratin layer: 2-6 wks. for hair and skin, up to 6 mon. for fingernails, and 12 mon. or more for infections of the toenails.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use it only when it is clearly indicated (Category C). Griseofulvin was embryotoxic and teratogenic rates. Cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy.
Lactation- Use caution. No available data.

Children- Safety not established in children less than two years old.
Liver Disease- It is contraindicated in the case of hepatic failure.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in the case of penicillin-sensitive patients since there is a possibility of the presence of cross-sensitivity between penicillin and griseofulvin.
-It may impair performance of skilled tasks (e.g. driving).
-It enhances the effect of alcohol.

- ***ADVERSE EFFECTS:***

Headache, nausea, vomiting, rashes, photosensitivity, dizziness, fatigue, agranulcytopenia and leucopenia have been reported; lupus erythematosus, erythema multiforme, peripheral neuropathy, confusion, and impaired co-ordination.

- ***INTERACTIONS:***

Overview of Griseofulvin Drug-Drug Interactions	
Drug	**Interaction**
Anti-coagulant	Griseofulvin increases the metabolism of nicoumalone and warfarin leading to a decrease in their anticoagulant activity.
Oral contra-ceptives	Griseofulvin increases the metabolism of OCs.
Pheno-barbitone	It increases the metabolism of griseofulvin, leading to a decrease in its anti-fungal activity.

- ***BRANDS:***

Grifulin Forte (Teva), Sporofulvin (JCL).

C) ANTIVIRAL AGENTS

Specific therapy of viral infections is generally unsatisfactory, and treatment is primarily symptomatic. Most agents are active against the virus, but do not eradicate them. Infections that do not respond to antivirals include mumps, poliomyelitis, rabies and rubella.

With the increased number of HIV infected people world wide, there are many antiviral drugs that are specific for this causative agent of AIDS. AIDS medications will not be discussed in our book at this time, since AIDS patients in our community seek special medical supervision, and will rarely be treated at the primary healthcare level.

This section will discuss the antiviral agent Acyclovir.

1) Acyclovir

- ***DRUG SUMMARY:***

Acyclovir, written as aciclovir in British English, is an antiviral agent (a synthetic purine nucleoside derivative) that inhibits the viral replication by inhibiting DNA synthesis. It is active against *Herpes simplex virus* 1&2, *Varicella zoster*, *Epstein-Barr* and *Cytomegalovirus*.

- ***INDICATIONS:***

For the treatment of initial episodes and management of recurrent genital herpes in certain patients. It is also used for the acute treatment of *Herpes zoster* (shingles) and *Varicella* (chickenpox).

- ***CONTRAINDICATIONS:***

Hypersensitivity to acyclovir or any of its components.

- ***DOSAGE FORMS:***

Tablets, capsules, suspension, ointment.

- ***RECOMMENDED DOSAGE:***

Adult: ***Herpes simplex:***
Initial genital herpes: 200 mg PO q. 4 h.; 5 times a day for 10 days.
Chronic/recurrent disease: 400 mg b.i.d. for up to 12 months followed by reevaluation of the case. Reevaluation will determine if there is a need to continue or discontinue the medication.
Intermittent therapy: 200 mg q. 4 h.; 5 times a day for 5 days. Therapy should start as soon as the first symptom of recurrence occurs.

Herpes zoster, acute treatment: 800 mg q. 4 h.; 5 times a day for 7 to 10 days.

Child: ***Chicken pox:***

20 mg/kg (not > 800 mg) q. 6 h. for 5 days. Therapy should be started at the earliest sign or symptom.

- ***USE IN SPECIAL CASES:***

Pregnancy- There are no adequate studies in pregnant women (Category C). Use during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Lactation- Acyclovir is excreted in the breast milk, but there have been no reports of adverse effects. Exercise caution when administering to a nursing woman.

Children- Safety and efficacy of oral acyclovir in children < 2 years of age have not been established.

Renal Disease- Dosage adjustment is required with renal function impairment depending on the creatinine clearance as indicated in the table below:

Oral Acyclovir Dosage In Renal Function Impairment		
Normal dosage regimen (5 x daily)	**CL_{cr} (ml/min/ 1.73 m^2)**	**Adjusted dosage regimen**
200 mg q. 4 h.	> 10	200 mg q.4 h., 5 x dly
	0-10	200 mg q.12 h.
400 mg q. 12.h.	> 10	400 mg q. 12 h.
	0-10	200 mg q. 12 h.
800 mg q. 4 h.	> 25	800 mg q. 4 h., 5 x daily
	10-25	800 mg q. 8 h.
	0-10	800 mg q. 12 h.

- ***PRECAUTIONS AND WARNINGS:***

-In the case of genital herpes, the patient should avoid sexual intercourse when visible lesions are present because of risk of infecting the other partner.

-Acyclovir does not eliminate latent herpes simplex virus and is not a cure. It only decreases the frequency and the severity of recurrences. Resistance might develop when acyclovir is used continuously over an extensive period of time. Another type of antiviral should be used in this case.

-Dosage depends on the estimated Creatinine clearance (CL_{cr}). Continuous checking of CL_{cr} is recommended for patients using acyclovir for long periods of time.

- ***ADVERSE EFFECTS:***

Several adverse effects may occur such as: nausea, vomiting, diarrhea, headache, skin rash, dizziness, edema, leg pain, sore throat, flatulence, constipation, and malaise.

- ***INTERACTIONS:***

Overview of Acyclovir Drug-Drug Interactions	
Drug	**Interaction**
Probenecid	Acyclovir may increase its effect.
Zidovudine	Acyclovir interacts with zidovudine and causes severe drowsiness and lethargy. Use with caution.

- ***OVERDOSE:***

Overdose may be treated with hemo-dialysis. Renal failure might result from the overdose. In such cases, hemodialysis should continue until renal function is restored.

- ***BRANDS:***

Zovirax (Wellcome).

Chapter 6: Endocrine System Drugs

A) ANTI-DIABETIC DRUGS
1. **Insulin**
2. **Glibenclamide (Glyburide)**
3. **Metformin**

B) THYROID DRUGS
1. **Thyroxine**
2. **Propylthiouracil**

C) CORTICOSTEROIDAL DRUGS
1. **Prednisone**

A) ANTIDIABETIC DRUGS

Diabetes Mellitus (DM) is a complex disease characterized by symptoms of glucose intolerance, as well as changes in lipid and protein metabolism. Over the long term, these metabolic abnormalities, particularly hyperglycemia, contribute to the development of complications such as retinopathy, nephropathy and neuropathy.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has developed new criteria for the diagnosis of DM *[Diabetes Care, 1997(Jul); 20(7)]*. There are two major types of diabetes: Type 1 previously known as insulin dependent diabetes mellitus (IDDM) or juvenile form, and Type 2 previously known as non-insulin dependant diabetes mellitus (NIDDM) or adult/maturity onset form.

There are three major components for the treatment of DM; diet, exercise, and drugs. Each of these components interacts with the other to the extent that no assessment and modification of one can be made without knowledge of the other two.

The goal of therapy is to keep the patient free of symptoms associated with hyperglycemia or hypoglycemia, to prevent glucose toxicity, to eliminate or minimize all other cardiovascular risk factors and further macrovascular and microvascular diseases, and to maintain normal growth and development in children.

Diet, exercise, and insulin must be delicately balanced in type 1. If diet and weight loss have failed in type 2 patients, an oral hypoglycemic agent can be used. If drugs are used properly they can be both safe and effective.

There are six categories of drugs approved for the management of diabetes mellitus (see table-6.1). Some of these agents maybe used as single therapy or in combination. The proper choice between them is not completely clear. The factors that should be considered when choosing a drug include cost, contraindications, side effects, amount of glycemic-lowering needed to get the patient to the desired glucose range, ability for compliance, the patient's weight and ideal weight, and the lipid profile (White, 1998).

Table 6.1: Antidiabetic Drugs

Category	Examples
Insulins	Regular insulin Lispro insulin Isophane insulin
Sulfonylurea 1st generation:	Acetohexamide Chlorpropamide Tolazamide Tolbutamide
2nd generation:	Glipizide Glibenclamide (glyburide) Gliclazide Liquidone Glimepiride
Thiazolidinediones	Pioglitazone Rosiglitazone Troglitazone*
Meglitinides	Repaglinide Nateglinide
Biguanides	Metformin
Alpha-Glucosidase Inhibitors	Acarbose Miglitol

*(*removed from market due to reports of serious hepatic injury.)*

The 1st generation sulfonylureas are considered equally effective, but differ with respect to their pharmacokinetic properties and adverse effects profile. The 2nd generation agents are approximately 100 times more potent than the first generation drugs on a mg-to-mg basis, and have a lower profile of side effects and drug-drug interactions. For this reason, a second-generation agent (glibenclamide) was recommended over first generation agents to be discussed in this chapter. A comparison between sulfonylureas and the

biguanide Metformin can be seen in table-6.2.

The newer agents, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors differ in their mode of action and effects. Even within a class, there are differences in terms of toxicities and effect on lipid profiles. It is important to note that not all these agents have long-term data and comparative studies yet.

One should emphasize to the patient the importance of testing and recording urine and blood glucose levels, as well as keeping records of medications, doses, diet and exercise for unstable patients to improve their diabetic control. Proper urine or blood testing for glucose and ketones are important for them to know their blood glucose levels and to prevent any diabetic ketoacidosis.

Also, note the importance of general hygiene, foot, dental and eye care since DM patients are more susceptible to have problems in these areas than the average person. Warn your patients of symptoms of hypoglycemia and hyperglycemia as noted in table-6.3.

Various medications may cause symptoms of hyperglycemia or hypo-glycemia, or clinically significant drug interactions (use caution in such cases) as noted in table-6.4.

Table – 6.3: Symptoms of Hyperglycemia vs Hypoglycemia

Hyperglycemia	Hypoglycemia
-Flushed, dry skin -Excessive thirst -Excessive urination -Low blood pressure -Drowsiness -Lethargy -Urinary glucose ketones	-Fatigue -Headache/Dizziness -Excessive hunger -Profuse sweating -Numbness of extremities or mouth -Visual disturbances -Delirium -Coma

Table – 6.2: Summary of Oral Sulfonylureas vs. Metformin

CHARACTERISTIC	ORAL SULFONYLUREA	METFORMIN
Indication	NIDDM not controlled	NIDDM, mostly obese patients
Diet and Exercise	extremely important	extremely important
Dosing Intervals	q.d. or b.i.d.	b.i.d. or t.i.d.
Adverse Side Effects - Lactic acidosis - Hypoglycemia - Cardiovascular mortality - Weight reduction - GI disturbances	 none very common decrease mortality might cause weight gain mild-moderate	 possible uncommon no record, but possible help decrease weight moderate- severe
Pregnancy (avoid both if possible)	category B + C	category B
Lactation	excreted, discontinue drug	excreted, not recommended
Children	not used	not used
Renal Disease	use caution and monitor	contraindicated
Hepatic Disease	use caution and monitor	use not recommended
Alcohol Intake	disulfiram reaction	lactic acidosis
Administration with Insulin	possible	possible

Table –6.4: Clinically Significant Drug Interactions in DM Patients [1]

Drug-Induced Hyperglycemia	Drug-Induced Hypoglycemia
- Glucocorticoids	- Ethanol (Alcohol)
- Diuretics	- High dose salicylates
- Pentamidine*	- Pentamidine*
- High dose phenytoin in NIDDM	- Propranolol*
- Oral contraceptives	- Disopyramide
- β-Adrenergic Blockers	- Phenobarbital
- Nicotinic acid/ Niacin	- Sulfonamide antibiotics
- Sympathomimietics (epinephrine)	

* can cause either hyperglycemia or hypoglycemia.

[1] *Adapted from: Herfindal G, eds. Clinical Pharmacy and Therapeutics, 5th ed. Williams and Wilkins, Baltimore. 1992.*

Table 6.5: Pharmacokinetics and Compatibility of Various Insulins

Type	Insulin -preps.	Onset (hr)	Peak (hr)	Duration (hr)	Compatibly mixed with
Rapid-acting	Regular (clear soln.)	0.5-1.0	3-4	6-8	All
	Semilente	1.0-1.5	6-10	12-15	Lente
	Lispro	0.25	0.5-1.5	6-8	Ultralente+ NPH
Intermediate	Isophane- NPH	1.0-1.5	6-12	18-24	Regular
	Insulin Zinc-Lente	1.0-2.5	8-14	18-24	Regular + semilente
Long-acting	PZI	4.0-8.0	12-24	36	Regular
	Ultralente	4.0-8.0	12-30	36-42	Regular + semilente

1) Insulin WHO,P

- ***DRUG SUMMARY:***

Insulin is a hormone that is secreted by islets of Langerhans by the beta-cells of the pancreas. It is the principal polypeptide hormone required for proper glucose use in normal metabolic processes. It plays an important role in the metabolism of carbohydrate, fat and protein. Insulin is biosynthetically prepared by recombinant DNA technology using *E. coli*.

- ***INDICATIONS:***

Type 1 DM, and Type 2 DM that cannot be properly controlled by diet, exercise and weight reduction. In hyperkalemic emergencies to produce a shift of potassium into cells and lower serum potassium levels. Only the regular insulin can be given IV or IM in severe ketoacidosis or diabetic coma. Also, for administration to pregnant and nursing diabetics, as well as during stressful conditions or severe infections.

- ***CONTRAINDICATIONS:***

Hypersensitivity to insulin animal proteins or preservatives.

- ***DOSAGE FORMS:***

Injection: 100 units/ml, in 10 ml vials.

- ***RECOMMENDED DOSAGE:***

The type of insulin used and its dose and frequency of administration depends on the particular needs of each individual patient.

Table-6.6 lists different regimens that are commonly recommended. Any of them can be used depending on the patient's needs. **Individualize dosing regimens**.

Dose guidelines for adult and children 0.5-1 unit/kg/24 h.

Adjust dose to achieve pre-meal and bedtime blood glucose levels of 80-140 mg/dl, and for children < 5 yrs. levels of 100-200 mg/dl.

Insulin requirements may be increased by infection, stress, accidental or surgical trauma, puberty, and during pregnancy.

Requirements may be decreased in patients with renal or hepatic impairment and in those with some endocrine disorders or celiac disease.

Table-6.6: Some Examples of Common Recommended Insulin Regimens*

Insulin	Regimen
1. Short-acting mixed with intermediate-acting insulin:	- twice daily (15-30 min. a.c.).
2. Short-acting mixed with intermediate-acting insulin:	- before breakfast only, will be sufficient in some patients.
3. a) Short-acting mixed with intermediate- acting insulin:	- before breakfast.
b) Short-acting:	- before evening meal.
c) Intermediate acting	- bedtime (onset of action is 1-2 hrs.).
4. a) Short-acting insulin:	- t.i.d. (15-30 min. before breakfast, midday and evening meals).
b) Intermediate acting insulin:	- at bedtime.

** BNF 2001(Sep); (42): 323.*

Directions: **Patients should be given the following advice about the uses and administration of insulin:**

*Patients should use the same type and brand of insulin and syringe unit to avoid any dosage errors.

*Store vials in refrigerator if not in use. Do not freeze.

*Do not inject cold insulin, it can lead to lipodystrophy, reduced rate of absorption and local irritation.

Can keep the vial in use at room temperature (up to 30 days), away from direct sunlight or temperature extremes.

*Agitate vial by rolling between palm of hands, do not shake vial vigorously.

*If mixing insulin, always measure Regular (clear) before NPH (cloudy)!

*Rotate administration/injection sites to prevent lipodystrophy.

*Insulin requirements may change in patients who become ill, especially with vomiting or fever. Also there is a need to reduce the dose when caloric intake is reduced, or abnormally high physical activity is undertaken, to avoid hypo-glycemia.

*Need to emphasize to the patient the importance of properly monitoring their blood glucose levels, and maintaining proper diet and exercise.

*Occasionally, redness, swelling and itching at the injection site may develop. This could occur if injection is not properly made; the skin may be sensitive to the antiseptic solution, or if the patient is allergic to insulin or insulin additives (preservative). This condition usually resolves in a few days. If not, may need to switch type of antiseptic or insulin.

- ***USE IN SPECIAL CASES:***

Pregnancy- Pregnancy may make the management of diabetes more difficult. Insulin is the drug of choice for controlling glucose levels during pregnancy; even in type 2 DM. Requirements may increase during the 2nd or 3rd trimester of pregnancy. The patient should be kept under experienced medical supervision. Following delivery, insulin requirements may drop for 24 to 72 hrs., rising towards the normal pre-pregnancy dose during the next 6 weeks.

Lactation- Insulin does not pass into breast milk. Breast-feeding may decrease insulin requirements despite the increase in necessary caloric intake.

Children- Safe when following the correct dosage and use.

Renal Disease- In severe cases, doses should be reduced. Insulin requirements fall, since the compensatory response to hypoglycemia is impaired.

Liver Disease- Use caution, the drug is metabolized primarily in the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Lipodystrophy is the breakdown of adipose tissue at the insulin injection site,

causing a depression in the skin. This may be the result of an immune response. Advise patient to rotate the injection site.

-Diabetic ketoacidoses (DKA) is a potentially life-threatening condition, requiring immediate treatment. May result from stress, illness, insulin omission, or may develop slowly after a long period of poor insulin control. Treatment involves administration of fluids, correction of acidosis and hypotension, and low dose regular insulin IM or IV in an emergency room.

-Hypoglycemia may result from excess insulin dose, or: increased work load or exercise without eating, food not being absorbed because of skipping a meal or in illness with vomiting, fever or diarrhea. Insulin requirements decline.

Refer to table-6.7 for summary of difference between Ketoacidosis and Hypoglycemia.

- ***ADVERSE EFFECTS:***

-Hypersensitivity; usually occurs when insulin is at peak action, localized allergic reactions at the injection site, general uricaria and rash.

-Hypoglycemia / hyperinsulinism *(refer to introduction of this chapter for symptoms)*.

-Post-hypoglycemia or rebound hyper-glycemia may occur:

- Somogyi Effect, a morning (3-7 am), phenomenon caused by counter-regulatory hormone release. This can be avoided by decreasing insulin dosage for critical time period, reduce insulin dose for the overnight, or increase pre-bedtime snack.
- Dawn Phenomenon, an early morning rise in plasma glucose due to greater surge of growth hormones in diabetics predisposing patient to development of hyperglycemia. Need to increase the overnight insulin coverage.

(Test blood glucose levels at 3 am to differentiate between the two phenomenon.)

Table – 6.7. Summary of Hypoglycemia vs. Ketoacidosis

Reaction	Hypoglycemia (insulin reaction)	DKA (diabetic coma)
Onset	sudden	gradual, hours or days
Urine glucose/acetone	0/0 *	+/+
CNS symptoms	fatigue, weakness, confusion, headache, diplopia, convulsions, dizziness, unconsciousness	drowsiness, dim vision
Respiration	rapid, shallow	air hunger
Mouth /GI	numb, tingling, hunger, nausea	thirst, **acetone breath**, nausea, vomiting, loss of appetite
Skin	pallor, moist, shallow or dry	dry, flushed
Miscellaneous	normal pulse, eyeball normal	rapid pulse, soft eyeballs

* 0/ 0 not found. +/+ found

Professional Guide to Patient Drug Facts &Comparisons. St. Loius :Facts and Comparisons 2000.

- ***INTERACTIONS:***

Decrease Hypoglycemic Effect of Insulin	
Corticosteroids	Oral contraceptives
Dextrothyroxine	Smoking
Diltiazem	Thiazide diuretics
Epinephrine	Thyroid hormone
Increase Hypoglycemic Effect of Insulin	
Alcohol	MAO inhibitors
Anabolic steroids	Phenylbutazone
Colifibrate	Salicylates
Non-selective β-blockers	Tetracyclines

- ***OVERDOSE:***

Symptoms: Insulin overdose causes hypoglycemic symptoms; refer to adverse effects.

Treatment: Eating sugar or sugar-sweetened product will correct simple conditions and prevent serious symptoms. Refer to emergency room if it cannot be controlled. Glucose and dextrose administration, or glucagon, may be necessary.

- ***BRANDS:***

Humulin-N, Humulin-R, Humulin-U, Humulin 70/30 (Lilly),
Novolin-N, Novolin R, Insulin Actrapid HM, Insulin Mixtard ... (Novo Nordisk)
See price list for other preparations.

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2) Glibenclamide (Glyburide) WHO,P

- ***DRUG SUMMARY:***

Glibenclamide is one of the most potent sulfonylurea, hypoglycemic agents. It is a 2nd generation sulfonylurea with a potency of more than a 100-fold over first generation agents. Glibenclamide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. With chronic use, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea drugs. In addition to the blood-glucose lowering action, this drug produces mild diuresis by the enhancement of free water renal clearance.

- ***INDICATIONS:***

Glibenclamide is indicated as an adjunct to diet to lower blood glucose in patients with type 2 DM **when diet and weight reduction alone fail to control their hyperglycemia.**

- ***CONTRAINDICATIONS:***

Known hypersensitivity to the drug. As single therapy in type 1, uncontrolled patients complicated by ketoacidoses; with or without coma. Diabetes when complicated by pregnancy.

- ***DOSAGE FORMS:***

Tablets 5 mg.

- ***RECOMMENDED DOSAGE:***

Adult: 2.5-5 mg daily with breakfast or first main meal (for patients very sensitive to the agent start with 1.25), increase by 2.5 mg every 1-2 weeks if needed. Doses of 15 mg in 2 divided doses can be given, but unlikely to produce additional effects.
Do not exceed 20 mg/24 hours.
Child: Not to be used for children.

Directions: To be taken 30 minutes before meals provided that the patient has no GI disorders, if so can give with food. Onset of action is about 1.5 hrs.

*Advise patients not to discontinue medication abruptly, not to take any OTC medications without consulting a health care professional, and to monitor their blood or urine glucose levels.

*Diet and weight control should be emphasized as the primary form of treatment for all patients.

*Use of this medication is by no means a substitution for diet control or avoidance of physical activity.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use of insulin is recommended during pregnancy. Sulfonylureas have been teratogenic in animals (except glyburide), no studies have been done on pregnant women. Use only if clearly needed.

If used, it should be stopped at least 2 days – 4 weeks before expected delivery date to prevent severe hypoglycemia in newborn (Category B).

Lactation- Avoid. It is not known whether glibenclamide is excreted in human milk. Some sulfonylureas are excreted, and had potential for hypoglycemia in nursing infants. If the drug is discontinued and diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Children- Safety and efficacy haven't been established. Use is not recommended.

Renal Disease- Avoid use in severe cases. Need dosage adjustments Cl_{cr} is < 30 ml/min. Renal impairment may cause decreased elimination of the drug leading to hypoglycemia. [*Can use tolbutamide (Orinase, Tolanase®), or glipizide (Glucotrol, Glibenese®); they are a better choice in renal failure.*]

Liver Disease- Drug is metabolized extensively in the liver. Increased risk of hypoglycemia in severe liver disease, so avoid use or use small doses. Can produce jaundice.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in renal or hepatic insufficiency, elderly (more susceptible to side effects), malnourished patients, adrenal or pituitary insufficiency.

-Diet and exercise remain the primary consideration in NIDDM patient management.

Drugs are an adjunct to, not a substitute for them. Dietary regulations should be taught to patients, as well as monitoring methods to keep patients well controlled.

-The administration of oral hypoglycemic drugs has been associated with increased cardiovascular mortality as compared to treatment with diet plus insulin. The patients have to be informed of potential risk.

-Patients needs to contact the physician if any side effects such as fever, sore throat, rash, unusual bruising or bleeding occurs, as well as frequent episodes of Hypoglycemia or Hyperglycemia *(refer to introduction of this chapter for symptoms)*.

- ***ADVERSE EFFECTS:***

Hypoglycemia: all sulfonylureas may produce severe hypoglycemia, more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested. Administer a simple sugar as soon as possible if patient feels dizzy and ready to faint.

Other symptoms: GI disturbances; epigastic fullness, weight gain, heartburn, nausea, jaundice; pruritis, erythema, skin eruptions (if skin reactions persist, discontinue the drug), photosensitivity, joint pain, leg cramps, elevated liver function tests, and blood dyscraisis.

- ***INTERACTIONS:***

Overview of Glibenclamide Drug-Drug Interaction

Drug	Interaction
Alcohol	It causes disulfiram-like reaction; facial flushing, occasional breathlessness, sometimes nausea and vomiting. Avoid drinking alcohol or eating foods that contain it, while taking this medication.
β-blockers*, *hydantoins*, *rifampin*, *thiazide diuretics*, and *steroids	These may diminish the hypoglycemic effect. Monitor blood glucose of patients closely and adjust the sulfonylurea dosage accordingly.

Chloram-phenicol*, *Co-trimox-azole*, *tetracyclines*, *butazones*, *salicylates*, and *sulfonamides	These increase the hypoglycemic effect of the medication. Monitor blood glucose concentrations and observe for symptoms of hypoglycemia. Use with caution, if needed adjust dose of sulfonylurea accordingly.
Digitalis glycosides	Concurrent administration increases digitalis serum levels, caution use. For patients who start therapy, monitor serum digitalis levels carefully until levels are stabilized.
Oral anti-coagulants	Metabolic degradation of sulfonylurea is slowed by dicumarol, leading to a greater risk of hypoglycemia.

- ***OVERDOSE:***

Symptoms: An acute overdose may produce hypoglycemia as well as tingling of the lips and tongue, nausea, diminished cerebral function (lethargy, confusion, agitation, nervousness), increased sympathetic activity (tachycardia, sweating, tremor, hunger) convulsions, stupor and coma.

Treatment: Treat mild hypoglycemia with oral glucose and adjustment in drug dosage or meal patterns. Severe cases require immediate hospitalization, administration of dextrose IV, and close monitoring.

- ***BRANDS:***

Daonil (Hoechst), Declamide (JCL), Diabeta (Hoechst-Roussel), Glibetic (Teva), Gluben (Dexxon), Glucocare (Pharmacare), Gluconil (JePharm).

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3) Metformin WHO,P

- ***DRUG SUMMARY:***

Metformin is a biguanide oral antihyperglycemic drug used in the management of type 2, NIDDM. It is not chemically or pharmacologically related to the oral sulfonylureas. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma response may actually decrease. In clinical studies, the drug has shown a favorable effect on serum lipids, which are often abnormal in type 2.

Metformin has a different mode of action than the sulfonylureas. It is also used for type 2 patients in adjunction to diet when all methods of glycemic control have failed. Metformin has been associated with weight loss, which seems to be the only advantage over the sulfonylurea agents, which has made it the drug of choice in obese (≥ 20% ideal body weight) diabetic patients. Cases of lactic acidosis, which can be fatal, is its major hazard, especially in renal disease patients. Metformin costs more than sulfonylureas, and has a more serious adverse effects profile. It may be best used in obese patients, or in cases when an oral sulfonylurea alone is ineffective. It could then be used alone or in combination with a sulfonylurea (refer to table-6.2).

- ***INDICATIONS:***

In type 2 DM. Metformin is used in the treatment when strict dieting and sulfonylureas have failed to control patients, especially in overweight patients, in whom it may if necessary, be used first.

It could be used concomitantly with a sulfonylurea when diet and metformin or sulfonylureas alone do not give control.

- ***CONTRAINDICATIONS:***

Renal disease or dysfunction, or abnormal Cl_{cr} which may result from conditions such as cardiovascular collapse, acute MI and septicemia.

Hypersensitivity to metformin. Acute or chronic metabolic acidosis.

Temporarily withhold metformin in patients undergoing radiological studies involving parenteral administration of iodinated contrast materials because these may result in acute changes in renal function.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: 500 mg PO t.i.d., or 850 mg b.i.d.; max. 3000 mg/day.

Child: Do not use in children.

Directions: Dosage should be individualized on basis of both effectiveness and tolerance. Give in divided doses with or after meals.

*Start with low dose 500 mg b.i.d., and gradually increase to identify the minimum dose required for adequate glycemic control.

*Use fasting plasma glucose to determine therapeutic response to metformin. Thereafter, measure glycosylated hemoglobin at intervals of ~ 3 months.

*Short-term administration may be sufficient during periods of transient loss of control on diet alone.

*Inform the patient about the importance of adherence to dietary instructions, regular exercise, regular blood glucose testing, renal function and hematological tests.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use. Safety has not been established (Category B). Use of insulin is recommended instead.

Lactation- Studies in rats show that it is excreted in milk. Safety in humans has not been established, exercise caution, and take into account the importance of the drug to the mother when discontinuing use. Use of insulin may be safer.

Children- Use not recommended. Safety and efficacy have not been established.

Renal Disease- Contraindicated. Do not use even in mild conditions due to the increased risk of lactic acidosis. The drug is excreted primarily unchanged in the urine.

Liver Disease- Avoid use due to increased risk of lactic acidosis.

- ***PRECAUTIONS AND WARNINGS:***

-Lactic Acidosis: LA is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment. When it occurs, 50% of cases are fatal. It is characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap. The risk of LA increases with the degree of renal dysfunction and the patient's age. Onset is often difficult to detect, and accompanied only by nonspecific symptoms such as malaise, respiratory distress, abdominal distress and hypotension.

-There is an increased risk or cardiovascular mortality with administration of oral anti-diabetic drugs. This warning may also apply to metformin although no sufficient data is available.

-Hypoglycemia does not usually occur under usual circumstances, but could occur with deficient caloric intake, excessive exercise not compensated by caloric supplementation, or during concomitant use with other glucose lowering agents or ethanol.

- ***ADVERSE EFFECTS:***

GI side effects are very common, and are mainly dose related; diarrhea, nausea, vomiting, abdominal bloating, flatulence and anorexia. Temporary reduction in dose may be useful, until the symptoms are controlled. Some patients may experience metallic taste, this may resolve spontaneously. Vitamin B_{12} absorption may be impaired, administration of supplementation may be done if necessary. Test levels every 2-3 years to prevent any anemia complications.

- ***INTERACTIONS:***

Overview of Metformin Drug-Drug Interaction	
Drug	**Interaction**
Alcohol	It enhances the effect of metformin on lactate metabolism; advise patients against excess intake whether acute or chronic use, to avoid precipitation of lactic acidosis.

Cationic drugs	Such as: amiloride, digoxin, morphine, quinidine, ranitidine, trimethoprim, vancomycin, which are eliminated by renal tubular secretion, have a potential for increasing levels of metformin. Use with caution.
Cimetidine	Caused a 60% increase in peak metformin plasma level. Do not administer concomitantly.
Furosemide	It increases level of metformin, while the half-life of furosemide was decreased. Use with caution.

- ***OVERDOSE:***

No hypoglycemia has been seen even with ingestion of up to 85 g of metformin. Lactic acidosis has occurred. If suspected, refer to hospital, hemodialysis is indicated.

- ***BRANDS*:**

Glucomet (BPC), Glucomin (Dexxon), Glucophage (Bristol-Myers Squibb).

B) THYROID DRUGS

The hormones synthesized and released by the thyroid gland affect such basic processes as oxygen consumption, heat production and metabolism of carbohydrates, fats and protein. Thyroid hormones are recognized as the regulators of the metabolic level in most tissues, and are required for normal growth and differentiation. They are required for the functioning of other hormones such as catecholamines, corticosteroids and anti-diuretic hormone.

Inadequate or excessive secretions of these hormones result in the clinical conditions called hypothyroidism and hyperthyroidism respectively.

Hypothyroidism requires thyroid replacement therapy; using thyroxine and levothyroxine (T_4). The majority of patients require lifelong replacement therapy. Hyperthyroidism requires anti-thyroid agents; such as propylthiouracil and methimazole. Generally after 1-2 years of control, medication can be stopped.

1) Thyroxine WHO,P

- ***DRUG SUMMARY:***

Thyroxine sodium (the levothyroxine-T_4 isomer) is the treatment of choice for maintenance therapy in hypothyroidism. Administration of levothyroxine alone may produce normal levels of both T_4 and T_3, since it is converted to T_3 naturally in the body. Drug action is not clearly understood, but is known to increase the metabolic rate of all body tissues.

- ***INDICATIONS:***

Hypothyroidism, as replacement therapy of any etiology, including: cretinism, myxedema, non-toxic goiter, total or partial absence of thyroid gland, or the effects of surgery, radiation or drugs. May be also used with anti-thyroid drugs to treat thyrotoxicosis.

- ***CONTRAINDICATIONS:***

Hypersensitivity to active or extraneous constituents. Acute myocardial infarction, and adrenal insufficiency.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: Doses are usually individualized depending on the basis of clinical response and biochemical tests. However the starting dose is 25-50 *u*g/24h (0.025-0.050 mg/24h) increased by 50-100 ug/24h every 3-4 weeks till response (usual recommended dose 100-200 ug/24h).

Patients > 50 yrs or with cardiac disease start with the lower dose (25 ug/24h) and titrated up more slowly.

Child: Recommended Pediatric Dosages for Congenital Hypothyroidism:

Age	Dose/day (mcg)	Daily dose/ kg (mcg)
0 - 6 mon.	25 - 50	8 - 10
6 - 12 mon.	50 - 75	6 - 8
1 - 5 yrs	75 - 100	5 - 6
6 - 12 yrs	100 - 150	4 - 5
> 12 yrs	> 150	2 - 3

Directions: Administer as a single dose, preferably before breakfast to prevent insomnia. Food interferes with absorption.
*Onset of actin requires 3-5 days.
*If a dose is missed, tell the patient to take it as soon as remembered, then to continue with the regular schedule. Do not administer a double dose.
*For children who can't swallow; tablets can be crushed and suspended in a small amount of water, then administered by spoon or dropper. The prepared suspension should not be stored for any period of time. Crushed tablets may also be sprinkled over a small amount of food such as apple-sauce.
*Inform the patient to report any signs of toxicity.
*Patient should be advised not to change brands of medications, due to the a narrow therapeutic window of thyroid hormone therapy, since there may be differences in bioequivalence between products.
*Caution patient to avoid OTC medications unless approved by the physician.

- ***USE IN SPECIAL CASES:***

Pregnancy- Compatible (Category A). Thyroid hormones do not readily cross the placenta. Do not discontinue medication in hypothyroid women during pregnancy.
Lactation- Use caution. Minimal amounts of thyroid hormones are excreted in breast milk. They are not associated with serious adverse reactions.
Children- Partial loss of hair may be experienced in the first few months of therapy, it is a usual transient phenomenon that later is recovered.
Renal Disease- Use with caution.
Liver Disease- Use with caution.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in cardiovascular disease, angina pectoris, hypertension, and in impaired renal function.
-In endocrine disorders, thyroid hormone therapy in patients with concomitant diabetes mellitus or insipides or adrenal insufficiency (Addison's disease) exacerbates the intensity or their symptoms. Appropriate adjustments in therapy in these cases are required.
-Long-term levothyroxine therapy has been associated with decreased bone density in the hip and spine in pre- and post-menopausal women. These effects may be avoided by using minimal dose required and periodically monitoring the patient. It may be beneficial to obtain a basal bone density measurement, and monitor closely for osteoporosis development.

- ***ADVERSE EFFECTS:***

Adverse side effects other than those indicating hyperthyroidism due to therapeutic overdosage, either initially or during maintenance period are rare.

- ***INTERACTIONS:***

Overview of Thyroxin Drug-Drug Interaction	
Drug	**Interaction**
Choles-tyramine* & *colestipol	These decrease efficacy of thyroid hormone and cause potential hypothyroidism. Administer 4-6 hrs. apart.
Estrogen	May decrease response to therapy in patients with non-functioning thyroid gland. Use with caution.
Anti-coagulants	Thyroid hormones increase action of *anticoagulants*, there might be a need to decrease the anticoagulant dose if necessary.
Digitalis glycosides	Serum level of digoxin may be reduced. Monitor levels.
Epinephrine* & *norepi-nephrine	Increase risk of cardiac insufficiency. Avoid concomitant use.

- ***OVERDOSE:***

Symptoms are those of hyperthyroidism and may include: palpitations, tachycardia, angina, tremors, nervousness, insomnia, diarrhea, vomiting, weight loss, sweating, heat intolerance and fever.

These agents rarely result in clinical toxicity.

Treatment is aimed at reducing GI absorption of the drug, and controlling side effects that arise, cardiac, fluid loss, fever, and hypoglycemia.

- ***BRANDS:***

Eltroxine (Glaxo).

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2) Propylthiouracil WHO,P

- ***DRUG SUMMARY:***

Propylthiouracil **(PTU)** is a synthetic, thioamide derivative, anti-thyroid agent. It interferes with iodine and blocks synthesis of thyroxin; T_3 and T_4.

- ***INDICATIONS:***

Hyperthyroidism.

- ***CONTRAINDICATIONS:***

Hypersensitivity to anti-thyroid drugs, and nursing mothers.

- ***DOSAGE FORMS:***

Tablets

- ***RECOMMENDED DOSAGE:***

Adult: Initially 300-600 mg/24h. in divided doses, depending on the severity of the disease, then the dose is reduced after euthyroid state to maintenance dose.

May need to increase 600-900 mg/day in some patients.

Maintenance- usually 100-150 mg/day in three equally divided doses. Max. 1200 mg/d.

Child: > *10 years;* initial dose 150-300 mg/24h.

6-10 years; 50-150 mg/24h.

neonates; 5-10 mg/kg/24h.

Maintenance- determined by patients' response.

Directions: Administer 3 equal doses at approximately 8 hrs. intervals, with food or milk to reduce stomach upset.

*Advise patient not to change time intervals throughout therapy.

Most patients achieve euthyroid state within 6-12 wks, depending on severity of the disease state.

*Clinical response is monitored through changes in weight and pulse. Advise patient to chart weight 2-3 times weekly. Teach them to take pulse accurately.

*They should report any signs of tremor, tachycardia, increased pulse rate, fever, diarrhea, vomiting, weight loss and anxiety states, which may be due to inadequate therapy. Adjust dosage accordingly.

*Caution use of iodized salt or of seafood in the diet.

- ***USE IN SPECIAL CASES:***

Pregnancy- Can use when clearly needed. The potential benefit for the mother is more than the potential risk. It readily crosses the placenta and can induce goiter in developing fetus. Still these agents are effective drugs in hyperthyroidism complicated by pregnancy, and should be used if the problem arises (Category D). The thyroid dysfunction diminishes as the pregnancy proceeds, thus making a reduction of dose possible.

Lactation- Post-partum patient receiving anti-thyroid preparations should not nurse their babies. But if necessary, it is acceptable to use PTU after a month or two.

Children- PTU has caused hepatotoxicity in pediatric patients. Discontinue the drug immediately if signs and symptoms of hepatic dysfunction develop.

Renal Disease- Use with caution; need to monitor patients. Cases of nephritis have been reported. The drug is excreted in the urine.

Liver Disease- Use with caution. The drug is rapidly metabolized and inactivated in the liver. Can cause jaundice.

- ***PRECAUTIONS AND WARNINGS:***

-Agranulocytosis is potentially the most serious side effect of therapy that may occur (rarely) in the first few months of treatment if at all. Instruct patient to report

any symptoms such as: hay fever, sore throat, skin eruptions, fever, consistent headaches or general malaise. The drug should be discontinued in such case, and a WBC count and differential should be made.

-Hemorrhagic effects: PTU may cause hypoprothrombinemia and bleeding. Monitoring of prothrombin time during therapy is advised.

-Treatment generally lasts 1-2 years. After control, medication can be stopped gradually. Relapse after one course of anti-thyroid drug therapy usually indicates the need for another form of treatment.

- ***ADVERSE EFFECTS:***

Occur in < 1 % of patients. Agranulo-cytosis is the most serious effect.

Possible side effects: headache, vertigo, CNS stimulation, nausea and vomiting, epigastric distress, loss of taste, skin rash, exfoliative dermatitis, aplastic anemia, jaundice, nephritis, abnormal hair loss, edema, or drug fever.

- ***INTERACTIONS:***

None reported.

- ***OVERDOSE:***

Symptoms include: nausea, vomiting, epigastric distress, fever, headache, pruritis, edema, possible; agranulocytosis, hepatitis, CNS stimulation or depression.

Treatment: need to protect patient's airway and support ventilation and perfusion till reach emergency room where general management of acute overdose is applied.

- ***BRANDS:***

Propylthiocil (Teva).

C) CORTICOSTEROIDAL DRUGS

The naturally occurring adrenal cortical steroids have both anti-inflammatory (glucocorticoid) and salt retaining (mineral-ocorticoid) properties. Glucocorticoids are adrenocortical steroids, both naturally occurring or synthetic, and cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Due to their glucocorticoid character, they are widely used in inflammatory conditions.

Hydrocortisone (cortisol) and cortisone, are used as replacement therapy in adrenocortical insufficiency states and may be used for their anti-inflammatory effects in severe cases. The synthetic steroid compounds prednisone, prednisolone and fludrocortisone also have both gluco-corticoid and mineralocorticoid activity, and are used primarily for their gluco-corticoid effects. The rest of the synthetic compounds are distinguished by the absence of any significant salt-retaining activity, and are very potent anti-inflammatory agents.

As can be seen from table-6.8, the major differences among the corticosteroids are potency of medication and variation in some secondary effects. If a patient is allergic to one corticosteroid, chances are they are allergic to all, and the use of such medication should be avoided.

Corticosteroids are prescribed for a wide variety of disorders from skin rash to cancer. If patients are not producing enough adrenal hormones, corticosteroids may be used as replacement therapy. They may also be prescribed to treat the following: bursitis, arthritis; severe skin reactions (such as psoriasis), severe respiratory diseases, blood disorders, gastrointestinal diseases (including ulcerative colitis), and inflammation of the nerves, heart and other organs.

In this section Prednisone will be considered the prototype drug of the corticosteroids. For other corticosteroids used in asthma, dermatology or ophthalmic preparations refer to individual chapters.

Table 6-8. Glucocorticoid Equivalencies [§]				
Glucocorticoid	**Approximate equivalence dose (mg) [Potency]**	**Relative anti-inflammatory (Glucocorticoid) potency**	**Relative Na^+ retaining (mineralocorticoid) potency**	**Plasma half-life (min.)**
Short-acting				
Cortisone	25	0.8	2	30
Hydrocortisone	20	1	2	80-118
Intermediate-acting				
Prednisone	5	4	1	60
Prednisolone	5	4	1	115-212
Triamcinolone	4	5	0	200
Methylprednisolone	4	5	0	78-188
Long-acting				
Dexamethasone	0.75	20-30	0	110-210
Betamethasone.	0.6-0.75	20-30	0	300

[§] *Drug Facts & Comparisons, 2000; p. 321.*

1) Prednisone [WHO,P]

- ***DRUG SUMMARY:***

Prednisone is an intermediate acting adrenal corticosteroid, a synthetic analog of hydrocortisone. Prednisone is inactive and is metabolized to prednisolone [WHO,P] in the body.

- ***INDICATIONS:***

Prednisone (or other intermediate acting corticosteroids) is indicated in the following conditions;

1. *Endocrine disorders:* primary or secondary adrenocortical insufficiency, congenital adrenal hyperplasia, hypercalcemia associated with cancer, autoimmune thyroiditis.
2. *Rheumatic disorders:* As adjunctive therapy for short term administration, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, acute and subacute bursitis, acute and nonspecific tenosynovitis [post traumatic osteoarthritis].
3. *Collagen disease:* systemic lupus erythematosus, systemic dermatomyosisitis, cranial arteritis, acute rheumatic carditis.
4. *Dermatologic diseases:* Pemphigus, bullous dermatitis herpetiformis, severe erythema multiform, exfoliative dermatitis, mycosis fungoides, severe psoriasis, severe seborrheic dermatitis
5. *Allergic states:* seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug anaphylactic and hypersensitivity reactions.
6. *Respiratory diseases:* symptomatic sarcoidosis, Loeffler's syndrome not manageable by other means, berylliosis, aspiration pneumonitis.
7. *Opthalmic disease:* Severe acute and chronic allergic and inflammatory process involving the eye, allergic corneal marginal ulcers, anterior segment inflammation, allergic conjunctivitis, keratitis, optic neuritis, iritis and iridocyclitis.
8. *Hematological disorders:* Idiopathic thrombocytopenic purpura in adults, acquired autoimmune hemolytic anemia, erythroblasopenia, congenital hypoplastic anemia.
9. *Gastrointestinal disease:* Ulcerative colitis, Crohn's disease, regional enteritis.
10. *Renal disease:* glomerulonephritis (minimal lesion).
11. *Other:* Only under specialists supervision: i.e., multiple sclerosis, neoplastic disease, edematous states, tuberculous meningitis, trichinosis with neurologic or myocardial involvement.

- ***CONTRAINDICATIONS:***

Known hypersensitivity to the drug and systemic fungal infections.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: 5 - 60 mg/d PO in single or divided doses, depending on the disease being treated. [When administered on alternate days; twice the usual daily dose is given every other day.]

Child: 0.1 - 0.15 mg/kg/d in single or divided doses.

Directions: Oral medication is administered at meal times or with a snack to reduce gastric irritation.

*Inform the patient to take the drug as prescribed and not to alter dosing regimens or stop medication without consultation with the treating physician.

*Single doses or alternate day doses should be taken in the morning prior to 9 am. Multiple doses should be evenly spaced at intervals throughout the day.

*Inform your patient of signs of adrenal insufficiency: fatigue, anorexia, vomiting, diarrhea, weight loss, dizziness and low blood sugar. Dosage reduction or withdrawal of therapy may be needed.

*For high doses or long-term therapy, avoid abrupt withdrawal of therapy, which may result in withdrawal symptoms. Withdrawal symptoms include myalgia, fever, malaise,

fatigue, dizziness, hypotension, and hypoglycemia. **It is important to taper the dose over several days to weeks to prevent withdrawal symptoms.**

*Small doses of corticosteroids or use for a short period (< wk.) may not produce withdrawal symptoms when the drug is discontinued, still, tapering the dose is advisable.

- ***USE IN SPECIAL CASES:***

Pregnancy- Pregnant women should not take corticosteroids unless the benefits outweigh the potential risks. Prednisone has the poorest transport in crossing the placenta compared to the other corticosteroids (Category C) and may be used in such cases. Chronic use of corticosteroids during the first trimester can lead to birth defects (i.e., hypoadrenalism, cleft palate). When using, the dose should be tapered of as for any other patient.

Lactation- Corticosteroids appear in breast milk, but small doses (< 20 mg/d) for a short period of time (< 10 days) may not harm the infant. Advise mother to wait 3-4 hours after the dose before breast-feeding. If larger doses are needed, advise mother against breast-feeding.

Children- Growth and development of infants and children on prolonged corticosteroid therapy, should be carefully observed.

Renal Disease- Use with caution. Edema may occur in the presence of renal disease with a fixed or decreased glomerular filtration rate.

Liver Disease- Use with caution. Use smaller doses in patients with liver problems.

- ***PRECAUTIONS AND WARNINGS:***

-Infections: Corticosteroids may mask the signs of infection, and new infections may appear during their use. If an infection occurs during therapy, it should be promptly controlled by suitable anti-microbial therapy.

-Use the lowest possible dose. Make a benefit/risk decision in each individual case as to the size of dose, duration of treatment and the use of daily or intermittent therapy, since complications of treatment, and side effects are dependent on these factors.

-Corticosteroid products often contain tartrazine dyes (color) and sulfites (preservatives) that many people are allergic to. If the coloring and the preservatives are not indicated on the box, the patient or doctor can ask the manufacture of the product for this information.

- ***ADVERSE EFFECTS:***

Most common possible side effects may include: nausea, vomiting, stomach upset, may lead to peptic or duodenal ulcers.

Other common side effects: edema, heart failure, fluid and electrolyte disturbances, potassium loss, muscle weakness, loss of muscle mass, calcium loss (osteoporosis in severe cases), growth suppression in children, slow wound healing, allergic skin rash, convulsions, headache, insomnia, and dizziness.

Less common side effects: irregular menstrual cycles, adrenal and/or pituitary gland suppression (specially following chronic doses > 7.5 mg/d), cushinioid state, hirsutism, hyperglycemia, precipitation of diabetes mellitus, cataracts, leukocytosis, increased appetite, euphoria, mood swings, personality changes, depression in patients with existing psychological problems.

- ***INTERACTIONS:***

Overview of Prednisone Drug-Drug Interaction	
Drug	**Interaction**
Anti-tubercular medications	Rifampin accelerates the metabolism of corticosteroids reducing their effect. Isoniazid serum concentrations may be decreased with corticosteroid use. Use caution and do not administer concomitantly.
Barbiturates* and *antiepileptics	These decrease the pharmacological effect of the corticosteroids. Use with caution.
Digitalis glycosides	Co-administration may enhance the possibility of digitalis toxicity associated with hypokalemia.
Diuretics; Potassium depleting agents	Patients who are on these agents and are administered cortico-steroids should be monitored for hypokalemia. Use with caution.

- ***OVERDOSE:***

Symptoms of overdosage may include anxiety, depression and/or stimulation, stomach bleeding, increased blood sugar, high blood pressure, and water retention.

Treatment: Patient should be taken to a hospital for supportive and symptomatic care. Gastric lavage or emesis can be applied. Prolonged use of large doses will results in Cushinoid symptoms (moonface, central obesity, hirsutism, acne, etc.). Gradually taper of the medication, to the lowest dose that will control of the original disease symptoms.

- ***BRANDS:***

Deltasone (Upjohn), Prednisone (Vitamed), Prednitab (BPC).

Chapter 7: Contraceptive Preparations

A) CONTRACEPTIVE DEVICES AND BARRIERS

1. **Intra-Uterine Devices (IUDs)**
2. **Spermicides and Condoms**

B) HORMONAL PREPARATIONS

1. **Estrogenic and Combined Oral Contraceptives:**
   (Ethinylestradiol, Norethindrone and Desogestrel)
2. **Progestin-Only Products:** *(including oral, injectables and implants)*
   (Norethindrone, Levonorgestrel, Medroxyprogestogene acetate)
3. **Emergency Pills**

CONTRACEPTIVES

Several contraceptive methods are available. In order to decide which is the most appropriate method to choose, the following factors should be considered: age, general health, frequency of intercourse, whether the reason for use is to prevent or to postpone pregnancy, personal preference, medical contraindication, expected efficacy, safety, and if the method provides protection against STD and HIV. The ideal contraceptive should be highly effective, safe, well tolerated, easily accessible, fully reversible and cheap.

The available methods and their effectiveness, risk of side effects, and protection against STD and HIV can be seen in the table-7.1. (Effectiveness depends mostly on the degree of compliance and user reliability).

Other methods like *douching* are not effective. The *postcoital contraception* used for emergencies has a failure rate of about 1%.

Natural family planning methods as *calendar, basal body temperature, cervical mucus* and *sympatothermal*, each requires keeping detailed records of women's menstrual cycle and other symptoms related to cyclic hormonal levels. The effectiveness of these methods depends on several unreliable factors like the presence of mild cold, infections or cycle irregularities.

A) CONTRACEPTIVE DEVICES & BARRIERS

1) Intra-Uterine Devices (IUDs)

This category is the most commonly used method. Copper IUDs are all effective in preventing pregnancy for up to 5 years, but can not provide full protection (refer to the table-7.1).

IUDs interfere with the implantation of the fertilized ovum. It is known that IUDs are most commonly used and are suitable for parous women (who have had at least one child).

The IUDs that contain progestogene, which should be changed every year, have lower risk of ectopic pregnancy and the pre-existing heavy menses may be alleviated. The progestogene that is released close to the site of action (on cervical mucus and endometrium) will decrease the progestinic side effects and interactions, in particular, the enzyme-inducing drugs are unlikely to have much influence on the contraceptive effect.

IUDs are contraindicated in cases of history of ectopic pregnancy, abnormalities of the uterine cavity, vaginal or cervical infections, acute pelvic inflammatory diseases (PID), genital malignancy, abnormal vaginal bleeding, previous tubal surgery, immunosupressive therapy and in women who are allergic to copper.

The most common side effects are menstrual irregularities with discharge and discomfort. One of the primary concerns is the relation between IUDs and PIDs. Recent studies have shown that increased incidence of PID occurs almost exclusively in the first 4 months after insertion (others mentioned after the first 20 days of insertion) and among women who are exposed to STDs. Some explains that this might be due to the septic techniques used during the insertion or to the pre-existing reproductive tract infections. Careful screening of potential IUD users can minimize complications related to PID. Moreover, education about the symptoms of PID can also help in reducing the complications after seeking early treatment.

Table – 7.1: Pregnancy Rates for Various Means of Contraception (%)[1]				
Method of Contraception	**Lowest expected[2]**	**Typical[3]**	**Risk of side effects #**	**Protect against STD/HIV#**
Oral contraceptives (in general)		3		
Combined	0.1	nd	medium	no
Progestin-only	0.5	nd	medium	no
Mechanical/Chemical				
Levonorgestrel implant	0.2	0.2	medium/high	no
Medroxyprogesterone injection	0.3	0.3	medium/high	no
IUD			high	no
Progesterone	2	nd		
Copper T 380A	0.8	nd		
Condom			low	yes
Without spermicide	2	12		
With spermicide[4]	1.8	4-6		
Spermicide alone	3	21	low	yes/no
Diaphragm (with spermicide cream or gel)	6	18	low	yes/no
Vaginal sponge			low	yes/no
Nulliparous	6	18		
Multiparous	9	28		
Female condom	2-4	12-25	low	yes/no
Periodic abstinence*	1-9	20	-	no
Sterility				
Vasectomy	0.1	0.15	low	no
Tubal ligation	0.2	0.4	medium	no
No contraception	85	85	-	-

nd= No data available.

[1] During first year of continuous use.

[2] Best guess of percentage expected to experience an accidental pregnancy among couples who initiate a method and use it consistently and correctly.

[3] A typical couple who initiate a method and experience an accidental pregnancy.

[4] Used as a separate product (not in condom package).

* Includes rhythm and sympatothermal methods.

Source: *Health Action International, 1993.*
Drugs Facts & Comparisons, 2000.

2) Spermicides and Condoms

Barriers *(e.g. diaphragm, condom)* may be preferred for older women who continue to smoke in whom there is a greater risk of side effects from OCs.

Spermicides kill sperms and have an antiseptic effect. They are considered as an additional safeguard but do not give adequate protection if used alone. They have 2 components: spermicide and a vehicle which itself may have some inhibiting effect on sperm activity. Moreover, spermicides may provide protection against STD.

The most commonly used products are Nonoxinol '9' and Benzylkonium chloride. Both can be used alone or with barrier methods like a condom.

Nonoxinol'9' is available in different dosage forms (foam, pessaries, gel, jelly,

cream). When used alone, it should be applied high in the vagina. It is contraindicated in people who are allergic to it. The main side effects are sensitization and irritation to mucous membranes.

Products like petrolatum jelly, baby oil and oil based vaginal and rectal preparations are likely to damage condom and diaphragms made from latex rubber, thus less protection even from STD.

B) HORMONAL PREPARATIONS

In this section, hormonal contraceptives will be discussed: combined oral contraceptives (OCs) and progestin-only products. Generally healthy women take these products, therefore, they should be extremely safe as well as effective.

1) Estrogenic and Combined OCs [WHO,P]

- ***DRUG SUMMARY:***

The combined OCs contain different estrogen-progestin combinations. They suppress ovulation by imitating the feedback effects of the woman's own estrogens and progesterones on the pituitary and the hypothalamus, thus inhibiting the secretions of FSH and LH. Additionally, these agents cause changes in the genital tract. The cervical mucous becomes thick (which inhibits sperm penetration) and the endometrium becomes thin and hypoplastic (which reduces the likelihood of implantation). The effect and the relative potency of these combined agents depend on the type and the relative combination of estrogenic and proges-tational activity.

The addition of progestins in a preparation may modify the effects of estrogens. These changes depend on the type or amount of progestin present and the ratio of progestin to estrogen.

The total estrogenic potency of OCs is based on the combined effects of the estrogen and the estrogenic/ antiestrogenic/ androgenic effect of the progestin.

The main *advantages* of OCs include: effectiveness, avoidance of dysmenorrhea, less iron deficiency anemia for women with heavy menstruation, avoidance of pre-menstrual tension, less benign breast disease, decrease the risk against pelvic inflammatory disease, provides protection against endometrial and ovarian cancer, and possible decreased risk of Alzheimer's.

Note:

- Estrogens have been reported to increase the risk of endometrial carcinoma. However, the risk appears to be decreased in OC users due to progestin component. In fact it has a protective effect, where users appear about half as likely to develop ovarian and endometrial cancers as women who have never used OCs.
- In spite of many studies, the relationship between OCs use and breast and cervical cancers, a cause and effect relationship has not been established.

There are 3 types of combined OC: monophasic, biphasic and triphasic.

***Monophasic*:** Fixed dosage of estrogen to progesterone throughout the cycle.

***Biphasic*:** The amount of estrogen is fixed for the first 21 days of the cycle. Progestin: estrogen ration is decreased in the first half of the cycle allowing endometrial proliferation. The ration is increased in the second half to provide adequate secretory development.

***Triphasic*:** Estrogen amount remains the same or varies throughout the cycle. Progestin amount varies.

The biphasic and triphasic OCs are intended to deliver hormones in a similar way as the physiological process.

The most commonly used estrogens are *ethinylestradiol and mestranol*. Pills containing > 50 mcg of estrogens are not currently used as their use is associated with an unacceptable incidence of venous thromboembolism.

Different progestinic derivatives are used. The progestogens *desogestrel, gestodene and norgestimate* in combination *with ethinylestradiol* have been reported to have less adverse effects on lipids than *ethynodiol, levonorgestrel and norethisterone* in combination with ethinylestradiol. However, desogestrel, gestodene have also been associated with an increased risk of venous thrombo-embolism.

- ***INDICATIONS:***

-As contraceptive agents.

-Some products might be used in emergency contraception in high doses as a postcoital contraceptive or "morning after" pill, but they are not licensed or packed for postcoital contraceptives (more details can be found under emergency pill in this chapter).

- ***CONTRAINDICATIONS:***

Absolute: Pregnancy, thromboembolic disease, certain cardiac abnormalities, thalassemia major, porphyria, familial hyperlipidemia, carcinoma of breast, idiopathic jaundice of pregnancy, liver diseases.

Relative: Diabetes mellitus, hypertension, osteosclerosis, secondary amenorrhea, undiagnosed vaginal bleeding, sickle cell disease, lactation, multiple sclerosis, obesity, depression, migraine, epilepsy, varicose vein, and in smokers > 35 yrs. old.

- ***DOSAGE FORMS:***

Tablets in different strengths depending on the estrogenic/ progestinic derivative used.

- ***RECOMMENDED DOSAGE:***

Start new patients with preparations containing ≤ 35 mcg estrogens.

<u>*Directions for use*</u>*:*

- One tablet should be taken at the same time every day with a meal or at bed time. Efficacy depends on strict adherence to the dosage schedule.

- *21-Day regimen*: Day 1 of the cycle is the first day of bleeding. Take one pill daily for 21 days starting on day 5 of the cycle. No tablets are taken for 7 days; whether bleeding stopped or not, start a new course of 21 days. Withdrawal flow will normally occur about 3 days after the last pill is taken.

- *28-Day regimen*: To eliminate the need to count the days between cycles, some products contain 7 inert or iron-containing tablets (21+7) to permit continuous daily dosage during the entire 28-day cycle. Take the 7- tablets on the last 7 days of the cycle.

- *Biphasic and triphasic OCs:* One tablet is taken daily; as the color of the tablet changes, the strength changes too (i.e., the estrogen/progestin ratio changes). Usually, it is clearly indicated on the package where to start and in what order to take the pills (marked with arrows), along with the appropriate week numbers.

- *Missed pills*: There is little likelihood of ovulation and consequent pregnancy occurring if only 1 tablet is missed, but the possibility of spotting and bleeding is increased. If 2 consecutive tablets are missed, the possibility of ovulation increases. *In general, other contraception precautions should be taken for the balance of the cycle until tablets have been taken for 7 consecutive days.*

∗ If <u>one tablet</u> is missed: take as soon as you remember, and the next one is at your normal time.

If you are late by 12 hours or more (especially if it is the first in the package) the pill may not work for this cycle. However, continue your normal pill taking whenever you remember and other safety precautions should be taken into account especially in the next 7 days. If these 7 days run beyond the end of the packet, start the second one immediately after finishing the present one without any lag period, this means that you will not have a period until after the 2 packets, but this would not be a problem. Nor does it matter if you see some bleeding during taking the tablets. If you are using every day pills, miss out the 7 inactive ones.

∗ If 2 consecutive tablets are missed: Take 2 tablets as soon as remembered with the next pill at the usual time, or take 2 tablets daily for the next 2 days, then resume the regular schedule.
∗ If 3 consecutive tablets are missed: begin a new packet of tablets starting day 1 of the cycle after the last pill was taken or starting 7 days after the last pill was taken.

- *Switching brands*: wait 7 days before starting the new pack (after the 21-day regimen) or start the next pack on the day after the last "reminder" pill (after the 28-day regimen).
- *Postpartum administration* in non-nursing mothers: it may begin at the first postpartum examination (4-6 weeks), regardless to whether spontaneous menstruation has occurred. Also, start no earlier than 4-6 weeks after a mid-trimester pregnancy termination. Immediate postpartum use is associated with increased risk of thromboembolism.
- *Changing from progestogen-only tablet*: start on first day of menstruation or any day if amenorrhea present and pregnancy has been excluded.
- *After abortion or miscarriage:* start on the same day.

- ***USES IN SPECIAL CASES:***

Lactation- Not recommended. Oral progestogen-only contraceptives are preferred.
Liver Disease- Exercise caution as steroids metabolism decreases in liver impairment conditions.

- ***PRECAUTIONS AND WARNINGS:***

A complete, detailed and clear medical and family history prior to initiation of therapy should be done.
a) Smoking: The risk of cardiovascular side effects increases with OCs in heavy smokers (> 15 cigarette/d) who are > 35 yrs. old. ***Women who use OCs should not smoke***.
b) Missed pill: see *"RECOMMENDED DOSAGE*".
c) Diarrhea and vomiting: may interfere with the absorption and limit the effectiveness. Additional precautions should be used during and for 7 days after recovery. If this happens during the last 7 tablets, the next pill free interval should be omitted.
d) The administration of OC should be stopped if any of the following symptoms occur: sudden severe pain in the chest, sudden breathlessness or cough with blood-stained sputum. Severe pain in calf of the leg or in the stomach. Unusual severe, prolonged headache (especially if it happens for the first time or if it increases gradually), diplopia, dysphasia, vertigo, bad fainting attack or collapse, weakness, numbness, motor disturbances.
e) Bleeding that resembles menstruation occurs rarely. Persistent bleeding requires patient's re-examination; consider non-hormonal causes. If pathology has been excluded, time or changing the formulation may solve the problem.
f) Missed menstrual period:
∗ If one period is missed (patient did not adhere to prescribed regimen): consider possible pregnancy, withhold OCs until ruling out pregnancy.
∗ If two consecutive periods are missed (patient adhered to the prescribed regimen): rule out pregnancy before continuing the contraceptive regimen.
∗ If menstrual bleeding is minimized: this might be due to long usage of medication for several months and not due to pregnancy.
g) Surgery: estrogen-containing OC should be stopped 4 weeks before major elective surgery and all leg surgeries. They are recommended again after the first menses occurring at least 2 weeks after mobilization. When discontinuation is not possible (i.e., after trauma) then sub-cutaneous heparin should be given prophylactically.
h) Contact-lens wearers who develop changes in vision or lens tolerance should

be assessed by an ophthalmologist; consider permanent or temporary cessation of wear.

i) OCs do not protect against HIV infection or other STDs (inform patients).

- ***ADVERSE EFFECTS:***

The aim of the prescriber should be to keep the level of both the estrogenic and the progestinic derivative as low as possible consistent with maximal effectiveness and minimal discomfort for the patient. Side effects that have been reported include:

-*CVS* ***(Serious)****:* Thrombophlebitis and venous thrombosis with and without embolism; pulmonary embolism; coronary thrombosis; MI; cerebral thrombosis or hemorrhage; hypertension; mesentric thrombosis.

-*GU:* breakthrough bleeding, spotting; change in menstrual flow; amenorrhea; change in cervical erosion and cervical secretions; invasive cervical cancer; vaginal candidiasis.

-*Breast changes:* tenderness; enlargement; secretion; diminution in lactation when given immediately postpartum.

-*GI:* Nausea; vomiting; abdominal cramps; cholestatic jaundice.

-*CNS:* migraine; mental depression.

-*Ophthalmic:* changes in corneal curvature; contact lens intolerance; neurocular lesions.

-*Miscellaneous:* photosensitivity may occur; edema; weight changes; reduced carbohydrate tolerance; prevalence of cervical clamydia trichomatis may be increased; gallbladder disease; hepatic adenoma.

- ***INTERACTIONS:***

(1) The following drugs will decrease OCs effectiveness, which means that pregnancy may occur. (Another contraceptive method should be used during treatment.)

a) Hepatic enzymes inducers such as barbiturates, hydantoin, rifampicin, carbamazepine.

b) ***Note***: *Rifampicin* is a potent enzyme inducer, that even if a course lasts for less than 7 days, the additional contraceptive precautions (e.g. IUD) should be continued for at least 4 weeks after stopping it. Changes in the strength or the regimen of the pills may be done.

c) Antibiotics such as penicillins, tetracylines and griseofulvin.

(2) Allopurinol, cimetidine, chloramphinicol, isoniazid and the phenothiazines may potentiate the actions and adverse effects of oral contraceptives.

(3) Coadministration of OCs with the following drugs will result in:

a) Anticoagulants effect would decrease.

b) Antidepressants (TCA), β-blockers, caffeine, corticosteroids, theophylline effects or toxicity may be increased.

c) Benzodiazepines effect or toxicity may be increased for some derivatives and decreased for lorazepam, oxazepam and temazepam.

d) Clofibrate effect may be decreased as its elimination is increased.

e) Salicylate effect may be decreased.

Drug /lab test interactions:

Estrogen-containing OCs may cause alterations in serum, blood or plasma concentrations of some hormones or clotting factors, etc. This means that continuous monitoring is needed, which may require a specialist clinic and not the general primary health care facility.

- ***OVERDOSE:***

Serious events have not been reported following acute overdosage. In case of overdose, one might get nausea. Withdrawal bleeding may occur in female children after accidental ingestion.

- ***BRANDS:***

Gynera (Schering/Agis), Microdiol (Organon), Nordette (Wyeth Ayerst).

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2) Progestin-Only Products

Progesterone is the primary principle of corpous luteum. It causes the transformation of the proliferative endometrium into secretory endometrium. Synthetic exogenous progesterone inhibits gonadotropines secretion, thus prevents maturation of the follicle and ovulation and results in endometrial thinning. Thus, exerting its contraceptive action.

These products are more suitable in the following cases:

- When estrogens are contraindicated.
- For women over the age of 40 years in whom fertility has declined so that the small risk of pregnancy is reduced even further.
- For patients with diabetes mellitus and migraine.
- Women with a history of thrombo-embolism and valvular heart disease.
- Women who have previously developed hypertension with combined pills.
- Breast feeding mothers.
- Women over 35 who smoke.

The dose of the progestin derivative in progesterone-only products is very much lower than the daily dose of progesterone in combined pills. Therefore, progestin-only products have a higher failure rate than combined preparations (refer to table-7.1). However, side effects are considered to be less. They are more likely to cause alteration in the menstrual patterns: Amount and duration of the flow, cycle length, BTB, spotting and amenorrhea varies. Although menstrual irregularities are more common than with OCs; but tend to resolve on long term treatment.

Another advantage is that a decline in serum HDL has occurred with progestins.

The progestin-only products are divided into oral (e.g. *levonorgestrel, ethynodiol acetate*), injections (*medroxyprogesterone acetate*), implants (*levonorgestrel*), and are added to IUD (*levonorgestrel*).

a) Oral Progestogen-only Preparations

- ***DRUG SUMMARY:***

These products are suitable for use as an alternative to combined oral contraceptives if estrogens are contraindicated and before major elective surgery.

- ***INDICATIONS:***

To prevent pregnancy.

(Refer to the introduction.)

- ***CONTRAINDICATIONS:***

Pregnancy, thrombophlebitis, thrombo-embolic disorders, undiagnosed vaginal bleeding, liver diseases, breast and genital tract carcinoma.

- ***DOSAGE FORM:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Directions:

- *Daily administration:* starting on the first day of menstruation. Take one tablet at the same time each day, every day of the year. And preferably, few hours before intercourse to obtain full effectiveness.

-*Postpartum administration:* may be initiated no earlier than 4 weeks postpartum. The risk of thromboembolic disease that is associated with the postpartum period should be considered. Moreover, heavy and irregular postpartum bleeding may occur.

-*Missed dose:*

∗One tablet: take as soon as remembered (within 3-4 hrs), then take next tablet at regular time. Extra precautions should be taken for the next 48 hrs.

∗Two consecutive tablets: DO NOT take the missed tablets; discard and take the next tablet at the regular time, or take one of the missed tablets, discard the other and take daily tablet at usual time.

∗Three consecutive tablets: discontinue immediately.

Use additional protection methods of contraception if 2 or more tablets are

missed until menstruation appears or pregnancy is ruled out. If menses does not occur within 45 days, regardless of circumstances, discontinue the drug, rule out pregnancy and use a non-hormonal method of contraception.

Because of the slightly higher failure of the progestin-only products, a more conservative approach is to discontinue the regimen if only one tablet is missed and use other non-hormonal contraceptive methods until menses occurs or pregnancy is ruled out.

- ***PRECAUTIONS AND WARNINGS:***

Pretreatment physical examinations, which include breast and pelvic organs, should be performed.

Women using progestin-only pills should be monitored for any manifestations or for the onset of any of the following symptoms: thrombotic disorders, fluid retention, depression, photosensitivity and ophthalmologic disorders.

- ***ADVERSE EFFECTS:***

Menstrual irregularities, nausea, vomiting, headache, breast discomfort and weight changes.

- ***INTERACTIONS:***

Effectiveness of oral progestogen-only products is not affected by broad-spectrum antibiotics but is reduced by enzyme-inducing drugs: Barbiturates, phenytoin, carbamazepine, ethosuximide, rifampicin, chlorpromazine, and griseofulvin.

- ***OVERDOSE:***

Refer to OCs.

- ***BRANDS:***

Femulen (Searle).

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b) Injectables: Medroxy-progesterone acetate WHO,P

- ***DRUG SUMMARY:***

It is a long acting progestogene given IM. It is useful for short-term interim contraception (e.g. before vasectomy becomes effective). For long-term contraceptive for women who have been appropriately counseled concerning the likelihood of menstrual disturbances (amenorrhea, heavy uterine bleeding) and the potential for a delay in return to full fertility, which is unrelated to the duration of use, but there is no evidence of permanent infertility.

- ***INDICATIONS:***

Prevention of pregnancy. It is a long-term contraceptive injection in women when administered at 3 months interval. Cautious use as severe side effects may persist during and longer than 3 months. It should be clear to the woman that these effects are irreversible once it is administered for at least 3 months**.**

- ***CONTRAINDICATIONS:***

As for oral progestogene.

- ***DOSAGE FORMS:***

Injections of 150 mg/3 months.

- ***RECOMMENDED DOSAGE:***

Directions:

-The woman should fill and sign the informed consent first.

-The first injection should be given only during the first 5 days after the onset of normal menstrual period, within 5 days postpartum (this might affect bleeding pattern) if not breast feeding and at sixth week postpartum if breast feeding.

-Shake well before use to ensure homogenous dose. The recommended dose is 150 mg/3 months administered deep IM in the gluteal or deltoid muscle (do not massage).

-If the period between injections is > 14 weeks, rule out pregnancy before new administrations.

- ***USES IN SPECIAL CASES:***

Lactation- It is detected in milk. Milk composition, quality and amount are not adversely affected. No adverse effects on breast-fed infants.

Children- Children exposed to medroxy-progesterone acetate in utero and followed to adolescence did not show any abnormal physical, intellectual, sexual or social development.

Liver Disease- Steroids metabolism may be affected in liver impairment cases.

- ***PRECAUTIONS AND WARNINGS:***

-Diabetic patients should be observed carefully as the therapy might result in a decrease in glucose tolerance.

-Blood pressure should be checked before each injection.

- ***ADVERSE EFFECTS:***

The most common side effect is menstrual irregularities (amenorrhea, bleeding) as well as delay of return to fertility.

- ***INTERACTIONS:***

As for oral progesterones. Moreover, aminoglutethimide decreases the efficacy of medroxyprogesterone.

- ***OVERDOSE:***

Refer to OCs.

- ***BRANDS:***

Depo-Provera (Upjohn).

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c) Implants: Levonorgestrel

- ***DRUG SUMMARY:***

Levonorgestrel is a synthetic and biologically active progestin that exhibits no significant estrogenic activity and is highly progestational. Unlike injectables, implants are almost reversible upon removal. The efficacy of the implant does not depend on the patient compliance.

The main disadvantages of the implants are the cost and the fact that the woman is dependent on the health professional for insertion and removal.

- ***INDICATIONS:***

Prevention of pregnancy, up to 5 years. It is a reversible contraceptive system. The capsules should be removed by the end of the 5th year. New capsules may be inserted at that time if continuing contraceptive protection is desired.

- ***CONTRAINDICATIONS:***

As for oral progestins.

- ***DOSAGE FORMS:***

Implants; the package consists of a set of six flexible closed capsules made of silastic, each containing 36 mg of the progestin levonorgestrel contained in an insertion kit to facilitate implantation. These capsules are sealed and sterilized.

- ***RECOMMENDED DOSAGE:***

The initial released dose from the inserted implant is about 85 mcg/day, followed by a decline to about a 50 mcg/day and to about 35 mcg/day by 18 months, with a further decline thereafter to about 30 mcg/day.

Directions: *Insertion and removal:*

* A specific training should be conducted for health workers who are involved in this procedure.

– An informed consent should be obtained before insertion. The capsules are inserted during the first 7 days of the cycle or immediately following an abortion. Before insertion, pregnancy should be ruled out. Insertion is not recommended before 6 weeks postpartum in breast feeding women.

– Healthcare professionals should provide proper insertion that will also provide proper and easy removal. Sterility is the major concern during this process.

– Proper insertion and removal should result in minimal scaring. If all capsules cannot be removed at the first time, try removal later when the site has healed. Bruising may occur at the implant site insertion or removal. In some women, hyper-pigmentation occurs over the implantation site but is usually reversible following removal.

– Aseptic techniques should be followed during insertion to prevent infections. Use

proper medication to treat infections but if it persists, capsules should be removed.

– Expulsion of capsules is uncommon.

– Provisions for removal: women should be advised that the capsules might be removed upon request at any time or at the end of the 5 years.

- ***USES IN SPECIAL CASES:***

Lactation- Levonorgestrel has been identified in breast milk. No significant effects were observed on those infants whose mothers used the implants beginning 6 weeks after parturition in comparative studies with mothers using IUDs or barrier methods.

Liver Disease- Steroid hormones metabolism may be decreased in liver impairment conditions.

- ***PRECAUTIONS AND WARNINGS:***

-A full medical examination and follow up should be performed before insertion and at least annually during its use.

-Women with strong family history of breast cancer or who have breast nodules should be carefully monitored.

-There may be an affect on carbohydrate and lipid metabolism. Women with hyper-lipidemia should be carefully monitored since the level of LDL may be altered.

- ***ADVERSE EFFECTS:***

The most common side effect is menstrual irregularities: Irregular, frequent bleeding, spotting, amenorrhea.

Other side effects are breast discharge, cervicitis, vaginitis, musculoskeletal pain, abdominal discomfort, pain, itching, infection at the implant sight.

- ***INTERACTIONS:***

-Carbamazepine and phenytoin (hepatic enzyme inducers) will reduce the efficacy of levonorgestrel, thus pregnancy may occur.

-Lab/Drug test interactions: certain endocrine tests may be affected, e.g. thyroxine concentration may be decreased.

- ***OVERDOSE:***

It can happen if > 6 implants are in situ. All implanted capsules should be removed before new insertion. Overdosage may cause fluid retention and uterine bleeding irregularities.

- ***BRANDS:***

Norplant (Discotrade).

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3) Emergency Pills

Today, emergency contraception (EC) is the most commonly used term to describe the post-coital use of levonorgestrel alone or the combination of ethinyl estradiol and levonorgestrel within 72 hrs of unprotected sexual intercourse to prevent pregnancy. It should not be confused with other agents such as mifepristone (also known as RU-486 or the "French abortion pill") that, unlike emergency contracption pills, can be used to terminate an existing pregnancy.

Just as with the daily use of oral contraceptives, EC pills prevent pregnancy primarily due to inhibition or delay of ovulation, and possibly by inhibition of fertilization or implantation. Once endometrial implantation has occurred, pregnancy is initiated and EC has no effect.

A combined tablet of 50 mcg ethinyl estradiol and 500 mcg norgestrel, or 50 mcg ethinyl estradiol and 250 mcg levonorgestrel is to be taken 2 tablets immediately, followed after 12 hours by another 2 tabs. This method is considered effective if taken within 72 hrs after intercourse but it is less effective than insertion of an IUD.

These tablets should not be administered if menstrual bleeding is overdue or if protected intercourse occurred more than 72 hours previously.

- These tablets are <u>contraindicated</u> in pregnancy, women with a history of thrombosis or who have focal migraine at that time.
- If vomiting occurs during 2-3 hrs after taking the tablets, 2 other tablets should be taken instead with antiemetic.

- The patient should be informed that there might be early or delayed period, also to use barrier methods till the next period. The doctor should ask about any abdominal pain or heavy bleeding or any menstrual irregularities.

Chapter 8: PSYCHOTHERAPUTIC DRUGS

PSYCHOACTIVE DRUGS:

A) ANTIDEPRESSANTS

1. **Amitriptyline**
2. **Imipramine**
3. **Fluoxetine**

B) HYPNOTICS AND ANXIOLYTICS

1. **Diazepam**
2. **Lorazepam**

C) NEUROLEPTICS

1. **Chlorpromazine**
2. **Haloperidol**

ANTICONVULSANT / ANTIEPILEPTIC DRUGS:

1. **Carbamazepine**
2. **Clonazepam**
3. **Ethosuximide**
4. **Phenobarbital**
5. **Phenytoin**
6. **Valproic Acid**
7. **Diazepam**

ANTIPARKINSONISM DRUGS:

A) ANTICHOLINERGIC DRUGS

1. **Benztropine Mesylate**
2. **Trihexyphenidyl (Benzhexol)**

B) DOPAMINERGIC DRUGS:

1. **Amantadine**
2. **Bromocriptine**
3. **Carbidopa / Levodopa**

Psychoactive drugs:
A) ANTIDEPRESSANTS

Depressive illnesses should not be confused with the transient feelings of unhappiness that everyone experiences; the periods of sadness associated with unhappy events and failures, or the emotional letdown that occur. Suicide is the most serious complication of depressive illnesses.

Depression can be a symptom secondary to organic brain syndrome, schizophrenia, anxiety disorders, obsessive compulsive disorders, hyperthyroidism, drug dependence, mental disorders, anemia, cardiovascular problems, or use of depressant drugs.

The American Psychiatric Association uses criteria for mood disorders (**DSM-R**), while the European community use the (**ICD10**), that permit clinicians to consistently distinguish between pathological states and normal changes in emotion in everyday life. The most common mood disorders are *major depression* (unipolar disorders) and *manic-depressive* illness (bipolar disorder).

Psychotherapy (talk therapy) has resulted in very positive outcomes in combination with pharmacotherapy. Drugs with clinically useful antidepressant effect include the tricyclic antidepressants (**TCA**s), the selective serotonin reuptake inhibitors (**SSRI**s), and the mono-amine oxidase inhibitors (**MAOI**s), as well as others included at the end in table-8.1.

The TCAs and the SSRIs are preferred over the MAOIs because they are more effective and do not show the dangerous interactions with some foods (that contain tyramine) and fewer major drug-drug interactions.

The SSRIs also have fewer anti-muscarinic side-effects than the older tricyclics, and they are less cardiotoxic in overdose. Although they are not more effective, they may be preferred where there is a major risk of overdose.

Each drug group has similar characteristics, contraindications, and side effects, but their pharmacokinetics profiles may differ, resulting in one drug having more or less side effects or indication for use than the other.

Drug selection is based on side effect profile, concomitant disease state (*i.e. benign prostatic hypertrophy, insomnia, MI, arrhythmias, obesity, glaucoma, hypertension, sexual dysfunction, suicide potential, etc.*), drug-drug interaction, cost, ease of use, and previous therapy.

Table-8.1: Examples of Antidepressant Drugs

TCAs Tertiary Amines	TCAs Secondary Amines	SSRIs	MAOIs	Miscellaneous Agents
Amitriptyline --→	*Nortriptyline	Citalopram	Isocarboxide	Bupropion
Clomipramine	Amoxapine	Fluoxetine	Moclobemide	Maprotiline
Doxepin	Protriptyline	Fluvoxamine	Phenelzine	Nefazodone
Imipramine ---→	*Desipramine	Paroxetine	Tranylcypromine	Trazodone
Trimpramine	Lofepramine	Sertraline		Venlafaxine

*Amitriptyline → metabolized to * Nortriptyline.*
*Imipramine → metabolized to * Desipramine.*

Lithium salts are used in the treatment of mania, affective disorders, and the prevention of recurrent attacks of manic-depressive illness. Lithium is not a sedative, nor a depressant or euphoriant. Lithium prescribing requires a specialist's advise, and should not be prescribed unless facilities for monitoring serum concentration levels are available. Abrupt withdrawal increases risk of relapse, and if there is a need for discontinuation, the dose should be reduced gradually over a period of a few weeks with caution. A specialist subscribes it to patients with normal sodium intake, and with normal cardiac and renal functions. Lithium is not suitable for children. Lithium will not be discussed in this chapter.

Prescribing more than one anti-depressant at the same time is not recommended. Compound preparations of an antidepressant and an anxiolytic are not recommended because the individual component should be adjusted separately. Where as antidepressants are given continuously over several months, anxiolytics are prescribed on a short-term basis.

Patients who are suicidal or potentially suicidal are prescribed only small quantities of medication to avoid possible overdose, until the patient is stabilized.

Treatment should be continued for 2 weeks before suppression of symptoms can be expected, and should be maintained at the optimum level for at least another month before the attempt is made for dose reduction. Treatment may last between 3 months to a year or more. Some patients appear to benefit from maintenance therapy with about half the therapeutic dosage for several months to prevent relapse.

Besides depression, many of these agents have other uses, which will be mentioned as each drug is discussed.

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1) Amitriptyline [WHO,P]

- ***DRUG SUMMARY:***

Amitriptyline is a CNS agent, psycho-therapeutic, tricyclic (tertiary amine) antidepressant. Among the most active TCAs in inhibition of serotonin uptake, also inhibits nor-epinephrine reuptake to a moderate degree. TCAs could occasionally be used as hypnotic because of their sedative property; this effect may be useful in the initial therapy of a depressed patient who is not sleeping well.

- ***INDICATIONS:***

Depressive illness, particularly where sedation is required.

Has been used for enuresis, but there is more experience with imipramine (refer to special cases for children, under imipramine).

- ***CONTRAINDICATIONS:***

Hypersensitivity to any tricyclic drug. Use following a recent MI or arrhythmias, concomitant use of a MAOI s (may precipitate hyperpyrexic crisis), history of seizure disorders.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: 50-75 mg/day PO in divided doses or as a single dose at bedtime, may increase to 150 mg/day.

(Elderly and adolescents start 25-50 mg/day: 10 mg t.i.d. and 20 mg h.s.).

Child: Not recommended for children < 12 years.

Directions: When increasing the dose, start with the night dose. Therapeutic antidepressant effect may take as long as 30 days to develop.

*Drug may be taken with or immediately after food to reduce possibility of GI irritations. Tablets may be crushed if patient is able to swallow.

*Advise patient not to discontinue therapy, or take other drugs or OTCs that may interact with the medication. Abrupt

discontinuation may cause nausea, headache and malaise. The dosage should be diminished slowly over 2 weeks.

*Maintenance regimen is usually continued for at least 3 months to prevent relapse. Therapy typically lasts 6 months to 1 year.

*Advise patient to stop taking this medication and get emergency help if any of the following occur: Seizures, difficult or fast breathing, fever with increased sweating, high or low blood pressure, loss of bladder control, severe muscle stiffness and unusual weakness.

*Elderly patients maybe more susceptible to the anticholinergic, antihistaminic and cardiovascular side-effects of amitryptyline and imipramine. If the patient can't tolerate these, desipramine and nortiptlyine are used for such patients.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only if potential benefits outweigh the hazards to the fetus (Catgegory D). Even though clinical experience is limited; amitriptyline has been reported to cause limb reduction anomalies in fetus *(Drug Facts & Comparisons. 2000)*.

Lactation- TCAs are excreted in breast milk in low concentrations. Clinical effects of exposure to infant are not known. Use is not recommended, unless clearly indicated.

Children- Not recommended for children less than 12 yrs old. Although some prescribe amitriptyline to children for enurisis, imipramine is more commonly used worldwide. *(Refer to imipramine.)*

Renal Disease- Use caution, the drug is excreted primarily in urine. Need to reduce doses in patients with significantly impaired renal functions.

Liver Disease- Avoid drug in severe liver disease. Use with caution and reduce doses in patients with hepatic impairment. Metabolism of the drug may be impaired leading to drug accumulation. It is metabolized to the active metabolite nortriptyline.

- ***PRECAUTIONS AND WARNINGS:***

-Due to the high incidence of anticholinergic side effects, use caution in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure, in patients receiving anticholinergic medications (antiparkinson agents), patient with cardiovascular disorders (since TCAs may produce arrhythmia, and increase frequencies and severity of angina and other problems).

-Psychiatric patients with schizophrenic or paranoid cases may exhibit a worsening of psychosis with TCA therapy. The possibility of suicide in depressed patients remains during treatment until significant remission occurs. Monitor patients. Patient should not have easy access to large quantities of drug, prescribe small quantity each time (one month supply at a time until patient is stabilized).

-Sexual dysfunction in males, and weight gain may be the major side effects that cause non-compliance. Warn patients.

- ***ADVERSE EFFECTS:***

Drowsiness, sedation, dizziness, restlessness; need to warn patient against hazardous activities like driving or operating machinery till response to the drug is known. Orthostatic hypotension; advise patient to change position slowly, tachycardia, ECG changes, blurred vision, dry mouth; increased fluid intake, increased appetite (especially to sweets) leading to weight gain, constipation, urinary retention, urine discoloration, interference with sexual function, interference with blood sugar levels; elevation or lowering has occurred, need to warn diabetic patients. Occasional reports or photosensitivity, metallic taste of the mouth, and convulsions have been noted.

- ***INTERACTIONS:***

Overview of Amitriptyline Drug-Drug Interaction	
Drug	**Interaction**
Alcohol	Will enhance the sedative effect. Advise patient not to drink or eat foods/ medicines that contain it while on this medication.

Anti-epileptics (phenytoin)	Has antagonistic effect, lowered seizure threshold, and reduced antidepressant effect. Do not administer concomitantly
Anti-hypertensives and ***diuretics***	Increased hypotensive effect. Do not administer at the same time; use caution.
Cimetidine	Increases serum level of TCAs, increasing anti-cholinergic symptoms. Avoid use, ranitidine might be a better alternative.
MAO Inhibitors	Concomitant use is **contraindicated**. It has been reported to cause hyperpyretic crisis, severe convulsions and death. Do not administer TCAs with or within 2 weeks of MAO Inhibitors use.
Oral contra-ceptives (OCs)	Inhibit the hepatic metabolism of TCAs and may increase their plasma levels, especially estrogen. Also *steroids* have same effect. Use caution.
Thyroid medication	Patients on these need close supervision because of possibility of cardiovascular toxicity, including arrhythmia.

- ***OVERDOSE:***

Children are reportedly more sensitive than adults to acute overdose. Consider any overdose in infants or young children as serious and potentially fatal.

Symptoms include confusion, agitation and hallucinations. Seizures are common. Flushing, dry mouth, dilated pupils, cardiac arrhythmia, depressed myocardial contractility, heart rate and coronary blood flow.

Treatment; Hospitalize and closely observe with ECG monitoring, even when the amount ingested is thought to be small.

- ***BRANDS:***

Amyvil (JePharm)**,** Elavil (Stuart), Endep (Roche), Elatrol/Elatrolet (Assia/Riesesl), Tryptal/ Tryptalette (Unipharm).

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2) Imipramine [P]

- ***DRUG SUMMARY:***

Imipramine is a CNS psychotherapeutic, tricyclic (tertiary amine) antidepressant; TCA. It has the same mechanism of action as amitriptyline, but somewhat has less sedative properties.

- ***INDICATIONS:***

Depressive illness, treatment of panic attacks. Nocturnal enuresis in children.

- ***CONTRAINDICATIONS:***

Same as Amitriptyline.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: Start with 75 mg/day PO h.s. or in divided doses, increased if needed to 150 mg/d in divided doses; max. 200 mg/d.

Adolescents and elderly: initially 30-40 mg/d, not to exceed 100 mg/d.

Child: For childhood enuresis: 25 mg PO h.s.

< 12 years may increase to 50 mg nightly; max. dose is 2.5 mg/kg/d.

> 12 years may increase to 75 mg nightly; max. dose is 2.5 mg/kg/d.

Directions: For children treated for **enuresis**; institute a drug free period following an adequate therapeutic trial with a favorable response. Gradually tapering dosage may reduce tendency to relapse. Children who relapse after drug discontinuation do not always respond to a subsequent course.

*Follow same directions as amitriptyline.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use unless potential benefit outweighs the potential hazard to the fetus (Category D). There have been clinical reports of congenital malformation associated with imipramine.

Lactation- Caution should be exercised. TCAs are excreted in breast milk.

Children- TCAs are used (mainly imipramine but amitriptyline can be used) to treat enuresis in children ≥ 6 years, mainly on

special occasion such as sleeping away from home or patients not responding to non-pharmacologic therapy.
Non-pharmacological approaches such as bladder retention training, motivational therapy and behavior modification are preferred and have a lower relapse rate. But many physicians and patients' families prefer drug therapy for fast response. Do not exceed 2.5 mg/kg/d.
Proper follow-up of such cases is important to prevent relapse, and long-term therapy is controversial. Effectiveness of imipramine in children for conditions other than nocturnal enuresis has not been established.
Renal Disease- Use with caution especially in patients with significantly impaired renal function.
Liver Disease- Use with caution and reduce dose to avoid accumulation of the drug. It is metabolized to desipramine (an active metabolite) by the liver.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS, OVERDOSE:***

Same as amitriptyline.

- ***ADVERSE EFFECTS:***

Same as amitriptyline, with less sedation.

- ***BRANDS:***

Tofranil (Ciba-Geigy), Primonil (Teva).

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3) Fluoxetine

- ***DRUG SUMMARY:***

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) antidepressant. A phenylpropylamine derivative chemically unrelated to the TCAs, with a very long half-life compared with other anti-depressants. Antidepressant effect is presumed to be linked to its inhibition of CNS presynaptic neuronal uptake of serotonin. SSRIs are less sedating than TCAs, with few antimuscarinic effects and with low cardiotoxicity.

- ***INDICATIONS:***

Primary indication is for depression. Other uses include obesity, bulimia nervosa, and obsessive compulsive disorder (OCD).

- ***CONTRAINDICATIONS:***

Hypersensitivity to SSRIs. In combination to a MAO inhibitor or within 14 days or discontinuing a MAO inhibitor.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: 20 mg/d PO in the morning time.
May increase to a max. 80 mg/d in 2 divided doses; morning and noon.
Child: Not used in children.

Directions: While patients may notice an improvement with therapy in 1-4 weeks, advise patients to continue therapy as directed. Approximately 2-3 weeks are required for SSRI therapeutic effects.
*Food does not affect systemic bioavailability of fluoxetine, so it may be given with or without food.
*If patient missed a dose, take as soon as remember, unless too close to the next dosing interval. Do not double the dose.
***Provide suicidal or potentially suicidal patients with small quantities of the prescribed medication to avoid possible overdose, especially when starting therapy.**

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid unless potential of benefit outweighs potential hazards. There are no adequate and well-controlled studies in pregnant women; but it was reported that 5.5% of 228 women who took fluoxetine the 1st trimester delivered infants with structural anomalities (Category C).
Lactation- Exercise caution. Fluoxetine is excreted in breast milk. One case only reported indicated that infant showed increased irritability.
Children- Safety and efficacy of SSRIs in children < 18 yrs. old have not been established.
Renal Disease- Use with caution. Additional accumulation of drug or metabolite has occurred with severely impaired renal function, with chronic use. Use a lower or less frequent dose.
Liver Disease- Use with caution in severe

liver impairment. SSRIs are extensively metabolized in the liver, (fluoxetine to active metabolite norfluoxetine), elimination is prolonged. Reduce initial dose with less frequent dosing intervals. Alternate-day dosing has been recommended for patients with significant hepatic impairment.

- ***PRECAUTIONS AND WARNINGS:***

-In patients receiving MAOIs in combination with SSRIs, serious sometimes fatal, reactions have occurred including hyperthermia, rigidity, seizures, extreme agitation progressing to delirium and coma.

-Rash and accompanying events; instruct patient that a rash could be a sign of a serious group of adverse effects, and should notify physician if noted. Most patients improved after discontinuation of medication.

-Significant weight loss, especially in underweight depressed patients, has occurred. Monitor weight loss particularly in elderly or nutritionally compromised patients.

-Observe and report increased anxiety, nervousness or insomnia, modification of drug dose may be needed. Warn patients with a history of seizures to use appropriate safety precautions if taking this medication.

- ***ADVERSE EFFECTS:***

Commonly observed: nervousness, insomnia, drowsiness confusion, and fatigue, anxiety, anorexia, nausea, dry mouth, diarrhea/loose stools, and excessive sweating.

Other less common: palpitations, angina, postural hypotension, tachycardia, delusions, neck pain, bone pain, hyperventilation, pneumonia, acne, alopecia, dry skin, urticaria, eye pain, mydriasis, abnormal ejaculation, amenorrhea, urinary incontinence/ retention/ urgency, anemia, hypoglycemia and hypothyroidism.

- ***INTERACTIONS:***

Overview of Fluoxetine Drug-Drug Interaction	
Drug	**Interaction**
MAO Inhibitors	Use is **contraindicated.** If patient was placed on an SSRI serious, sometimes fatal reactions, may occur.
TCAs, ***anti-histamines*** and ***carbama-zepine***	All enhance toxicity and side effects of SSRIs. Do not use concurrently.
Tryptrophan (L-trypto-phan)	May produce symptoms related to both central and peripheral toxicity. Do not use concurrently.

- ***OVERDOSE:***

Symptoms: Nausea and vomiting are prominent, also agitation, restlessness, hypomania and other signs of CNS excitation.

Treatment: There is no specific antidote. Activated charcoal with sorbitol may be as or more effective than emesis or lavage. Refer to emergency room for management.

- ***BRANDS:***

Affectine (Taro), Flutine (Teva), Fluoxicare (Pharmacare), Prizma (Unipharm), Prozac (Dista/Eli Lilly).

B) HYPNOTICS AND ANXIOLYTICS

The primary use of drugs classified in this group is to encourage calmness (anxiolytics or sedative), or to produce sleep (sedative hypnotics). When symptoms become intolerable or interfere with the treatment of the underlying disease and counseling is not sufficiently effective, drug treatment can be considered as a means of helping patients. Specific cases such as phobias, panic disorder, obsessive-compulsive disorders (OCD) need further evaluation and specific drug regimens.

Patients with insomnia should be counseled about non-pharmacological measures before starting a drug regimen, such as:

- Avoidance of stimulants before retiring.
- Maintenance of a proper diet.
- Initiation of an exercise program.
- Avoidance of stressful or anxiety provoking situations.
- Maintaining a stable schedule; time of going to bed, avoiding mid-day naps.
- Not eating heavy meals before going to bed.

When evaluating a patient with a sleeping disorder, cases that need to be ruled out include:

- Medication induced insomnia: use of sympathomimetics such as pseudoephedrine, or other medication like fluoxetine, or methylphenidate.
- Substance abuse; alcohol, cocaine, amphetamines, and narcotics.
- Medical conditions; sleep apnea, hyperthyroidism, gastroesophogeal reflux or CHF.

Benzodiazepines are closest to the ideal hypnotics, and are the most commonly used group. Alternative drugs such as barbiturates (e.g. phenobarbitol) or meprobamate, have a high risk of abuse potential as well as producing a number of serious and potentially lethal interactions with other drugs. They are not recommended unless there is no other choice. They do not induce liver enzymes, and their effectiveness may be reduced by smoking tobacco. When used for insomnia, may cause early morning awakening and next day restlessness.

The main differences within the family relate to potency and duration. Table-8.2 gives some examples of available drugs and compares them.

Diazepam and Lorazepam will be discussed as the prototypes of this group of drugs. *Other drugs in this group include: Chlordiazepoxide, Clonazepam, Clorazepate, Halazepam, Prazepam, and Nitrazepam.*

Table – 8.2: Some Examples of Benzodiazepines

Drug	Potency	Onset	Duration	Route of elimination
Alprazolam	High	Fast	Short	Hepatic metabolism with some active metabolites
Clobazam	Low	Moderate	Short	Hepatic metabolism with active metabolites
Diazepam	Low	Very Fast	Intermediate	Hepatic metabolism with active metabolites
Lorazepam	High	Fast	Short	Hepatic metabolism with inactive metabolites
Oxazepam	Low	Slow	Short	Hepatic metabolism with inactive metabolites
Triazolam	Low	Fast	Short	Hepatic metabolism with small amounts excreted unchanged in urine)

1) Diazepam WHO,P

- ***DRUG SUMMARY:***

Diazepam is a CNS agent, very fast acting benzodiazepine, anticonvulsant, anxiolytic-hypnotic. It appears to act at both the limbic and subcortical levels of the CNS.

- ***INDICATIONS:***

Used for management of anxiety disorders or for short-term relief of the symptoms of anxiety.

Also used as adjunct for the relief of skeletal muscle spasms (muscle relaxant), and in status epilepticus and severe recurrent seizures.

- ***CONTRAINDICATIONS:***

Hypersensitivity to benzodiazepines, psychoses, oral dose in children < 6 months, acute narrow-angle glaucoma, respiratory depression, during or within 14 days of a MAO inhibitor therapy.

- ***DOSAGE FORMS:***

Tablets, injection.

- ***RECOMMENDED DOSAGE:***

Adult: *Dose should be individualized for each person, and be increased cautiously to avoid adverse effects.*

Recommended doses for anxiety disorders/ depending on severity: 2-10 mg PO b.i.d. to q.i.d.

Elderly or presence of debilitating disease: 2-2.5 mg q.i.d. or b.i.d., increased gradually if needed and tolerated.

Child: > 6 yrs. old; 1 - 2.5 mg PO b.i.d. or t.i.d., *or* not to exceed 0.12-0.8 mg/kg/d given 3-4 times a day.

In **status epilepticus or severe convulsive seizures**, diazepam is given initially intravenously, where facilities of resuscitations are not immediately available, with caution because of the risk of respiratory depression. Small doses are given: **Adults:** 5-10 m initially, may be repeated at 10-15 min. to a max. of 30 mg if necessary. Therapy may be repeated in 2-4 hrs. **Children ≥ 5 yrs:** 1 mg every 2-5 minutes up to max. 10 mg.

Directions: May be taken with food or water if stomach upset occurs.

*Concomitant ingestion of diazepam with *antacid* may alter the rate of absorption. If antacid is to be taken it should be 1 h. before or 2 hrs. after diazepam. administration.

*Durg should not be discontinued abruptly, this might cause withdrawal syndrome. If a dose is missed, it should be taken as soon as remembered, unless too close to next dose. The next dose should be taken only. Do not double the dose.

*Maximum effect requires 1-2 weeks; patient tolerance to therapeutic effects may develop after 4 weeks.

- ***USE IN SPECIAL CASES:***

Pregnancy- Risk-benefit issue (Category D). Benzodiazepines freely cross the placenta and accumulate in fetal circulation. If patient becomes pregnant during therapy, discuss possibility of discontinuing the drug. Neonatal withdrawal has been reported as well as prolonged CNS depression.

Lactation- Avoid use during breast-feeding. Benzodiazepines are excreted in breast milk. Chronic diazepam use in nursing mothers reportedly caused infant to become lethargic and lose weight.

Children- Oral dose is contraindicated in < 6 months. > 6 months: the initial dose should be small, increased gradually as tolerated. Hypotension is rare, however cardiac complications have been noted, use caution. Safety of injectable not established in neonates < 30 days of age.

Renal + Liver Disease- Use with caution, decrease dose to avoid accumulation. The drug is metabolized in the liver to active metabolite, and excreted primarily in the urine.

- ***PRECAUTIONS AND WARNINGS:***

-Caution in epilepsy, psychoses, mental depression, drug abuse, impaired hepatic or renal function, and addiction-prone individuals. Use extreme caution in elderly, and patient with chronic obstructive pulmonary disease (COPD).

-Long term use (> 4 months); effectiveness has not been assessed, need to periodically evaluate your patient.
-Dependence and withdrawal: Prolonged use of therapeutic doses can be habit-forming, tolerance or psychological and physical dependence may occur. Withdrawal syndrome has occurred after as little as 4-6 weeks of treatment. Symptoms may appear 8-12 hours after the last dose; and can range from dysphoria to muscle twitch and sweating, to tremor and convulsions. When discontinuing the drug, especially for long-term therapy patients, decrease the dose gradually over 4-8 weeks.
-Paradoxical reactions, i.e. excitement, aggression, stimulation of acute rage have occurred in psychiatric patients and hyperactive aggressive children.

- ***ADVERSE EFFECTS:***

Drowsiness, sedation, confusion, dizziness, vertigo, headache (warn patient not to perform hazardous activity like driving or operating machinery until full effect of the drug is known). Benzodiazepines can cause vivid nightmare or sleep terrors. Also, hypotension, blurred vision, diplopia, constipation, dry mouth, nausea, menstrual irregularities, tachycardia, and edema are possible.

- ***INTERACTIONS:***

Overview of Drug-Drug Interaction	
Elimination of benzodiazepines may be decreased by the following drugs due to the inhibition of hepatic metabolism, need to use caution: ***-Cimetidine*** ***-Oral Contraceptives*** ***-Isoniazid*** ***-Fluoxetine*** ***-Ketoconazole*** ***-Metoprolol*** ***-Propoxyphene*** ***-Valproic acid***	
Drug	**Interaction**
Alcohol & *anti-depressants* (barbiturate, narcotics)	Increase CNS depression. Avoid alcohol use with this medication.
Oral contraceptive	May result in prolongation of benzodiazepines $t_{1/2}$; a reduction in benzodiazepine may be needed.
Digoxin	Digoxin serum concentration may increase, need to monitor digoxin levels.
Ranitidine	May reduce GI absorption of diazepines, do not use concomitantly.

- ***OVERDOSE:***

Symptoms: mild; including drowsiness, confusion, impaired co-ordination, diminished reflexes and lethargy. Serious; include ataxia, hypotonia, hypotension, hypnosis, coma, and rarely death.
Treatment: Induce vomiting if it has not occurred. Refer to hospital as soon as possible. Ipecac and gastric lavage are needed with the general supportive measures.

- ***BRANDS:***

Assival (Teva), Disopam (Dexxon), Harmonal (JCL), Serepam (Birzeit), Valium (Roche).

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2) Lorazepam

- ***DRUG SUMMARY:***

Lorazepam is an intermediate-acting benzodiazepine, anxiolytic and sedative-hypnotic.

- ***INDICATIONS:***

Labeled use: management of anxiety disorders and short-term use to relief symptoms of anxiety associated with depressive symptoms. Preanesthetic medication, to reduce anxiety and recall of events related to day of surgery.
Other uses: antiepileptic, chemotherapy-induced nausea and vomiting, chronic insomnia, alcohol withdrawal.

- ***CONTRAINDICATIONS:***

Hypersensitivity to benzodiazepines, psychoses, acute narrow-angle glaucoma, during or within 14 days of a MAOI therapy, PO use for children <12 years, and in shock and coma cases.

- ***DOSAGE FORMS:***

Tablets, injection.

- ***RECOMMENDED DOSAGE:***

Adult: ★ *Antianxiety:*
2-6 mg/day PO in divided doses, take largest dose at bedtime; max. 10 mg/day.
★ *Insomnia:*
2-4 mg PO at bedtime.
Child: Use is not recommended.

Directions: May take with food or water if GI upset occurs.
*Do not increase dose without consulting doctor. If need to increase dosage, increase the nighttime dose before the daytime.
*If patient can sleep without this medication, discuss discontinuing the drug. Do not stop taking the medication abruptly, taper off over a few weeks if patient has been using it for prolonged therapy.
*Advise your patients to avoid large volume intake of coffee. Anxiolytic effects of lorazepam can be altered even by 500 mg caffeine (1 cup = 125-250 mg).

- ***USE IN SPECIAL CASES:***

Pregnancy- Risk benefit issue (Category D). Benzodiazepines freely cross the placenta and accumulate in fetal circulation. If patient becomes pregnant during therapy, discuss possibility of discontinuing the drug. Neonatal withdrawal has been reported as well as prolonged CNS depression.
Lactation- Use is not recommended. It is not known whether it is excreted in breast milk as with other benzodiazepines.
Children- < 18 yrs. old do not use injection, Safety and efficacy for use in < 12 yrs. orally has not been established.
Renal + Liver Disease- Use with caution. The drug is not metabolized to active metabolites, it is safer to use than other benzodiazepines in patient with mild liver disease. It is excreted in the urine.

- ***PRECAUTIONS AND WARNINGS:***

Same as diazepam.

- ***ADVERSE EFFECTS:***

Same as diazepam.

- ***INTERACTIONS:***

Same as diazepam.
Smoking and caffeine decrease sedative and antianxiety effects.

- ***OVERDOSE:***

Same as diazepam.

- ***BRANDS:***

Ativan (Wyeth-Ayerst), Lorivan (Dexxon), Lorocare (Pharmacare).

C) NEUROLEPTICS

Antipsychotic drugs are also known as neuroleptics and as major tranquilizers. They generally tranquilize without impairing consciousness and without causing paradoxical excitement, but they should not be regarded merely as tranquilizers. They can be used for short term to calm down disturbed patients whatever the underlying psychopathology, which may be brain damage, mania, toxic delirium, agitation, depression, or anxiety.

Specialists, according to certain criteria, diagnose psychotic conditions. Symptoms must be present for 6 months or more for the diagnosis to be made. Anti-psychotic drugs relieve Ford-psychotic symptoms, and prevent relapse.

Extrapyramidal symptoms are the most troublesome side effects of antipsychotic agents. They depend partly on the dose, partly on the type of drugs, and on the patients susceptibility. They consist of:

- *Parkinsonian* symptoms (including rigidity and tremor), which may occur gradually and are reversible.
- *Dystonia* (abnormal spasms of the face, tongue, and body movement) which may appear after only a few doses.
- *Akathisia* (restlessness) may resemble an exacerbation of the condition being treated.
- *Tardive Dyskinesia*: involuntary oral-facial movements, choreiform movement of the extremities, which is the most serious. Medication should be discontinued if such symptoms occur.

Table-8.3 lists examples of available antipsychotic drugs. In this section chlorpromazine and haloperidol will be discussed as the main drugs used.

Table- 8.3: Available Antipsychotic Drugs	
Phenothiazines- Aliphatic	**Thioxanthenes**
Chlorpromazine	Chlorprothixene
Promazine	Thiothixene
Triuoperazine	**Butyrophenone**
Phenothiazines- Piperidines	Haloperidol
Thioridazine	**Dihydroindolone**
Mesoridazine	Molindone
Phenothiazines- Piperazines	**Dibenzodiazepine**
Acetophenazine	Clozapine
Perphenazine	**Benzisoxazole**
Prochlorperazine	Resperidone
Fluphenazine	**Benzamide**
Trifluoperazine	Sulpiride

1) Chlorpromazine [WHO,P]

- ***DRUG SUMMARY:***

Chlorpromazine (**CPZ**) is a CNS agent, antipsychotic (neuroleptic/tranquilizer) agent, belonging to the aliphatic phenothiazine derivatives. Mechanism of action is not clearly understood, but is believed to be due to the blocking of dopamine receptors within the CNS.

- ***INDICATIONS:***

To control the manic phase of manic-depressive illness, for symptomatic management of psychotic disorders including schizophrenia. Also indicated for the control of nausea and vomiting, and relief of intractable hiccups.

- ***CONTRAINDICATIONS:***

Do not use CPZ in comatose or severely depressed states. Hypersensitivity, cross sensitivity between phenothiazines may occur. Bone marrow depression, blood dyscrasias, liver damage, withdrawal from alcohol, severe hypotension or hypertension, and closed-angle glaucoma.

- ***DOSAGE FORMS:***

Tablets, injection.

- ***RECOMMENDED DOSAGE:***

Adult: ★*Psychotic disorders, agitation*;
PO: 25-100 mg t.i.d. or q.i.d.,
Usual dose 75-300 mg/day, but may need up to 1000 mg/day for psychosis.
IV/*IM*: 25-50 mg up to 600 mg q. 4-6 h.
★*Nausea and vomiting, intractable hiccups;*
PO: 25-50 mg t.i.d. or q.i.d. prn.
Elderly or debilitated need third to half adult dose.
Child (> 6 mon.):
★*Psychotic disorders, agitation*;
PO: 0.5 mg/kg q. 4-6 h. prn., up to 500 mg/day.
IV: 0.5 mg/kg q. 6-8 h. prn.
★*Nausea and vomiting;*
PO: 0.5 mg/kg q. 4-6 h.
IV/*IM*: 0.5 mg/kg q. 6-8 h. prn., up to 40 mg/day.

Directions: Chlorpromazine should be taken with food or a full glass of water or milk (240 ml), to reduce possibility of gastric irritation.
*Some patients may fail to experience improvement until 7-8 weeks into therapy, therefore may not be compliant. Stress necessity of keeping appointments for follow up, and maintaining dose regimens. Do not increase dose more than once weekly if needed, the drug needs 4-7 days to reach steady state levels.
*When deciding to discontinue medication after prolonged therapy, taper off dose over several weeks to avoid onset of extrapyramidal symptoms.
*CPZ may cause urine discoloration, caution patient.
*Avoid prolonged exposure to sunlight or use sunscreens, since photosensitivity reactions may occur, as well as increased susceptibility to heat stroke.
*Need to discontinue medication if any of the following occur: sore throat, fever, skin rashes, tremor, impaired vision or jaundice.
*Smoking increases metabolism of phenothiazines resulting in more rapid

clearance of the drug. Higher dosage in smokers may be required. Advise patient to stop or at least reduce smoking if possible.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use CPZ only when potential benefits outweigh potential hazards to the fetus (Category C). Safety for use during pregnancy has not been established.

Lactation- CPZ has been detected in breast milk. Safety for use in nursing mothers has not been established. Infant should be observed for sedation.

Children- In general phenothiazines are not recommend for children < 6 months of age except when potentially lifesaving.

Renal Disease- Administer cautiously to those with diminished renal function. Monitor renal function in long term therapy, lower dose or discontinue if BUN becomes abnormal.

Liver Disease- Use with caution. The drug is metabolized in the liver.

- ***PRECAUTIONS AND WARNINGS:***

-Neuroleptic malignant syndrome (NMS) reportedly occurs more frequently than recognized (more in men). It is potentially fatal, but can be reversible if recognized and treated early. It resembles severe form of parkinsonian muscle rigidity, autonomic instability, hyperthermia, labile blood pressure, diaphoresis and altered mental status that could progress to coma, acute respiratory or renal failure or cardiovascular collapse. Symptoms of NMS can appear suddenly after initiation of therapy or after months of taking neuroleptic medication. To treat, one needs to stop the drug immediately and give intensive symptomatic and supportive care.

-Tardative dyskinesia, a syndrome consisting of potentially irreversible, involuntary movements. Prevalence appears highest among the elderly, especially women. Risk is increased as the duration of treatment and the total cumulative dose of the drug administered increase. Due to this fact, always prescribe neuroleptics in a way to minimize occurrence of NMS. In patients who require chronic treatment, use the smallest-effective dose and the shortest duration of treatment producing satisfactory clinical response. Periodically re-evaluate the need for continued treatment. If signs and symptoms appear, consider drug discontinuation.

-Various blood dyscrasias have occurred. If sore throat or other signs of infection occur, or if white cell and differential count indicate cellular depression, stop treatment and institute an antibiotic and other suitable therapy.

-Use caution in patients with cardiovascular disease, worsening of angina patients has been noted, pulse rate has increased, hypotensive phenomena with patients receiving antipsychotics all have been noted.

-Abrupt withdrawal of the drug or deliberate dose skipping, especially after prolonged therapy with large doses can cause onset of extrapyramidal symptoms, and severe GI disturbances. Taper the dose when deciding to discontinue.

-Diabetic or prediabetic patients should be monitored for reduced glucose tolerance and loss of diabetes control. Warn these patients.

- ***ADVERSE EFFECTS:***

Extra-pyramidal effects are the most troublesome and unpredictable, i.e. dystonia, akathisia and tardative dyskinesia, in phenothiazine therapy (*refer to introduction of neuroleptics)*.

Other effects include dry mouth, constipation, nasal congestion, drowsiness (caution patient against performing hazardous activities like driving or operating machines until full response to the drug is known), disturbances in temperature control and endocrine function (monitor diabetic and thyroid patients and adjust dosing regimens), lower convulsion threshold (might need to increase anticonvulsant dose and do not administer at

the same time), postural hypotension-especially after parenteral therapy, cholestatic jaundice, photo-sensitization (avoid over exposure to sun or sunlamp), blood dyscrasis, and skin reaction. Perform CBC, liver function tests, urinalysis, and EEG periodically during prolonged therapy.

- ***INTERACTIONS:***

Overview of Chlorpromazine Drug-Drug Interaction	
Drug	**Interaction**
Alcohol	Co-administration may result in additive CNS depression, as well as increased occurrence of extra pyramidal reactions, alcoholic drinks or drugs containing alcohol should not be coadministered; while taking this medication.
Antacids and ***anti-diarrheals***	Decrease absorption, space administration 2 hrs before or after administration of CPZ.
Anti-histamines; (**astemizole** & **terfenadine**) and ***anti-malarials***	Concomitant use with these drugs may increase risk of ventricular arrhythmia.
Anti-depressants	TCAs and SSRIs increased plasma concentrations of them, or of the phenothiazine, increasing side effects. Avoid concomitant use.
Epinephrine and ***norepi-nephrine***	Effects of these may be antagonized by CPZ. Do not coadminister these drugs. Warn patients from OTC use.
Propranolol	Co-administration results in increased plasma levels of both drugs, leading to hypo-tension. Use extreme caution.

- ***OVERDOSE:***

Symptoms primarily include CNS depression to the point of somnolence, deep sleep to coma. Hypotenison and extrapyramidal symptoms may occur, as well as agitation, convulsions, fever, hypothermia, hyperthermia, and cardiac arrhythmias.

Treatment includes supportive measures. Emetics are unlikely to be of value, take to emergency room.

- ***BRANDS:***

Largactil (Rhone-Poulenc Rorer), Taroctyl (Taro), Thorazine (SKF).

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2) Haloperidol [WHO,P]

- ***DRUG SUMMARY:***

A CNS agent, a potent, long acting butyrophenone derivative, with anti-psychotic (tranquilizer) effects. Haloperidol is pharmacologically similar to those of piperazine phenothiazines but with somewhat higher incidence of extra-pyramidal effects, and less hypotensive and relatively low sedative activity. Exerts strong antiemetic effects and impairs central thermoregulation. Produces weak central anticholinergic effects and transient orthostatic hypotension. Action thought to be related to competitive blockade of post-synaptic dopamine receptors in the brain.

- ***INDICATIONS:***

Psychotic disorder management. Tourette's disorder, severe behavioral problems in children with combative, explosive hyper-excitability, also in hyperactive children (short-term treatment) who show excessive motor activity with combative, impulsive mood or aggression. For patients with chronic schizophrenia requiring prolonged parenteral neuroleptic therapy. It can also be used as an antiemetic in small doses.

- ***CONTRAINDICATIONS:***

Parkinson's disease, seizure disorders, coma, alcoholism, severe mental depression, thyrotoxicosis and hyper-sensitivity.

- ***DOSAGE FORMS:***

Tablets, injection.

- ***RECOMMENDED DOSAGE:***

Adult: ★ *Psychosis*;
PO: 0.2-5 mg b.i.d. or t.i.d.
IM: 2-5 mg q. 4-8 h. prn.
★*Severe Psychosis*;
PO: 3-5 mg b.i.d. or t.i.d., may need up to max. 100 mg/day.
IM: 2-5 mg, may repeat q.h. prn. (Also for severe vomiting).
Child (3-12 y. or weight 15-40 kg):
★*Psychosis*:
PO: initially 0.5 mg/day (25-50 mcg/kg/d) divided to b.i.d. or t.i.d., may increase by increments of 0.5 each 5-7 days, until up to 0.15 mcg/kg/d or therapeutic effect is obtained, (max. of 10 mg/d).
(Do not give IM)
★*Behavioral Disorders, Agitation/ Hyperkinesia*;
PO only: 0.03-0.075 mg/kg/d, severe cases may require more, use only for short-term administration.

Directions: Individualize dosage.
*Debilitated or geriatric patients, and those with a history of adverse reactions to neurolepics, require less haloperidol.
*Tablets may be taken with a full glass of water or with food or milk.
*Injection should be administered by deep IM injection into the gluteus. Do not exceed 3 ml per injection site.
*Dosing regimen should be tapered when therapy is to be discontinued. Abrupt termination of treatment can initiate extrapyramidal symptoms.
*Advise patient not to drive a car or engage in other activities requiring mental alertness and physical co-ordination until drug response is known.
*Because of long half-life of haloperidol, therapeutic effects are slow to develop in early therapy. 4-7 days are required to reach steady state levels, therefore do not make more than weekly dosage adjustments in chronic therapy. Re-evaluate every 6 weeks.

- ***USE IN SPECIAL CASES:***

Pregnancy- Same as chlorpromazine, (Category C).
Lactation- Haloperidol is excreted in breast milk, but safety in nursing mothers has not been established. Adverse effects in the infants have not been reported.
Children- Not used for children < 3 yrs. old.
Renal Disease- Use caution, 40% of the drug is excreted in urine within 5 days.
Liver Disease- Use caution, the drug is metabolized in the liver.

- ***PRECAUTIONS AND WARNINGS:***

Same as chlorpromazine.

- ***ADVERSE EFFECTS:***

Same as chlorpromazine, but with less sedation and fewer antimuscarinic symptoms.

- ***INTERACTIONS and OVERDOSE:***

Same as chlorpromazine.

- ***BRANDS:***

Haldol (McNeil-CPC), Halidol (Abic), Haloper (CTI), Peridol (Eastern Chem.), Peridor (Unipharm).

Anticonvulsant / Antiepileptic Drugs:
SEIZURES

The terms seizures and convulsion maybe used interchangeable with epilepsy. A seizure (convulsion) is defined as a paroxysmal involuntary disturbance of brain function that maybe manifested as an impairment or loss of consciousness, abnormal motor activity, behavioral abnormalities, sensory disturbances, or autonomic dysfunction. Epilepsy is the condition of having chronic recurrent seizures. A seizure originates in unstable cell membranes, or its surrounding supporting cells. This causes a small number of cells to fire spontaneously. When this activity transmits to adjoining areas, a seizure occurs. Seizures are nearly always correlated with abnormal and excessive discharges in the brain. This can be detected and recorded on an electro-encephalogram (EEG).

When evaluating a patient, one should attempt to define factors that have resulted in the convulsion and to provide a detailed description of the seizure, so as to classify its type. The first step in the management of epilepsy is to confirm that the patient has a seizure disorder, and not a condition that mimics it. Then we need to identify what are the causes to remedy them.

Antiepileptic drugs either prevent the spontaneous firing or inhibit the propagation of abnormal firing.

Recent studies have shown that up to 70% of newly diagnosed children and adults can be successfully treated (complete control of seizure for several years) with anti-epileptic drugs. After 2-5 years of successful treatment drugs can be withdrawn in about 70% of children and 60% of adults without relapse *(WHO. 1997)*. Up to 30% of patients may not respond to drug therapy.

The object of treatment in epilepsy is to prevent the occurrence of seizures by maintaining an effective plasma concentration of the medication. Careful adjustment of doses is necessary. **Always start with low doses and increase gradually** until seizures are controlled, or there are over-dose effects. Dosage increase should not occur until there has been enough time for steady state concentration. Patients should be warned that activities requiring alertness could be affected. Alcohol and other CNS depressants may aggravate these effects and should be avoided.

Therapy with several antiepileptic drugs concurrently (polypharmacy) should be generally avoided. **Patients are best controlled with a single antiepileptic.** The most appropriate choice of drug depends of the type of epilepsy. Table-8.4 summarizes the recommended agents for certain cases. Combination drug regimen should be added only if seizures continue despite high plasma concentration or toxic effects. **Abrupt withdrawal** of antiepileptics **should be avoided** since this may precipitate severe rebound seizures. Reduce dose in stages, even if it may take months. Changing from one drug regimen to another should be made cautiously.

In recent years, several new anti-epileptic agents have reached the market to treat very specific conditions as monotherapy or combination. Such drugs include lamotrigine, gabapentin, vigabatrin, oxcarbazepine and zonisamide. **Due to the high cost and insufficient post-marketing data about these agents, they will not be discussed at this time.**

[Advise patient to carry medical identification card or jewellery bearing information about the diagnosis or medications in use, in case of emergency.]

Table – 8.4: Summary for Use of Antiseizure Medication (monotherapy)		
Seizure Type	**Primary Agent**	**Secondary Agent**
Partial seizures	Carbamazepine (*#1*) Clobazam	Phenytoin, Valproic acid Phenobarbital
Tonic-clonic (Grand mal)	Carbamazepine (*#1*) Phenytoin, or Valproic Acid	Primidone/Phenobarbital Clobazam
Absence seizures (Petit mal)	Ethosuximide (*#1*) Valproic acid	Clonazepam, Lamotrigine
Myoclonic, Atonic	Valproic acid Clobazam	Phenytoin Clonazepam Lamotrigine
Status Epilepticus (Initial therapy)	Diazepam IV	Lorazepam IV

#1: First choice for treatment.
Reference: Seear M, editor. The pocket pediatrician (low price edition). Cambridge: Cambridge University Press, 1997; p. 356.

Pregnancy and lactation: There is an increased risk of birth defects with the use of anticonvulsants. In view of the risk of neural tube and other defects, patients who may become pregnant should be informed of the risk and referred for advice. Pregnant patients should be offered counseling and antenatal screening. Nevertheless, the advantage of using proper antiepileptic drugs during pregnancy outweighs the disadvantage.

Antiepileptic therapy may become less effective in pregnancy because the drugs are cleared from the body. Hence, doses may have to be increased in some drugs.

To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy. In view of the risk of neonatal bleeding with carbamazepine, phenol-barbital and phenytoins, prophylactic vitamin k_1 (phytomenadione) is recommended for the neonate and the mother before delivery. Antiepileptic drugs can be used safely during lactation, with the exception of phenobarbital and ethosuximide.

Table-8.5 gives a summary of the available agents and compares their pharmacokinetic characteristics.

Table-8.5: Summary of Antiepileptic Drugs and Their Characteristics						
Drug	**CBZ**	**CLZ**	**ESX**	**PHNOB**	**PHNY**	**VALP**
Character	inostilbene	benzo-diazepine	succinimide	barbiturate	hydantoin	nahlanot related to any
Half-life (hrs.)	15 - 20	20 - 60	~ 60	50 - 120	8 - 60	8 - 12
Therapeutic blood level (mcg/ml)	4 - 12	20-70 mg/ml	40 - 100	15 - 40	10 - 20	50 - 100
Time (hr) to steady-state	2 - 4	5 - 10	10 - 15	14 - 28	5 - 10	2 - 4
Pregnancy	Cat. C	Cat. D	Cat. C	Cat. D	Cat. D	Cat. D
Lactation	excreted, caution	excreted, avoid	excreted, avoid	excreted, avoid	excreted, caution	excreted, caution
Children*	NE < 6 y	NE, caution	NE, < 3 y	caution all	safe	no < 2 y
Renal Disease	caution	warning, avoid	caution	contra-indicated	caution	caution, avoid
Hepatic Disease	caution	caution, warn in severe cases	caution	caution, avoid	caution	avoid

** Safety and efficacy; NE: not established.*

*- **CBZ**: carbamazepine, **CLZ**: clonazepam, **ESX**: ethosuximide, **PHNOB**: phenobarbital, **PHNY**: phenytoin, **VALP**: valproic acid.*

- Refer to the individual monographs for more detail.

1) Carbamazepine WHO,P

- ***DRUG SUMMARY:***

Carbamazepine (**CBZ**) is an inostilbene derivative related to the Tricyclic Antidepressants (TCAs). Its mechanism of action is not clearly known. CBZ has a wider therapeutic index than phenytoin. The relationship between dose and plasma concentration is linear, but monitoring plasma concentration is important in determining optimum dosage.

- ***INDICATIONS:***

CBZ is used as first line treatment in simple and complex partial (temporal lobe) seizures, generalized tonic-clonic (Grand mal). It can be used for most types of epilepsy except absence seizures.

Other cases that CBZ is used for (even though there is no specific indication) include: psychiatric disorders, including prophylaxis for manic-depressive illness, trigeminal neuralgia pain, resistant schizophrenia, dyscontrol symptoms, and management of alcohol withdrawal.

- ***CONTRAINDICATIONS:***

Hypersensitivity to CBZ or to TCAs. Patient with atrioventricular conduction abnormalities (unless paced). Patient on MAOI regimens or within 2 weeks of MAOI therapy.

- ***DOSAGE FORMS:***

Tablets, suspension.

- ***RECOMMENDED DOSAGE:***

Adult: 100-200 mg PO b.i.d. increased by 200 or 400 every 2 to 3 days.

In frail or elderly patients: 50 mg PO b.i.d.

Maintenance usual dose; 800 - 1200 mg/d in divided doses; max. 1600 mg/d.

Child: < 6 yrs.: initially 10-20 mg/kg/d, given b.i.d or t.i.d (suspension q.i.d), then increased at 5-7 day intervals; maintenance dose not to exceed 35 mg/kg/d.

6-12 yrs.: 100 mg PO b.i.d. (50 mg 4 times daily of suspension). gradually increased at increments of 20%, not to exceed 1000 mg/d (maybe calculated on basis of 20-30 mg/kg/d in 3 or 4 divided doses/day).

Directions: Start dosing low then increase over 1-2 wks, until clinical benefit.

*Time to reach steady state for the drug: 2-4 days.

*Therapeutic blood level: 4-12 mcg/ml.

*CBZ suspension will produce higher peak levels than the same dose given as the tablet, therefore start with low doses (i.e. Child 6-12 years ½ tsp q.i.d.), then increase slowly.

*Shake suspension well before use, and do not administer it with other liquid medicinal agents or diluents.

*Administer with food.

*Regular patient visits should be scheduled to check progress, and perform lab tests.

*When adding CBZ to existing anti-convulsant therapy, gradually do so, monitoring the other drug that may be gradually decreased (phenytoin increased).

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when potential benefit outweighs the risk of teratogenesis/ congenital malformation potential including Spina Bifida, Category C.

Lactation- Use with caution. CBZ is excreted in breast milk. Because of potential serious side effects, decide whether to discontinue nursing or to discontinue drug taking into account the importance of drug to mother.

Children- Safety and efficacy are not established for children < 6 years old.

Renal Disease- Use with caution, the drug is eliminated in urine and feces. Prescribe CBZ if benefit outweighs risk of use.

Liver Disease- Use with caution, since CBZ is metabolized in liver to active metabolites, and can induce liver microsomal enzymes.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in patients with bone marrow depression, hypertension, history of hepatic or cardiac disease.

-Patients on oral contraceptives should be informed that CBZ may cause break through bleeding and may affect the reliability of oral contraceptive. Use alternative contraceptive methods.

- ***ADVERSE EFFECTS:***

GI disturbances, dizziness, drowsiness, visual disturbances (especially double vision associated with peak plasma concentration), constipation, anorexia, cholestatic jaundice are common side effects, most should decrease within few days of therapy. Other effects that may occur include acute renal failure, agranulocytosis, aplastic anemia, thrombocytopenia, hypothyroidism, and other blood disorders.

Patients should be monitored every 6 months.

- ***INTERACTIONS:***

Overview of Carbamazepine Drug-Drug Interaction

Drug	Interaction
Anti-Epiletpics	CBZ may increase level of ***lithium***, and markedly decrease the levels of other antiepiletpics. CBZ and ***phenytoin*** may mutually enhance one another's metabolism.
Erythromycin or ***Isoniazid***	May increase the effects of CBZ. Avoid combination if possible; otherwise monitor serum CBZ concentration to avoid toxicity.

Barbiturates	(i.e. phenobarbital, primidone) are liver enzyme inducers thus when CBZ is given concurrently, CBZ levels are decreased due to increased metabolism thus increased rate of clearance. No loss of seizure control has been reported, but avoid concomitant use of barbiturates unless clearly indicated, and the patient's CZB blood levels and therapeutic efficacy should be observed very closely then.
Oral anti-coagulants and ***theophylline***	CBZ may decrease the effects of oral anticoagulants and theophylline, use with caution.

- ***OVERDOSE:***

Symptoms and signs first appear after 1-3 hours. Neuromuscular disturbances are the most prominent symptoms. Cardiovascular disorders are generally mild, unless very high doses (> 60 g) have been ingested. Other symptoms include: irregular breathing, respiratory depression, hypotension, nausea, vomiting, and urinary retention.

Treatment: There is no specific antidote. Need to irrigate the stomach repeatedly even if more than 4 hours have passed following ingestion. Charcoal administration is effective in enhancing the elimination; 50-100 g can be given initially followed by 25 g q. 4 h.

- ***BRANDS:***

Carbi (Alphapharm/Genmedix), Tegrepine (JePharm), Tegretol (Ciba-Geigy), Teril (Taro).

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2) Clonazepam WHO,P

- ***DRUG SUMMARY:***

Clonazepam is a CNS drug, benzodiazepine derivative with strong anticonvulsant activity and several other pharmacological properties characteristic of the drug class. It suppresses spike and wave discharge in absence seizures, and decreases amplitude, frequency, duration, and spread of discharge in minor motor seizures. Its sedative side-effects may be prominent.

- ***INDICATIONS:***

Indicated for use alone or with other drugs in absence seizures, myoclonic and akinetic seizures, and Lennox-Gastaut syndrome. Also in absence seizures not responding to succinimides or valproic acid, infantile spasms and restless legs.

- ***CONTRAINDICATIONS:***

Hypersensitivity to benzodiazepines, respiratory depression, porphyria, acute narrow-angle glaucoma, and breast-feeding.

- ***DOSAGE FORMS:***

Tablets, drops.

- ***RECOMMENDED DOSAGE*:**

Adult: 1.5 mg/d PO in 3 divided doses, increased by 0.5-1 mg every 3 days, until seizures are controlled or until intolerable side effects, max. 20 mg/d.

Child: (up to 10 y or 30 kg)
0.01-0.03 mg/kg/d (not to exceed 0.05 mg/kg/d) in 3 divided doses, may be increased to 0.25-0.5 mg/kg every 3 days; max. 0.2 mg/kg/d or 3 mg daily.

Directions: This drug needs 5-10 days to reach steady state concentrations.

*Therapeutic blood level ranges from 20-70 ng/ml.

*If doses cannot be equally divided, the largest dose should be given at bedtime.

*May take with food or water if stomach upset occurs.

*Up to 30% of patients have shown a loss of anticonvulsant activity within 3 months

of administration. Dosage adjustment might be needed.

*Patient should be advised not to stop taking medication abruptly, and if missed a dose can take it as soon as remembered, or if too close to next dose, just take then. The dose should not be doubled (2 tablets taken at the same time).

- ***USE IN SPECIAL CASES*:**

Pregnancy- Use only if benefit of treatment outweighs risk to fetus (Category D). Benzodiazepines and their metabolites cross the placenta freely and can accumulate in the fetal circulation, causing malformation, neonatal drowsiness and withdrawal symptoms.

Lactation- Contraindicated use; lethargy and weight loss may occur in infant. Benzodiazepines are excreted in breast milk and can accumulate in circulation, since neonate cannot metabolize the drug.

Children- Use with caution, since long term use on growth and development is unknown. Use smaller doses if have to use.

Renal Disease- Warning, in case of presence of severe impaired renal function. The drug is excreted primarily in urine, with half-life of 18-40 hrs.

Liver Disease- Use with caution, drug is metabolized in the liver. Use smaller doses. Warning in severe cases; can precipitate coma.

- ***PRECAUTIONS AND WARNINGS*:**

-Use caution in renal disease, COPD, drug controlled open-angle glaucoma, children (because of unknown consequences of long-term use on growth and development), and mixed seizure disorders.

-Prolonged use of therapeutic doses can lead to dependence.

-Withdrawal syndrome has occurred after as little as 4-6 weeks of treatment. Do not discontinue drug abruptly, decrease gradually over 4-8 weeks if patient has been on medication for prolonged time. Withdrawal symptoms include: convulsions, tremor, abdominal and muscle cramps, vomiting and sweating.

- ***ADVERSE EFFECTS:***

Most common: drowsiness, sedation and dizziness; *(advise patient not to drive or engage in activities requiring mental alertness and physical co-ordination until the drug reaction is fully known),* ataxia, behavioral changes, hyperactivity, irritability, aggressiveness, violent behavior, disobedience, bronchial hypersecretion, rash and thrombocytopenia.

- ***INTERACTIONS:***

Overview of Clonazepam Drug-Drug Interaction	
Drug	**Interaction**
Alcohol and Other ***CNS depressants***	Concomitant use of these with clonazepam will increase sedation and CNS depression.
Antacids	Use of ***antacids*** may alter the rate of absorption, do not use concomitantly, space administration time if needed.
Anti-epileptics	Use with other ***antiepileptics*** accelerates metabolism of clonazepam, reduce its effect, *phenytoin* levels may increase. Monitor blood levels.
Antihyper-tensives	Concomitant use enhance hypotensive effect, use with caution.
Opioid analgesics, & *muscle relaxants* (**baclofen**)	These enhance sedative effects. Use with caution.

- ***OVERDOSE:***

Symptoms: drowsiness, confusion, somnolence, impaired co-ordination, diminished reflexes and lethargy. Severe cases cause serious symptoms like hypotonia, hypotension, hypnosis, coma but rarely death.

Treatment: induce vomiting if it has not occurred spontaneously, employ general supportive measures, along with immediate gastric lavage or ipecac, follow with activated charcoal administration and a saline cathartic.

- ***BRANDS:***

Clonex (Teva), Klonopin/ Rivotril (Roche).

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3) Ethosuximide [WHO,P]

- ***DRUG SUMMARY:***

Ethosuximide is a succinimide anti-convulsant that reduces frequency of epileptic attacks. There is little information about its mechanism of action. Unlike phenytoin and carbamazepine, it does not inhibit voltage-gated Na^+ channels; unlike phenobarbital and clonazepam, it does not enhance the postsynaptic actions of GABA.

- ***INDICATIONS:***

Treatment of choice for absence seizure (petit mal); which is its only indication.

- ***CONTRAINDICATIONS*:**

Hypersensitivity to succinimides, severe liver or renal disease.

- ***DOSAGE FORMS:***

Capsules, syrup.

- ***RECOMMENDED DOSAGE:***

Adult: 20 mg/kg/d or 250 mg b.i.d. PO, may increase every 4-7 days by 250 mg prn.; max. dose of 1.5 g/d should be administered under direct specialized medical supervision.

Child: 6-12 y; Same as adult, optimal dose is 20 mg/kg/d.

3-6 y; 250 mg/d, may increase every 4-7 days prn.; max. 20 mg/kg/d or 1 g/d.

Directions: Therapeutic levels are from 40 - 100 ug/ml. Inadequate dosage is the major cause of therapeutic failure.

*Start at 20 mg/kg/d to get lowest effective therapeutic level and titrate up as needed.

*May be taken with food if GI distress occurs.

*Warn patient not to discontinue medication abruptly or change dosage, except on doctor's advice. This may precipitate a seizure.

- ***USE IN SPECIAL CASES:***

Pregnancy- Ethosuximide may be teratogenic, elevated incidence of birth defects, risk vs. benefit evaluation has to be made (Category C).

Lactation- Avoid. Significant amount has been detected in breast milk. Hyper-excitability and poor suckling have been reported in infant.

Children- Safety in children < 3 y. has not been established.

Renal Disease- Use with caution. 20% of drug is excreted unchanged via the kidney. Abnormal renal function has been reported in humans while using this medication. Perform urinalysis periodically.

Liver Disease- Use with caution. The drug is metabolized in the liver. Abnormal liver function has been reported. Administer with extreme caution to patients with known liver disease, and perform liver tests periodically.

- ***PRECAUTIONS AND WARNINGS:***

-**Hematologic effects**; blood dyscrasias (some fatal) have occurred, therefore, perform periodic blood counts. If signs or symptoms of infection (i.e. sore throat, fever) develop, consider blood counts at that point.

-Dosage adjustment or changes should be done slowly. Abrupt withdrawal of anticonvulsant medication may precipitate absence status.

-Need to order blood, liver or renal tests if any of the following occur: Skin rash, joint pain, unusual bleeding or bruising, unexplained fever, and/or blurred vision. Advise patient to report any of these. Recommend strict caution against pregnancy as your patient starts on this medication, with hormonal and non-hormonal methods.

- ***ADVERSE EFFECTS:***

Most common; GI upset (take with food to lower incidence), anorexia and weight loss (advise patient to monitor weight on a weekly basis, if excessive loss, might need to lower the dose), epigastric distress, hiccups, drowsiness, dizziness (warn

against hazardous tasks such as driving or operating machinery) and headache. Rarely, psychotic states, rashes including erythema multiforme, Stevens Johnson Syndrome, lupus erythematosus, and blood dyscrasias have been reported.

- ***INTERACTIONS:***

Overview of Ethosuximide Drug-Drug Interaction	
Drug	**Interaction**
Anti-bacterials	Isoniazid increases plasma level of ethosuximide, high risk of toxicity. Avoid concomitant use.
Anti-depressants and ***anti-psychotics***	These have antagonistic effects; the convulsive threshold may be lowered. Use with caution.
Other anti-epileptics	Use with other antiepileptics enhance toxicity and effect, increase sedation, i.e. CBZ decreases ethosuximide level, phenytoin level is increased. Monitor patient carefully until you stabilize condition.

- ***OVERDOSE:***

Symptoms of acute ethosuximide overdose include: confusion, sleepiness, unsteadiness, coma with slow, shallow respiration, hypotension, hypo- or hyper-thermia, absent reflexes, nausea, vomiting, coma with respiratory depression can occur.

Treatment includes usual supportive measures, charcoal, hemoperfusion, hemo-dialysis may be indicated.

- ***BRANDS:***

Zarontin (Park-Davis).

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4) Phenobarbital WHO,P

- ***DRUG SUMMARY:***

Phenobarbital/Phenobarbitone is a long-acting barbiturate, that is classified as a CNS agent, anticonvulsant, sedative hypnotic. Phenobarbital limits the spread of seizure activity by causing an increase in the threshold for motor cortex stimuli, its activity is not related to the sedative effect. It exerts maximal anticonvulsant action at doses below those required for hypnosis, this has made its clinical utility as an antiepileptic accepted. It is the drug of choice for febrile and neonatal seizures.

Tolerance or **psychological and physical dependence** may occur with continued use. Restrict use, limit prescribing and dispensing to the amount required for the interval until the next appointment.

- ***INDICATIONS:***

As an anticonvulsant; use for treatment of partial and generalized tonic-clonic (grand mal), cortical focal seizures, and in prolonged (≥ 15 min.) febrile convulsions or recurrent convulsions in neonates and young children. Not used for absence seizures. Also used as injection in emergency control associated with status epilepticus unresponsive to diazepam, tetanus and toxic reactions. Used as hypnotic sedative for short-term (2 wks.) treatment of insomnia.

- ***CONTRAINDICATIONS:***

Sensitivity to barbiturates, manifest hepatic or familial history of porphyria, severe respiratory or renal disease, history of previous addiction to sedative hypnotics, and pregnancy.

- ***DOSAGE FORMS*:**

Tablets, suppository.

- ***RECOMMENDED DOSAGE*:**

Adult: 60-180 mg/day PO; max. 6 mg/kg/d in divided doses.

(For acute convulsions 200-320 mg IM or IV, repeated q. 6 h. as necessary).

Child: 3-8 mg/kg/day PO.

(In Status Epilepticus 15-20 mg/kg IV over 10-15 min.).

Directions: Therapeutic serum concentrations of 15-40 ug/ml produce anti-convulsant activity in most patients; these are usually reached after 2-3 weeks of therapy.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use. Barbiturates are reported teratogenic drugs, (Category D). Barbiturates readily cross the placental barrier and distribute throughout fetal tissues. Withdrawal symptoms occur in infants born to mothers who have received the drug during the last trimester. Neonatal coagulation defects that may cause bleeding within 24 h of birth have been associated with barbiturate use as well, Vitamin K should be given then.

Lactation- Avoid use. Small amounts are excreted in breast milk. Drowsiness in nursing infant has been reported.

Children- Barbiturates repeatedly produce excitement rather than depression in some people. They may produce irritability, aggression, and cognitive deficits in children. Significantly lower IQs were noted after long term use, for up to 6 months from discontinuation of therapy. For infants who develop physical dependence, phenobarbital can be given, and after withdrawal symptoms are relieved, gradually decrease the dosage, until you completely withdraw the medication over 2-3 weeks.

Renal Disease- Contraindicated in patients with impaired renal function. Barbiturates are excreted either partially or completely unchanged in the urine.

Liver Disease- Do not use in patients showing premonitory signs of hepatic coma. Barbiturates are metabolized primarily by hepatic microsomal enzymes. Administer with caution and initially in reduced doses in susceptible hepatic disease patients.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in impaired hepatic, respiratory functions, and in patients with diabetes mellitus. Elderly and children sometimes have paradoxical response (behavioural disturbances and hyperkinesia), inform family members.

-Warn patient to avoid potentially hazardous activities until full response to the drug is known.

-Patient should inform the doctor if any of the following occur: fever, sore throat, mouth sores, easy bruising or bleeding, tiny broken blood vessels under the skin.

-Phenobarbital increases incidence of osteomlacia, rickets, and anemia. Advise patient to increase intake of vitamin D-fortified foods *(i.e. milk)* and folate intake *(fresh green leafy vegetables, fruits, etc.)* or take supplements if deficiency symptoms occur.

-Caution patients to adhere to barbiturates regimen, intervals between doses should not be changed. Patient should not stop taking drug abruptly because of danger of withdrawal symptoms (8-12 h. after last dose), which can precipitate status epilepticus, or death.

- ***ADVERSE EFFECTS:***

Drowsiness, headache, dizziness, nystagmus, ataxia, anemia, osteomalacia (vitamin D and folic acid deficiencies), liver damage, paradox excitement and hyperactivity in children, dulled intellect, restlessness and confusion in the elderly.

- ***INTERACTIONS:***

Overview of Phenobarbital Drug-Drug Interaction	
Drug	**Interaction**
Alcohol	Alcohol should not be consumed while taking phenobarbital due to additive CNS effects, may severely impair judgment and abilities, and possible death.
Anti-depressants	These potentiate adverse effects of phenobarbital. Use caution.
Oral contra-ceptives	Phenobarbital increases metabolism of OC, need to use alternative methods of contraception in addition or instead of hormonal OC to prevent pregnancy.
Oral anti-coagulants, ***anticonvul-sants***, ***corticosteroids***, ***digoxin***	Phenobarbital may decrease absorption or increase metabolism of these drugs; patients might need dosage adjustments and monitoring.

- ***OVERDOSE:***

Symptoms: Onset of symptoms may not occur until several hours after phenobarbital ingestion. CNS and respiratory depression, constriction of the pupils, ataxia, tachycardia, hypotension, lower body temperature and coma.

Treatment is mainly supportive. Maintain adequate airway with assisted respiration and oxygen administration as necessary. If the patient is conscious and has not lost the gag reflex, emesis may be induced with ipecac. After completion of vomiting, administer 30 gm of activated charcoal in a glass of water. If emesis is not possible perform gastric lavage and continue with the supportive and symptomatic treatment measures as required.

- ***BRANDS:***

Phenobarb (Eastern Chem.), Phenobarbital (Rekah).

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5) Phenytoin [WHO,P]

- ***DRUG SUMMARY:***

Phenytoin is a CNS agent, anticonvulsant, cardiovascular and antiarrhythmic agent, hydantoin derivative chemically related to phenobarbital. The mechanism of action is not exactly known. It has a narrow therapeutic index and the relation between dose and plasma concentration is non-linear; therefore, a small dose increase may produce large rise in plasma concentration with acute toxic side effects.

- ***INDICATIONS:***

Epilepsy; status epileptics, grand mal (tonic-clonic) and partial seizures.

Also it is used as an antiarrhythmic agent.

- ***CONTRAINDICATIONS:***

Pregnancy, hypersensitivity to hydantoin products, sinus bradycardia, complete or incomplete heart block.

- ***DOSAGE FORMS:***

Capsule, pediatric suspension.

- ***RECOMMENDED DOSAGE:***

Adult: 100 mg (125 mg suspension) PO t.i.d., increased gradually by 100 mg/wk. until seizures are controlled.

Can start with a loading dose of up to 15-18 mg/kg or 1 g.

Usual maintenance dose: 300-400 mg/d; max. dose 600 mg/d.

Child: initially 5 mg/kg in 2-3 divided doses may be increase gradually to max. 300 mg/d after the therapeutic level is reached.

Usual maintenance dose: 4-8 mg/kg/d.

Directions: Start with small dose and gradually increase. Time to reach steady state for the drug is 5-10 days. Therapeutic blood level; 10-20 mcg/ml.

*Treatment must continue as long as condition continues.

*If the patient has been free of seizures for several years, then the drug should be slowly withdrawn. **Do not stop medication abruptly** which may precipitate status epilepticus, reduce gradually.

*Take medication with food to reduce GI upset possibility.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use. Teratogenic effects have been reported (Category D). CBZ might be safer to use.

Lactation- Use with caution, phenytoin is excreted in small amounts. Drowsiness and decreased suckling activity have been reported in one infant. But therapeutic levels have little risk to the nursing infant.

Children- Safe. The absorption of oral phenytoin is slower in pediatrics and is poor in neonates. Monitor carefully to avoid toxicity.

Renal Disease- Use caution, metabolites are excreted by the kidney.

Liver Disease- Reduce dose to avoid toxicity. Phenytoins are metabolized in the liver and can induce liver microsomal enzymes.

- ***PRECAUTIONS AND WARNINGS:***

-Caution use in impaired hepatic and renal function, alcoholism, and severe myocardial insufficiency.

-Adjustment of phenytoin dosage for patients on insulin or of sulfonylurea dosage may be necessary. Patients on prolonged therapy should have adequate intake of vitamin D containing foods.

-Observe for symptoms of folic acid deficiency; neuropathy or mental dys-function. Advise patient not to change drug brand when refilling prescription. Differences in brands can alter phenytoin serum levels (change bioavailability).

- ***ADVERSE EFFECTS:***

Usually dose related; drowsiness, dizziness, ataxia, confusion, GI disturbances. Also hirsutism, gingival hyperplasia (very common, need to advice patient on proper oral hygiene), blood dyscrasias, folate deficiency, megaloblastic anemia, osteo-malacia due to interference with vitamin D metabolism.

- ***INTERACTIONS:***

Overview of Phenytoin Drug-Drug Interaction	
Drug	**Interaction**
Antacids	Antacids decrease effect of hydantoins. If there is a need to administer an antacid, give 1 hr before or 2 hrs after phenytoin administration.
Chloram-phenicol, ***isoniazid***, and ***benzo-diazipines***	Marked inhibition of the metabolism of these drugs may occur. Use with caution.
TCAs, ***phenyl-butazone***, ***valproic acid*** and ***salicylates***	Phenytoin may displace these drugs. Use with caution.
Influenza vaccine	Using this vaccine during phenytoin treatment may increase seizure activity. Use caution, and monitor patient if need to give the vaccine.

- ***OVERDOSE:***

Lethal dose in adults is estimated to be 2-5 g. *Symptoms* include nystagmus, ataxia, tremor hyperflexia, lethargy, slurred speech, nausea and vomiting. Patient may become comatose and hypotensive.

Treatment: Supportive measures are required to prevent respiratory or circulatory depression. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Repeat dose of activated charcoal by mouth to enhance elimination.

- ***BRANDS:***

Dilantin / Epanutin (Park Davis).

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6) Valproic Acid WHO,P

(and derivatives)

- ***DRUG SUMMARY:***

(Divalproex sodium, sodium valproate) Valproic acid (**VA**) is an antiepileptic agent, chemically unrelated to other drugs. Its mode of action is not fully understood but may involve a modification in levels of GABA in the brain. Plasma concentrations are not a useful index of efficacy. Need to monitor patient's therapeutic response.

- ***INDICATIONS:***

Epilepsy; effective in both absence and mixed types of generalized seizures.

- ***CONTRAINDICATIONS:***

Hepatic disease or significant hepatic dysfunction, and hypersensitivity to valproic acid.

- ***DOSAGE FORMS:***

Tablets as sodium valproate; capsule: valproic acid; syrup (200mg/5ml), solution (200mg/ml): sodium valproate.

- ***RECOMMENDED DOSAGE*:**

(Doses should be adjusted to the needs of individual patients to achieve adequate control of seizures).

Adult: 15 mg/kg/d in divided total daily doses, increase at 1 week intervals by 5-10

mg/kg/d, until seizures are controlled. Max. dose 60 mg/kg/d.

Child: For children up to 20 kg or about 4 yrs.; initially start with 10-15 mg/kg/d in divided doses. Increase gradually (in 5-10 mg/kg/wk) to therapeutic effects. (range 20-30 mg/kg/d).

For children > 20 kg; initially 400 mg/d in divided doses, increased gradually to 20-30 mg/kg/d; max. 35 mg/kg/d.

Directions: If GI disturbances occur, may administer this drug with food.

*Dose should be gradually increased over a couple of weeks.

*Time of administration (intervals) should be standardized for patients to avoid inappropriate fluctuations in plasma concentrations.

*The drug is readily absorbed from the GI tract, and needs 2-4 days to reach steady state. Therapeutic blood level ranges from 50 - 100 mcg/ml.

- ***USE IN SPECIAL CASES:***

Pregnancy- Need to evaluate benefit/risk situation (Category D). Increased risk of neural tube defects, neonatal bleeding and hepatotoxicity in the fetus.

Lactation- Use with caution. Concentration of VA in breast milk are 1-10 % of serum concentrations. It is not known what effect this would have on a nursing infant.

Children- Children < 2 yrs. are at increased risk of developing fatal hepatotoxicity, especially those with history of liver disease, metabolic disorder, or are on multiple anticonvulsants.

Renal Disease- Use with caution. Excretion is primarily in urine. Need to avoid accumulation.

Liver Disease- Avoid use. Contraindicated in active or severe liver disease states. Can precipitate hepatotoxicity or liver failure in susceptible patients. The drug is metabolized in the liver, and is a liver enzyme inducer.

- ***PRECAUTIONS AND WARNINGS:***

- Liver function tests should be done at least every 2 months especially during first 6 months of therapy.

– Tell patient not to stop taking medication without consultation, and to take medication the same time every day.

– In elderly, due to a decrease in unbound clearance of valproate, reduce starting dose, and base therapeutic dose on clinical response.

– Inform diabetic patient that VA may cause a false positive test for urine ketones.

- ***ADVERSE EFFECTS:***

GI disturbances, increased or decreased appetite and weight, transient hair loss, headache, CNS depression (advise patient not to engage in hazardous activities like driving or operating heavy machinery until they know that they don't become drowsy from taking the drug), drowsiness, emotional upset, and prolonged bleeding time. Rarely in children: mental stimulation, aggressiveness and hyperactivity has been reported.

- ***OVERDOSE:***

Symptoms: May result in somnolence, heart block, visual hallucinations, and deep coma. *Treatment:* Valproic acid is absorbed very rapidly, efficacy of gastric lavage varies with time since ingestion. Use general supportive measures and carefully maintain adequate urinary output.

- ***INTERACTIONS:***

Overview of Valproic Drug-Drug Interaction	
Drug	**Interaction**
Phenytoin, ***carba-mazepine***, or ***pheno-barbital***	Concomitant administration of hepatic enzyme inducers such as ***phenytoin***, ***CBZ***, or ***phenobarb.***, may enhance the metabolism of valproic acid. In turn, valproic acid has been reported to cause rises in phenobarb. (and primidone) concentrations in plasma. The interaction between VA and phenytoin is complex and involves inhibition of phenytoin metabolism as well as competition for protein binding sites.
Warfarin	Valproic acid can displace ***warfarin*** from protein binding sites, need to monitor coagulation tests. Unlike phenytoin and CBZ, valproic acid does not induce hepatic enzymes.

- ***BRANDS:***

Depakote (Abbott), Depalept (CTI), Valporal (Teva).

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7) Diazepam [WHO,P]

- ***DRUG SUMMARY:***

Diazepam is a CNS agent, very fast acting benzodiazepine, anticonvulsant, anxiolytic-hypnotic. Refer to page 181 for monograph.

Antiparkinsons drugs:

PARKINSON'S DISEASE

Parkinsonism is a neurological disease that is characterized by tremor, rigidity, akinesia and disorders of posture and equilibrium. It is a progressive degeneration of pigment-containing cells of the substantia nigra leading to deficiency of dopamine. The onset is slow and progressive with symptoms advancing over months to years. Diagnosis is based on clinical presentation, where at least 2 of tremor, bradykinesia or rigidity must be present. Patient disability can be classified by the Hoehn and Yahr scale as; early (stage 1 and 2), middle (stage 3), or advance (stages 4 or 5) Parkinson (*Drug & Therapeutic Prespective, 2001*).

Current therapy for Parkinson's is palliative (will ease the symptoms only but does not cure). Drug therapy is aimed at correcting or modifying the neuro-transmitter defects by inhibiting the effect of acetylcholine or enhancing the effect of dopamine. The goal is to provide maximum relief from symptoms and mobility of the patient. Drug therapy is initiated when the patients find that their symptoms interfere with their functional status. All patients with gait impairment postural instability should be treated, as these symptoms can lead to falls and serious injury. Therefore, functional status is what determines therapy. *Treatment philosophy*: **do not** start or increase the doses of drugs until there is loss of function.

Up-to-this-date, there are no neuro-protective agents that have demonstrated to be effective in preventing or slowing the development of symptoms in this disease, thus improving the quality and expectancy of life of most patients, and research is undergoing in this field. About 10-20% of patients are unresponsive to current treatments (*BNF 2001, p. 237*).

Drugs that are used to treat Parkinson disease symptoms are divided into **two groups:**

First, the **anticholinergic drugs** (include antimuscarinic) which are most useful in improving symptoms of tremor and rigidity. Patients with minimal symptoms (mostly young onset) benefit from them. These agents seem to be equally effective.

The second group consists of the **dopaminergic agents**, which combat the dopamine deficiency. Effectiveness of medication varies from one individual to the other. Levodopa has been the gold standard for treatment, even with many new drug classes being discovered. It remains the most effective agent and maintains a key role in the management of Parkinsonism (*Drug & Therapeutic Perspective, 2001*). However the on-off phenomenon and dyskinesia associated with the long-term dose lead to the greater use of alternative drugs.

A) ANTICHOLINERGIC DRUGS

1) Benztropine Mesylate

- ***DRUG SUMMARY:***

A synthetic centrally acting anticholinergic (antimuscurinic) agent, that is chemically similar to atropine and diphenhydramine. Acts by diminishing excess cholinergic effect associated with dopamine deficiency. Suppresses tremor and rigidity, but does not alleviate tardive dyskinesia. (It is similar to benzhexol/ trihexyphenidyl, but excreted more slowly).

- ***INDICATIONS:***

For use in the therapy of all forms of parkinsonism. May also be used to control of extrapyramidal disorders (except dyskinesia) due to neuroleptic drugs like phenothiazines, haloperidol. Commonly used with levodopa therapy.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug, angle-closure type glaucoma, obstructive disease of GU or GI tracts, susceptibility to tachycardia, and children < 3 years of age.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE*:**

Adult: 0.5-1 mg/d PO gradually increase in increments of 0.5 at 5-6 day intervals, to the smallest amount necessary for optimal relief of parkinsonism; max. 6 mg/d.
1-2 mg PO b.i.d. for extrapyramidal reactions.

Directions: Onset needs 1 h., and duration 6-10 h.
*Administer immediately after meals to prevent GI irritation.
*Patients taking drug at bedtime have shown greater relief and better compliance.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use when clearly needed and potential benefits outweigh potential hazards to fetus (Category C). Safety for use during pregnancy has not been established.

Lactation- Use with caution. An inhibitory effect on lactation will occur. Safety on lactating infant has not been established.
Children- Contraindicated in children < 3 yrs. Safety and efficacy in older children have not been established.
Renal Disease- Use with caution. Safety has not been established
Liver Disease- Use with caution. Safety has not been established.

- ***PRECAUTIONS AND WARNINGS:***

-Rapid or pounding heart beat, confusion, eye pain or rash may be an indication of hypersensitivity.
-In geriatric patients (> 60 yrs) of age, the possibility of increased sensitivity increases. Strict dosage regulations are required.
-Mental confusion, disorientation, and psychotic-like symptoms may develop.
-Antihistamines (e.g. diphenhydramine) have mild antiparkinsons effect and can be useful in patients with minimal symptoms.
-Caution in cardiovascular disease, hepatic or/and renal impairment.
-Avoid abrupt discontinuation of treatment.
-Advise the patient to use caution in hot weather to avoid heat stroke or heat exhaustion.

- ***ADVERSE EFFECTS:***

Dry mouth; which can be relieved by sucking hard candy, chewing gum or adequate fluid intake. Difficult urination or constipation may occur; stool softeners can be used. Also sedation, drowsiness, restlessness, mental confusion, tachycardia, decreased sweating (increased susceptibility to heat stroke), and blurred vision.

- ***INTERACTIONS:***

Overview of Benztropine Drug-Drug Interactions	
Drug	**Interaction**
Alcohol, CNS depressants	These have additive sedative and depressant effects. Warn patients about the side effects, if they have to be given concomitantly.
Amantadine, TCAs, MAO inhibitors, and ***quinidine***	These have additive anticholinergic effects. Monitor patients response if concomitant use cannot be avoided, and adjust the anticholinergic drug dose accordingly.
Digoxin	Serum level of digoxin may be increased, use caution, monitor levels to avoid toxicity.
Haloperidol	Effects are variable. A delayed reaction may occur, where worsening of schizophrenic symptoms occur. Avoid concomitant use. If cannot avoid, monitor patients routinely and closely, and tailor haloperidol dose as necessary.
Phenothiazines	Therapeutic action of phenothiazines may be decreased. Tailor the dose of the phenothiazine as needed.

- ***OVERDOSE:***

Symptoms: Characterized by the adverse reactions. Can include: circulatory collapse, cardiac arrest, respiratory depression or arrest, toxic psychosis, shock, coma, stupor, foul smelling breath, dilated and sluggish pupils.

Treatment: Immediately following ingestion, remove remaining drug from the stomach by inducing emesis, or by gastric lavage (unless patient with convulsive or psychotic state). Activated charcoal is an effective adsorbent. Treatment is symptomatic, need advanced life support setting.

- ***BRANDS:***

Cogentin (MSD).

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2) Trihexyphenidyl [P]

- ***DRUG SUMMARY:***

Trihexyphenidyl HCl, or Benzhexol, is a synthetic tertiary amine, anticholinergic, antimuscarinic agent similar to atropine. Synthetic anticholinergics have more selective CNS activity than naturally occurring belladonna alkaloids, so they cause fewer side effects. It acts by blocking excess acetylcholine at certain cerebral synaptic sites.

- ***INDICATIONS:***

Adjunct in treatment of all forms of parkinsonism. It is also used in controlling extrapyramidal disorders (except tardive dyskinesia) due to neuroleptic medication.

- ***CONTRAINDICATIONS:***

Hypersensitivity, narrow-angle glaucoma, pyloric or duodenal obstruction, prostatic hypertrophy or bladder-neck obstructions, and megacolon.

- ***DOSAGE FORMS:***

Tablets, elixir.

- ***RECOMMENDED DOSAGE:***

Adult: 1-2 mg the first day, increase by 2 mg increment at intervals of 3-5 days, until total usual dose of 6-10 mg is given daily; max. 15 mg/d.

Directions: Dosage should be individualized, initial dose should be low and increased gradually. May be taken before or after meals depending on how patient reacts.

*Elderly > 60 years; better to give them after meals since they are more sensitive to the drug. If cause excess mouth dryness, better to administer before meals unless causes nausea.

*Trihexyphenidyl is best tolerated at 3 divided doses, given at meal times. High doses may be divided into 4 parts: mealtimes and bedtime.

*Need to reduce dose if use concomitantly with levodopa. Trihexyphenidyl 3-6 mg/d in divided doses is adequate in this case.

*When substituting for another anti-cholinergic drug, usual procedure is partial substitution initially, with progressive reduction in other medications as the dose of trihexyphenidyl is increased.

- ***USE IN SPECIAL CASES:***:

Pregnancy- To be used only if potential benefits justify the potential risks (Category C). Risk cannot be ruled out.

Lactation- Safety has not been established. An inhibitory effect on lactation may occur. Infants are usually sensitive to anti-cholinergic agents, hence better to stop use of medication.

Children- Safety and efficacy have not been established.

Renal Disease- Use with caution. The drug is excreted in urine. Safety has not been established.

Liver Disease- Use with caution, safety has not been established.

- ***PRECAUTIONS & WARNINGS:***

Same as benztropine.

- ***ADVERSE EFFECTS & OVERDOSE:***

Same as benztropine.

- ***INTERACTIONS:***

Overview of Trihexyphenidyl Drug-Drug Interactions	
Drug	**Interaction**
Chlorpromazine, ***haloperidol***, and ***phenothiazines***	Trihexyphenidyl reduces effect of ***these***. Do not administer together unless clearly indicated *(see interactions of benztropine)*.
Digoxin	Increases bioavailability of digoxin, monitor levels of digoxin to prevent toxicity and tailor dose as needed.
MAO Inhibitors	These potentiate action of trihexyphenidyl, avoid use concomitantly.

- ***Brands:***

Artane (Lederle), Parkizol (JePharm.), Partane (Taro).

B) DOPAMINERGIC DRUGS

1) Amantadine

- ***DRUG SUMMARY:***

A synthetic primary amine, antiviral agent that has modest antiparkinson effect. It improves bradykinetic disabilities, as well as tremor and rigidity. Its exact mechanism is not clear, but thought to be due to increase release of dopamine. It is less effective than levodopa, but slightly more effective than anticholinergic agents are. It has the advantage of having a low incidence of side effects.

- ***INDICATIONS:***

Parkinson's Disease/Syndrome, drug induced extra-pyramidal reactions, idiopathic or post encephalitic cases, as initial therapy or as adjunct with anticholinergic drugs or levodopa.

Also used for prophylaxis and symptomatic treatment of influenza A infections.

- ***CONTRAINDICATIONS:***

Hypersensitivity to amantadine.

- ***DOSAGE FORMS:***

Tablets, capsules.

- ***RECOMMENDED DOSAGE:***

Adult: 100 mg 1-2 times/day;
max. 400 mg/day.

Dosing Guidelines in Renal Impairment	
Cl_{Cr} (ml/min./ 1.73m^2)	**Suggested Maintenance regimen**
> 80	100 mg b.i.d.
60	200 mg/100 mg, on alternate days
50-40	100 mg/day
30	200 mg twice weekly
20	100 mg three times weekly

Directions: Start with 100 mg/day, then after one to several wks., increase if patient has other serious illness or is on other antiparkinsonism medication.

*Use with levodopa has been shown to exhibit rapid effect.

*After few months a patient might show decreased efficacy, may increase dose or

temporarily discontinue drug for several weeks.
*If patient is not responding, other antiparkinson drugs might be necessary.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid. There are no adequate or well-controlled studies of amantadine in pregnant women (Category C).
Lactation- Use caution. It is excreted in breast milk, but safety has not been established.
Children- Safety and efficacy are not established.
Renal Disease- 90% of drug is excreted in urine unchanged. Elimination is prolonged in renal insufficiency. Dose reduction is necessary in renal impairment to prevent accumulation. Refer to recommended dosage.
Liver Disease- Use Caution. The drug is not metabolized, most of it is eliminated from the body unchanged.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in patients with history of epilepsy or other type seizures.
-Dose reduction of amantadine is recommended, in patients with hepatic disease, psychosis, congestive heart failure (CHF), peripheral edema, and renal impairment.

- ***ADVERSE EFFECTS:***

Usually dose related; dizziness, light-headedness, difficulty in concentrating, insomnia, irritability, dry mouth, constipation, and orthostatic hypotension.

- ***OVERDOSE:***

Symptoms include nausea or vomiting, anorexia, CNS effects, tremor, blurred vision, possible convulsions.
Treatment: There is no specific antidote. Refer to emergency room immediately. For CNS toxicity: IV physostigmine may be administered. Apply supportive measures along with immediate gastric lavage or induction of emesis. Force fluids, IV if necessary. Acidification of urine to increase elimination of drug from the body maybe used.

- ***INTERACTIONS:***

Overview of Amantadine Drug-Drug Interactions

Drug	Interaction
Anti-cholinergic drugs	Anticholinergic side effects may be increased. If cannot avoid concomitant use, monitor patient's response and adjust doses accordingly.
Hydrochlorothiazide plus triamterene	This combination decreases urinary excretion of amantadine. Use with caution.
Quinidine derivatives	These may inhibit renal clearance of amantadine in males (but not females), increasing risk of amantadine toxicity. Use with caution in males.
Thiazide diuretics	These may increase the risk for developing adverse effects of amantadine. Use with caution.

- ***BRANDS:***

A-parkin (Dexxon), Partivel (Trima), Symmetrel (Ciba-Geigy).

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2) Bromocriptine [P]

- ***DRUG SUMMARY:***

Bromocriptine mesylate is a semi-synthetic potent dopamine receptor agonist. The dopaminergic neurons are involved in the control of motor function. Bromocriptine acts by direct stimulation of surviving dopamine receptors. It should be reserved for patients for whom levodopa alone is no longer adequate or can't be tolerated. If patients did not respond to levodopa, they are poor candidates for bromocriptine. Bromocriptine relieves akinesia, rigidity and tremor. Some studies have shown that using bromocriptine as first-choice sole therapy in earlier stages of disease has improved disability. But there is a decline in efficacy with long term use. Addition of levodopa then may be necessary.

- ***INDICATIONS:***

Parkinsonism, but not drug induced extrapyramidal symptoms.
Also used for endocrine disorders (i.e. acromegaly, amenorrhea, galactorrhea).

- ***CONTRAINDICATIONS:***

Hypersensitivity to ergot alkaloids, severe ischemic heart disease, pituitary tumor, and glaucoma. Bromocriptine may cause first-dose phenomenon that can trigger sudden cardiovascular collapse. Do not use in patients with a history of myocardial infarction (MI) or severe arrhythmia.

- ***DOSAGE FORMS:***

Tablets.

- ***RECOMMENDED DOSAGE:***

Adult: Initially 1.25 mg twice daily, titrate every 2 wks. by 2.5 mg/d to ensure that the lowest dosage producing an optimal therapeutic response is not exceeded.
Usual range is 10 - 40 mg/day.
(Safety of dosages exceeding 100 mg/d has not been demonstrated.)

Directions: Take with meals to avoid GI disturbances.
*Always start with lowest dose possible and titrate up.
*Do not discontinue drug abruptly.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid. Discontinue medication without delay if patient should get pregnant during therapy (Category B).
Lactation- Avoid. Bromocriptine prevents lactation, therefore, do not administer to mothers who want to breast-feed.
Children- Safety and efficacy in children < 15 years have not been established.
Renal Disease- Use with caution. Safety has not been established. 85% of drug is excreted in feces in 5 days, while only 3-6% is eliminated in urine.
Liver Disease- The drug is metabolized in the liver. Use with caution in patients with liver disorders.

- ***PRECAUTIONS AND WARNINGS:***

-Some patients are very sensitive to the hypotensive effect of the drug, and may even collapse within an hour of the first dose. Advise patient to take first dose with food and in bed. Patients often tolerate subsequent doses well.
-Warn patients against driving or operating machinery due to the side effects especially early in therapy (the dizziness, drowsiness, and hypotension).
-Use caution in renal and hepatic dysfunction.
-Need to perform periodic evaluation of hepatic, renal, hematopoietic and cardiovascular systems with long term therapy.

- ***ADVERSE EFFECTS:***

Mostly are dose related. Headaches, dizziness, light-headedness, sedation, dyskinesia, depression, or mania, delusions, orthostatic hypotension, palpitation, arrhythmia, constipation or diarrhea, nasal congestion, and abdominal pain. Painless digital vasospasm is a common complication of long term treatment (usually in treatment of acromegaly), that can be reversed with lowering dose; advise patient to avoid exposure to cold.

- ***INTERACTIONS:***

Overview of Bromocriptine Drug-Drug Interactions

Drug	Interaction
Alcohol	Bromocriptine decreases tolerance to alcohol, advise patient not to drink while on this medication.
Antihyper-tensive	These agents add to hypo-tensive effect, use caution, inform patient not to change body position very quickly when rising or sitting down.

Oral Contra-ceptives	May interfere with action of the drug. Avoid use concomitantly. Advise patient to use alternative measures of contraception.
Pheno-thiazines	These decrease the efficacy of bromocriptine. Use caution.
Sympatho-mimetics	These increase/exacerbate the side effects of bromocriptine like tachycardia and cardiac dysfunction.

- ***OVERDOSE:***

Treatment: Acute overdose, employ general supportive measures, along with immediate gastric lavage. Administer IV fluids and maintain an adequate airway. Monitor ECG to observe any developments of arrhythmia.

- ***BRANDS:***

Lactopar (Birzeit), Parilac (Teva), Parlodel (Sandoz).

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3) Carbidopa/Levodopa WHO,P

- ***DRUG SUMMARY:***

Co-careldopa, is a mixture of carbidopa and levodopa. Levodopa is a metabolic precursor of dopamine, a catecholamine neurotransmitter, which unlike dopamine readily crosses the blood brain barrier. Levodopa, being a dopaminergic agent, combats the dopamine deficiency in Parkinson's.

Carbidopa, a derivative of methyldopa, is a peripheral dopa-decarboxylase inhibitor. Decarboxylase inhibitors, (i.e. carbidopa, benserazide) are given with levodopa. When levodopa is given alone, large doses must be administered to compensate for peripheral decarboxylation to provide adequate amounts of dopamine at the appropriate sites. Decarboxylase inhibitors prevent the metabolism of levodopa and thereby make more levodopa available to transport to the brain. The decarboxylase inhibitors do not cross the blood brain barrier and therefore do not affect metabolism of levodopa in the brain. The addition of carbidopa reduces the amount of levodopa required by about 75% because levodopa plasma levels and $t½$ are increased. This decreases the incidence of side effects like nausea and vomiting associated with levodopa. A disadvantage is an increased incidence of abnormal involuntary movement.

- ***INDICATIONS:***

Symptomatic treatment of idiopathic, postencephalitic Parkinson's disease, and parkinsonism following carbon monoxide and manganese intoxication.

- ***CONTRAINDICATIONS:***

Hypersensitivity to carbidopa or levodopa, narrow angle glaucoma, and history of suspected melanoma.

- ***DOSAGE FORMS:***

The mixture is expressed in *x/y* proportions, where *x* and *y* are the strengths in milligrams of carbidopa and levodopa respectively.

Tablets: 10/100, 25/100, 25/250

- ***RECOMMENDED DOSAGE:***

Adult: ★*For patients not currently receiving levodopa:*

1 tablet carbidopa 10 mg/ levodopa 100 mg or 25/100 t.i.d. increased by 1 tablet q.d. or q.o.d up to 6 tablets/day.

★*For patients receiving levodopa already:*

1 tablet of 25/250 t.i.d. or q.i.d., adjusted by 0.5 or 1 tablet, up to 8 tablets/day, or max. 200 mg carbidopa.

Directions: The optimum daily dose must be determined by careful titration in each individual patient. When transferring patients from levodopa, 3 tablets of carbidopa/levodopa 25/250 should be substituted for 4 g levodopa. The levodopa should be discontinued 8-12 hrs before-hand.

*Therapeutic effects may take few weeks.

*Administer with food if GI upset occurs.

*Avoid vitamin products containing vitamin B_6 (pyridoxine), due to drug-drug interactions.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly needed (Category C). Effects in pregnancy are unknown, both levodopa and carbidopa have caused malformations in rabbits.

Lactation- Avoid. Do not administer to nursing mothers, the drug is widely distributed in most tissues and excreted in breast milk.

Children- Safety for use in children < 18 years is not established for carbidopa. Safety for use in children < 12 years is not established for levodopa.

Renal Disease- The drug is excreted in urine. Use caution in renal disorders.

Liver Disease- Use with caution.

- ***PRECAUTIONS AND WARNINGS:***

-Use caution in cardiovascular, hepatic, pulmonary or renal disorders, history of peptic ulcer, psychiatric states, endocrine diseases, seizure disorders.

-Monitor vital signs particularly during period of dosage adjustment, and report alterations in BP, pulse and respiratory rate, behavior changes.

-Uncontrollable movements of the face, eyelids, mouth, tongue, arms, hands or legs, mood or mental changes, irregular heartbeat or palpitations, severe or persistent nausea and vomiting can be signs of intolerance to the medication.

-For diabetic patients: warn patient that the medication may interfere with urine tests for sugar or ketones, causing false results.

- ***ADVERSE EFFECTS:***

Are those of enhanced levodopa effects; involuntary movements (dyskinetic, dystonic, choreiform), muscle twitching, headache, dizziness, confusion, insomnia, mental disturbances, suicidal tendencies in psychiatric patients, blurred vision, diplopia, nausea, dry mouth, dysphagia, dark urine, urinary frequency, hoarseness, hemolytic and nonhemolytic anemia.

Elevations of liver function; BUN, AST, ALT, LDH, alkaline phosphates have been reported.

- ***INTERACTIONS:***

Overview of Co-careldopa Drug-Drug Interactions	
Drug	**Interaction**
Anti-cholinergic agents	These may enhance levodopa effects, but can exacerbate involuntary movements. If necessary increase levodopa or decrease anticholinergic.
Iron salts, Oral	The pharmacologic effect of levodopa may be decreased. If necessary to coadminister, observe patient's response and increase the co-carledopa accordingly.
MAOI	It may precipitate hyper-tensive crisis. Avoid concomitant use.
Methyldopa	Increases hypotensive CNS effects. Use with caution.
Pheno-thiazines, *haloperidol*	These may antagonize effects of levodopa.
Phenytoin, ***papaverine***	These may interfere with levodopa effects. Avoid use unless clearly indicated; monitor patient's response.
Pyridoxine (B_6)	Reduces effectiveness of levodopa; avoid concomitant use.
Tricyclic antidepress ants	TCAs potentiate postural hypotension. Use with caution.

- ***OVERDOSE:***

Same as bromocriptine**.**

- ***BRANDS:***

Dopicar (Assia/Riesel), Sinemet (Dupont Pharm).

Chapter 9: OPHTHALMIC PREPARATIONS

A) ANTI-INFECTIVE PREPARATIONS
- **1) Antibiotics**
- **2) Antivirals**

B) ANTI-INFLAMMATORY PREPARATIONS
- **1) Corticosteroids**
- **2) Other anti-inflammatory preparations**

C) β-BLOCKERS
- **1) Timolol**

D) MYDRIATICS AND CYCLOPLEGICS
- **1) Atropine sulphate**

E) MISCELLANEOUS OPTHALMIC PREPARATIONS

OPTHALMIC PREPARATIONS

The eye is vulnerable to any external insult. Common problems that are seen include infections (conjunctivitis-red eye, and trachoma), injury or burns, allergy and glaucoma (raised intraocular pressure in the eye).

Eye drops and eye ointments are the most commonly used dosage forms for the management of eye problems. Eye drops penetrate the globe, probably through the cornea, in order to produce their therapeutic effect.

Some eye drops have systemic effects that result from the absorption of the drug into the general circulation. This occurs either through the conjunctival vessels, or from the nasal mucosa after the excess of the preparation has drained down through the tear duct. These systemic effects are usually undesirable. For example, timolol (a β-blocker) administered as eye drops may induce bronchospasm or bradycardia in susceptible individuals. Eye ointments are often applied to lid margins, or may also be used in the conjunctival sac for other conditions especially when a prolonged action is required.

When two different preparations in the form of eye-drops are required at the same time of the day, for example *pilocarpine* and *timolol* in glaucoma, dilution and overflow may occur when one immediately follows the other. The patient should therefore leave an interval of a few minutes between the two drugs. At night, an eye ointment for the second drug will reduce the problem.

In addition to these two dosage forms, we have eye lotions that are used for the irrigation of the conjunctival sac. They act mechanically to flush out irritants or foreign bodies as a first aid treatment.

Preparations for the eye should be sterile when issued. For routine use, they are supplied in multiple-application containers for individual use. Eye-drops contain a suitable preservative, never-the-less, ***they should not be used for more than 4 weeks after opening the container*** (unless stated specifically by the manufacturer). After that, a new container should be opened (if treatment has to be continued) and the old one should be discarded.

Note: *Generally it is unadvisable for patients to continue to wear contact lenses-unless medically indicated when receiving eye-drops. Some drugs can spoil hydrophilic soft lenses. Therefore, unless eye-drops are specifically indicated as safe to use with hydrophilic contact lenses, the lenses should be removed before instillation and not worn during the period of treatment.*

A) ANTI-INFECTIVE PREPARATIONS

Infections of the eye can be due to bacteria or viruses. Most acute eye infections can be treated topically. Ideally, eye-drops should be instilled very frequently (at least every 2 hours). In order to avoid sleeping disturbances, one can use eye-ointment for nighttime because of its longer duration of action. An eye-ointment will also soften crusts that cause the lids and eyelashes to adhere together when the patient is asleep. A small quantity of eye ointment is applied to the eye or inside the lower lid.

It is very important to educate the patient of prevention of the spread of eye infections; minimize physical contact with other people, do not use same handkerchief or towel, a child should not attend school until the infection is cured.

This chapter will discuss some antibiotics used in ophthalmic preparations and some antiviral agents that are used mainly in ophthalmic herpes infections.

1) Antibiotics

- ***DRUG SUMMARY:***

It is preferred to use antibiotics that are rarely used to treat systemic infections (see precautions below). Always take in consideration the possibility of systemic absorption and systemic effects of these antibiotics. Some of the most commonly used antibiotics have a wide spectrum of activity, these include:

Tetracycline [WHO,P] Chloramphenicol [WHO,P], Framycetin, Gentamicin [WHO,P], and Neomycin.

Norfloxacin has a spectrum of activity similar to that of gentamicin. Gentamicin and tobramycin are effective for treating infections due to *Pseudomonas aeruginosa*. Fusidic acid is useful in the treatment of infections caused by *Staphylococcus spp*.

Note:

1) Propamidine isethionate is of little value in bacterial infections, but is specific for the treatment of acanthamoeba keratitis that is a rare but devastating condition. Mercuric oxide eye ointment, even for short periods, is NOT recommended.

2) Many antibiotic preparations contain a corticosteroid. Such mixtures should not be used unless a patient is under close specialist supervision. They should not be prescribed for undiagnosed 'red eye' which is sometimes caused by herpes simplex.

- ***INDICATIONS:***

Trachoma, ocular infections: Treatment of superficial ocular infections involving the conjunctiva or cornea due to strains of microorganisms susceptible to the antibiotics.

Table-9.1 indicates the main used antibiotics for the treatment of eye infections.

- ***DOSAGE FORM:***

Drops, ointments and tablets.

Table-9.1: Antibiotics Used For Eye Infections

Medication	Indication
Erythro-mycin	Prophylaxis of ophthalmia neonatorum due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.
Chloram-phenicol	Use only in those serious infections for which less potentially dangerous drugs are ineffective or contra-indicated.
Chlortetra-cycline	Local treatment for infections, including trachoma.
Tetracycline HCl	Massive (endemic areas) trachoma (recommended by WHO).

*For detailed information about these antibiotics, refer to anti-infective chapter.

- ***CONTRAINDICATIONS:***

Hypersensitivity to any component of these products; epithelial herpes simplex keratitis (dendritic keratitis); vaccinia; varicella; mycobacterial infections of the eye; fungal diseases of the ocular structure; use of steroid combinations after uncomplicated removal of a corneal foreign body.

- ***RECOMMENDED DOSAGES:***

Eye-drops: Apply at least every 2 hours; reduce frequency as infection is controlled; continue for 48 hrs. after healing.

Eye-ointment: Apply either at night (if eye-drops used during the day) or 3-4 times daily (if eye-ointment used alone).

Short-term courses with tetracyclines can be used for control of bacterial infections during seasonal epidemics of con-junctivitis, and may be repeated annually.

Directions: Tilt the head back, place medication in conjunctival sac and close eyes. To reduce systemic absorption, apply light finger pressure on lacrimal sac for 1 min. following instillation; this retards passage of drops via nasolacrimal duct into areas of potential absorption, such as: nasal and pharyngeal mucosa. Eye-ointments are

often applied to lid margins for blepharitis, they may also be used in the conjunctival sac for other conditions especially where a prolonged action is required. To avoid contamination, do not let the tip of container touch any surface. Close cap well after using.

In case of Trachoma:

-Tetracycline hydrochloride eye ointment applied to both eyes twice daily for 5 consecutive days or once daily for 10 days, each month for 6 months.

-Chlorotetracycline eye ointment may also be used. Chloramphenicol is not as effective.

-For active trachoma in the individual, one or both of the following is/are effective:

(i) For adults, orally administered sulphonamides for 2 weeks; for children, erythromycin should be used.

(ii) Tetracycline eye ointment three times daily for 6 weeks. *Also see drug summery above.*

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly indicated. Avoid fluoroquinolones and chloramphenicol. Category B; *erythromycin, tobramycin*. Category C; *gentamicin, tetracyclines, ciprofloxacin, norfloxacin, ofloxacin, and polymyxin B*.

Safety of eye preparations for use during pregnancy has not been established.

Lactation- It is not known whether *ciprofloxacin, norfloxacin, or ofloxacin* appear in breast milk following ophthalmic use. Exercise caution when administering *ciprofloxac*in to a nursing mother. Because of the potential for adverse reactions in nursing infants from *norfloxacin, ofloxacin, chloramphenicol,* and *tobramycin;* decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Children- *Tobramycin* is safe and effective in children. Safety and efficacy of ophthalmic *fluoroquinolones* in infants < 1 y., and *polymyxin-B/trimethoprim* in infants < 2 mon. have not been established.

- ***PRECAUTIONS AND WARNINGS:***

1. *Sensitization* might occur from the topical use of an antibiotic, this may contraindicate the later use of the drug in serious infections. For this reason it is preferred that the antibiotics used topically are ones that are not ordinarily used systemically. Also there is a possibility of cross-sensitivity to occur.
2. *Hematopoietic toxicity* has occurred occasionally with the systemic use of chloramphenicol and rarely with topical administration.
3. Do not use topical antibiotics in deep-seated ocular infections or in those that are likely to become systemic. Use of antibiotics (especially prolonged or repeated therapy) may result in bacterial or fungal overgrowth of non-susceptible organisms. Such growth may lead to a *secondary infection*.

- ***ADVERSE EFFECTS:***

*Sensitivity reactions such as transient irritation, burning, stinging, itching, inflammation, etc.

**Chloramphenicol:* Grey-syndrome in infants, hematological events including aplastic anemia have been reported, but it is rare; and transient stinging.

**Aminoglycosides:* Localized ocular toxicity and hypersensitivity, lid itching, lid swelling, conjunctival erythema, etc.

**Fluoroquinolones:* White crystalline precipitates (it resolves in most patients within 2 weeks), lid margin crusting, conjunctival hyperemia, bad/bitter taste in the mouth, allergic reactions, lid edema, tearing, corneal staining, photophobia, corneal infiltrates, nausea, decreased vision, chemosis.

- ***OVERDOSE:***

Symptoms: Most include exaggerated side effects of each category. Symptoms of tobramycin overdose include punctate keratitis, erythema, increased lacrimation, edema, and lid itching. These may be similar to adverse reactions.

Treatment: A topical overdose of any antibiotic may be flushed from the eyes with warm tap water.

- ***BRANDS:***

Refer to price list.

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2) Antivirals

Herpes simplex infections are the most common ophthalmic viral infections. They produce, for example, dendritic corneal ulcer and can be treated with acyclovir; alternatively idoxuridine may be used. Treatment has to be started early in the infection for the antiviral agent to be effective and inhibit the replicating virus.

Idoxuridine WHO

- ***DRUG SUMMARY:***

Idoxuridine is a pyrimidine nucleoside used in the topical and ophthalmic treatment of viral infections. It inhibits replication of the virus.

- ***INDICATIONS:***

Herpes simplex keratitis: Epithelial infections (especially initial attacks), characterized by the presence of dendritic ulcers, respond better than stromal infections.

- ***CONTRAINDICATIONS:***

Hypersensitivity to idoxuridine or any component of the formulation.

- ***DOSAGE FORMS:***

Drops, ointments.

- ***RECOMMENDED DOSAGE:***

There are two different schedules as indicated in table-9.2.

Note: *Topical corticosteroids may be used with idoxuridine in some conditions as indicated by the specialist. It is important to continue idoxuridine therapy a few days after the steroids have been withdrawn (see precautions and warnings).*

Table-9.2: Schedules for Recommended Doses of Idoxuridine

Primary Schedule	**Initially,** place 1 drop into infected eye(s) every hour during the day and q. 2 h. at night. Continue until corneal ulcers have healed, usually within 7 days. Then reduce dosage to 1 q. 2 h. during the day and q4h at night. To minimize recurrences, continue therapy at this reduced dosage for 3-7 days after complete healing. Max. treatment period is ≤ 21 d.
***Alternative* Schedule**	Instill 1 drop every minute for 5 minutes. Repeat q. 4 h., day and night. Maximum treatment is for 21 days, or for 3-5 days after healing is complete.

Directions: For optimal results, keep infected tissues saturated with the antiviral.

- ***USE IN SPECIAL CASES:***

Pregnancy- Idoxuridine crosses the placenta barrier and produces fetal malformations when administered topically to the eyes of pregnant rabbits in clinical doses and when administered by various routes in high doses to other rodents. Safety for use during pregnancy has not been established.

Use only if clearly needed and when the potential benefits outweigh the potential hazards to the fetus (Category C).

Lactation- It is not known whether idoxuridine is excreted in breast milk. Because of the potential for tumorigenicity shown for idoxuridine in animal studies, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Children- Safety and efficacy have not been established.

- ***PRECAUTIONS AND WARNINGS:***

1. May cause sensitivity to bright light; his may be minimized by wearing sun glasses.
2. Recurrences of infection may be seen if medication is not continued for 5-7 days after the epithelial lesion has apparently healed.

3. **Corticosteroids** can accelerate the spread of a viral infection and are usually contraindicated in herpes simplex epithelial infections.

4. Some strains of herpes simplex appear to be resistant.

- ***ADVERSE EFFECTS:***

Occasional irritation, pain pruritus, inflammation or edema of the eyes or lids, allergic reactions, photophobia, corneal clouding, stippling, and punctate defects in the corneal epithelium.

- ***INTERACTIONS:***

Boric acid containing solutions: Co-administration may result in a precipitate formation which may cause irritation.

- ***OVERDOSE:***

Local: Overdose will not ordinarily cause acute problems. Should accidental over dosage in the eye(s) occur, flush with water or normal saline.

Accidental ingestion: Animal data indicate that the minimum systemic dose that will produce toxic effects is many times greater than the quantity in a commercial bottle. Also metabolic breakdown and excretion take place very rapidly. Thus, no untoward consequences should be expected from accidental ingestion of even an entire bottle of the solution. Drink fluid to dilute.

- ***BRANDS:***

Virusan (Teva).

B) ANTI-INFLAMMATORY PREPARATIONS

Inflammatory problems of the eye are best treated by corticosteroids. In addition other anti-inflammatory preparations are used. In this chapter, these drugs will be discussed.

1) Corticosteroids

- ***DRUG SUMMARY:***

Corticosteroids can be used topically, by subconjunctival injection, and systemically to treat uveitis and scleritis; they are also used to treat inflammation following eye operations.

Topical corticosteroids should normally be used only under expert supervision and they should not be prescribed for undiagnosed 'red eye'.

There are two main dangers from topical corticosteroids. First the 'red eye' may be caused by herpes simplex virus that produces a dendritic ulcer; corticosteroids aggravate the condition which may lead to loss of vision or even loss of the eye. Second, arising from the use of eye-drop formulation, a 'steroid glaucoma' may be produced, after a few weeks of treatment, especially in patients predisposed to chronic simple glaucoma.

Use of a combination product containing a corticosteroid with an anti-infective is rarely justified.

There are large numbers of corticosteroidal preparations that are used in ophthalmic preparations. Examples of these corticosteroids are: *betamethasone, dexamethasone, fluorometholone, hydrocortisone acetate, and prednisolone.*

All have similar indications, cautions, and side effects.

Betamethasone [WHO,P]

Will be discussed as the prototype of this group.

- ***INDICATIONS:***

Local treatment of inflammation.

- ***CONTRAINDICATIONS:***

Acute superficial herpes simplex keratitis; fungal disease of ocular structures; vaccinia, varicella and most other viral diseases of the cornea and conjunctiva; ocular tuberculosis; hypersensitivity; after

uncomplicated removal of a superficial corneal foreign body.

- ***DOSAGE FORMS:***

Tablets, drops, ointments.

- ***RECOMMENDED DOSAGE:***

Treatment duration varies with type of lesion and may extend from a few days to several weeks, depending on therapeutic response.

Relapse may occur if therapy is reduced too rapidly; taper dose over several days. (Relapses are more common in chronic active lesions than in self-limited conditions that usually respond to re-treatment).

Suspensions and solutions: Instill 1 to 2 drops into the conjunctival sac every hour during the day and every 2 hours during the night. When a favorable response is observed, reduce dosage to 1 drop every 4 hours. Later, 1 drop 3 to 4 times daily may suffice to control symptoms. For post-operative inflammation, instill 1 to 2 drops 4 times daily beginning 24 hours after surgery; continue throughout the first 2 weeks of the postoperative period.

Ointments: Apply a thin coating in the lower conjunctival sac 3 or 4 times a day. When a favorable response is observed, reduce the number of daily applications to twice, and later to once a day as a maintenance dose if sufficient to control symptoms. Ointments are particularly convenient when an eye pad is used and may be the preparation of choice when prolonged contact of drug with ocular tissue is needed.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only when clearly indicated and when potential benefits outweigh potential hazards (Category C).

Lactation- It is not known whether topical steroids are excreted in breast milk. Exercise caution when administering to a nursing mother.

Children- Safety and efficacy have not been established in children.

- ***PRECAUTIONS AND WARNINGS:***

-If there is moderate to severe inflammation, use higher strengths. Under certain conditions systemic therapy may be required.

-Prolonged use may result in glaucoma, elevated IOP, optic nerve damage, defects in visual acuity and field of vision, posterior subcapsular cataract formation, or secondary ocular infections from pathogens liberated from ocular tissues.

-Acute untreated eye infection may be masked or activity enhanced by steroids. Fungal infections of the cornea have been reported with long-term local steroid applications. Therefore suspect fungal invasion in any persistent corneal ulceration where a steroid has been used, or is being used.

- ***ADVERSE EFFECTS:***

Glaucoma (elevated IOP) with optic nerve damage, loss of visual acuity and field defects; posterior subcapsular cataract formation; secondary ocular infection from pathogens, including herpes simplex liberated from ocular tissues; exacerbation of viral and fungal corneal infections; transient stinging or burning; blurred vision, discharge, discomfort, ocular pain, foreign body sensation, hyperemia, and pruritis.

- ***BRANDS:***

Refer to price list.

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2) Other Anti-Inflammatory Preparations

Other preparations used for the topical treatment of inflammation and allergic conjunctivitis include antihistamines, oxyphenbutazone, and sodium cromoglycate. From these agents sodium cromoglycate will be discussed.

Sodium Cromoglycate [P]
(Cromolyn Sodium)

- ***DRUG SUMMARY:***

It has been shown that cromolyn sodium inhibits the degranulation of sensitized mast cells that occurs after the exposure to specific antigens. Cromolyn has no intrinsic vasoconstrictor, antihistaminic or anti-inflammatory activity.

- ***INDICATIONS:***

Conjunctivitis: Treatment of vernal kerato-conjunctivitis, vernal conjunctivitis, and vernal keratitis.

- ***CONTRAINDICATIONS:***

Hypersensitivity to cromolyn or to any of the other ingredients.

- ***DOSAGE FORMS:***

Drops, ointment.

- ***RECOMMENDED DOSAGE:***

1 or 2 drops in each eye for 4 to 6 times a day at regular intervals. One drop of 2% contains approximately 1.6 mg cromolyn sodium.

Directions: The effect of cromolyn sodium therapy is dependent on its administration at regular intervals, as directed.

- ***USE IN SPECIAL CASES:***

Pregnancy- There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed (Category B).

Lactation- It is not known whether the drug is excreted in breast milk. Exercise caution when cromolyn is administered to a nursing woman.

Children- Safety and efficacy in children < 4 years of age have not been established.

- ***PRECAUTIONS AND WARNINGS:***

1. Patients may experience a transient stinging or burning sensation following instillation of cromolyn.
2. The recommended frequency of administration should not be exceeded. Symptomatic response to therapy (decreased itching, tearing, redness, and discharge) is usually evident within a few days, but longer treatment for up to 6 weeks is sometimes required. Once a symptomatic improvement has been established, continue therapy for as long as needed to sustain improvement.
3. Corticosteroids may be used concomitantly with cromolyn ophthalmic solution.

- ***ADVERSE EFFECTS:***

Transient ocular stinging or burning upon instillation is the most common side effect.

- ***BRANDS:***

Opticrom (Fisons).

C) β-BLOCKERS

Glaucoma is a condition characterized by an increase in the intraocular pressure (IOP). It is primarily a disease of middle age. In most cases the rise in the ocular pressure is due to the reduction in the aqueous humor outflow while the inflow remains constant.

Glaucoma is treated by the application of eye-drops containing β-blockers, miotics, or adrenaline (and guanethidine). Also acetazolamide and dichlorphenamide are given by mouth in emergency or before surgery, mannitol may be given by intravenous infusion.

Probably the most common condition is chronic simple glaucoma where the obstruction is in the trabecular meshwork. It is commonly first treated with a topical β-blocker and other drugs added as necessary to control the intraocular pressure, e.g. adrenaline or pilocarpine.

The most commonly used β-blocker for the treatment of glaucoma is Timolol.

1) Timolol [WHO,P]

- ***DRUG SUMMARY:***

The exact mechanism of its ocular antihypertensive action is not established, but it appears to be a reduction of aqueous production. However, some studies show a slight increase in outflow facility with timolol.

- ***INDICATIONS:***

Glaucoma: Lowering IOP in patients with chronic open-angle glaucoma. They are mainly used in chronic simple glaucoma.

- ***CONTRAINDICATIONS:***

Bronchial asthma, a history of bronchial asthma or severe chronic obstructive pulmonary disease; sinus bradycardia; second-degree and third-degree AV block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the products.

- ***DOSAGE FORMS:***

Drops of 0.25% and 0.5%.

- ***RECOMMENDED DOSAGE:***

Initial therapy: 1 drop of 0.25% twice daily. If clinical response is not adequate, change the dosage to 1 drop of 0.5% solution twice a day. If the IOP is maintained at satisfactory levels, change the dose to 1 drop once a day. Since the pressure-lowering response may require a few weeks to stabilize, evaluation should include a determination of IOP after approximately 4 weeks of treatment.

Replacement therapy (single agent):

When the patient is transferred from one topical ophthalmic β-blocker to timolol, discontinue that agent after proper dosing on one day, and start treatment the next day with 1 drop of 0.25% timolol twice daily. Increase to 1 drop of 0.5% solution twice a day if response is inadequate. When changing from an agent other than an ophthalmic β-blocker, on the first day continue with the agent being used and add 1 drop 0.25% timolol twice daily. The next day, discontinue the previously used agent completely and continue with timolol. If a higher dosage is required, substitute 1 drop 0.5% twice daily.

Replacement therapy (multiple agents):

When transferring a patient from several concomitantly administered agents, individualize dosage. If any of the agents is an ophthalmic β-blocker, discontinue it before starting timolol. Adjust 1 agent at a time, at intervals of not less than 1 week. Continue the agents being used and add 1 drop of 0.25% twice a day. The next day, discontinue one of the other agents. Decrease or discontinue remaining agents according to patient response. If a higher dosage is required, use 1 drop of 0.5% timolol twice daily.

Directions: Tilt head back, place medication in conjunctival sac, and close eyes. To reduce systemic absorption, apply light finger pressure on lacrimal sac for 1 min. following instillation; this retards passage of drops via nasolacrimal duct into areas of potential absorption such as nasal and pharyngeal mucosa.

- ***USE IN SPECIAL CASES:***

Pregnancy- There have been no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefits outweigh potential hazards to the fetus (Category C).

Lactation- Topical timolol is excreted in milk. Because of the potential for serious adverse reactions from timolol in nursing infants, decide whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

Children- Safety and efficacy for use in children have not been established.

- ***PRECAUTIONS AND WARNINGS:***

-Systemic absorption may follow topical application. Therefore the same adverse reactions found with systemic β-blockers may occur with topical use (*refer to β-blockers in the cardiovascular chapter*).

-It can reduce resting and maximal exercise heart rate even in healthy subjects. Also it

might precipitate cardiac failure. Discontinue at the first sign or symptom of cardiac failure.

-Non-allergic bronchospasm patients or patients with a history of chronic bronchitis or emphysema should receive β-blockers with caution since they may block bronchodilation produced by catechol-amine stimulation of β_2-receptors.

-Withdraw β-blockers before major surgery, since their use then is controversial.

-Administer with caution to patients subject to spontaneous hypoglycemia or to diabetic patients. It may mask the signs and symptoms of acute hypoglycemia.

-β-blockers may mask the signs of hyperthyroidism (e.g., tachycardia). Manage patients suspected of developing thyrotoxicosis carefully to avoid abrupt withdrawal of β-blockers that might precipitate a thyroid storm.

-Use with caution in patients with cerebrovascular insufficiency.

-The immediate objective in the treatment of angle-closure glaucoma is to reopen the angle by constricting the pupil with miotics. β-blockers have little or no effect on the pupil. When they are used to reduce elevated IOP in angle-closure glaucoma, use with a miotic.

-β-blockers may potentiate muscle weakness.

-Diminished responsiveness to timolol after prolonged therapy has been reported.

- ***ADVERSE EFFECTS:***

Ophthalmic adverse effects as:

Ocular irritation including conjunctivitis; blepharitis; keratitis; blepharoptosis; decreased corneal sensitivity; visual disturbances including refractive changes (due in some cases to withdrawal of miotics); diplopia; ptosis. In addition, systemic side effects may occur from the systemic absorption of timolol, these include: bradycardia, heart failure, bronchospasm, peripheral vasoconstriction, GI disturbances, fatigue, and sleep disturbances.

- ***INTERACTIONS:***

Overview of Timolol Drug-Drug Interactions	
Drug	**Interaction**
Other ***β-blockers*** *(oral)*	Use caution due to the potential for additive systemic effects.
Epinephrine *(ophthalmic)*	Use of epinephrine with topical β-blockers is controversial. Some reports indicate that the initial effectiveness of the combi-nation decreases over time.
Quinidine	One case of sinus bradycardia has been reported with the coadministration of ophth. timolol.
Verapamil	Coadministration of ophth. timolol has caused brady-cardia and asystole

- ***OVERDOSE:***

Symptoms: With excess use, or an overdose, systemic β-blockers side effect such as bradycardia, hypotension, bronchospasm and acute cardiac failure may occur. If these occur, discontinue therapy and initiate appropriate supportive therapy.

Treatment: If ocular overdosage occurs, flush eye(s) with water or normal saline. If accidentally ingested, efforts to decrease further absorption may be appropriate (gastric lavage).

- ***BRANDS:***

Sinoptic (Eastern Chem.), Tiloptic (Assia/Riesel), Timolin (JePharm).

D) MYDRIATICS & CYCLOPLEGICS

Anticholinergic agents block the response of the sphincter muscle of the iris and the muscle of the ciliary body to cholinergic stimulation, producing papillary dilation (mydriasis) and paralysis of ciliary muscles (cycloplegia). They vary in potency and duration of action. Short acting, relatively weak mydriatics, such as tropicamide 0.5% (duration of action 3 hr.), facilitate the examination of the fundus of the eye. Cyclopentolate 1% (duration of action up to 24 hrs.) or atropine (duration of action 7 days or longer) are preferable for producing cycloplegia for refraction in young children.

1) Atropine Sulphate WHO,P

- ***INDICATIONS:***

-For cycloplegic refraction and for dilating the pupil in inflammatory conditions of the iris and uveal tract.

-Treatment of iridocyclitis mainly to prevent posterior synechiae, often with phenylephrine 10% eye-drops (2.5% in children, elderly, and those with cardiac disease).

- ***CONTRAINDICATIONS:***

Primary glaucoma or a tendency toward glaucoma (e.g., narrow anterior chamber angle); hypersensitivity to belladonna alkaloids or any component of the products; adhesions (synechiae) between the iris and the lens; children who have previously had a severe systemic reaction to atropine.

- ***DOSAGE FORMS:***

Drops, ointment.

- ***RECOMMENDED DOSAGE:***

See table -9.3.

Directions: To avoid contamination, do not touch the dropper's tip to any surface and replace cap after using. Keep out of the reach of children; wash your own hands and the child's following administration; keep away from heat.

- ***USE IN SPECIAL CASES:***

Pregnancy- Safety for use during pregnancy has not been established. Give to a pregnant woman only if clearly needed (Category C).

Lactation- It may be detectable, in very small amounts, in breast milk. But even though it is compatible with breast-feeding.

Children- Use with extreme caution in infants and small children. Excessive use in children and in certain susceptible individuals may produce systemic toxic symptoms.

Table-9.3: Recommended Doses of Atroptine Sulphate

Solution	**Adults**	**Uveitis**	Instill 1 or 2 drops of 1% solution into the eye(s) up to 4 times daily.
		Refraction	Instill 1 or 2 drops of 1% solution into eye(s) 1 hr before refracting.
	Children	**Uveitis**	Instill 1 or 2 drops of 0.5% solution into the eye(s) up to 3 times daily.
		Refraction	Instill 1 or 2 drops of 0.5% solution into the eye(s) twice daily for 1 to 3 days before examination.
Ointment	Apply a small amount in the conjunctival sac up to 3 times daily. Compress the lacrimal sac by digital pressure for several minutes after instillation.		

Note: Individuals with heavily pigmented irises may require larger doses.

- ***PRECAUTIONS AND WARNINGS:***

-Use it with caution in the elderly and others where increased IOP may be encountered.
-Determine the IO tension and the depth of the angle of the anterior chamber before and during use to avoid glaucoma attacks.
-Avoid excessive systemic absorption by compressing the lacrimal sac by digital pressure for 1 to 3 min. after instillation.
-Use cycloplegics with caution in Down's syndrome patients and in children with brain damage.
-May produce drowsiness, blurred vision or sensitivity to light (due to dilated pupils); observe caution while driving or performing other tasks requiring alertness, coordination or physical dexterity.
-May cause sensitivity to light. Protect eyes in bright illumination during dilation.

- ***ADVERSE EFFECTS:***

Local: Increased IOP; transient stinging/burning; irritation with pro-longed use (e.g., allergic lid reactions, hyperemia, conjunctivitis, etc.).

Systemic: Dryness of the mouth and skin; blurred vision; photophobia with or without corneal staining; tachycardia; headache; parasympathetic stimulation; somnolence; visual hallucinations. In addition to other toxic manifestations of antichlolinergic drugs.

- ***OVERDOSE:***

Ocular: If ocular overdosage occurs, flush eye(s) with water or normal saline. Use of a topical miotic may be required.
If accidentally ingested, treat with symptomatic and supportive care..
Systemic: If symptoms develop (*see adverse reactions*), patients usually recover spontaneously when the drug is discontinued. In cases of severe toxicity, give physostigmine salicylate. Have atropine (1 mg) available for immediate injection if physostigmine causes bradycardia, convulsions or broncho-constriction.

- ***BRANDS:***

Atrospan (Fisher), Atroped (Eastern Chem.).

E) MISCELLANEOUS OPHTHALMIC PREPARATIONS USED

These agents should be prescribed by specialists and can be summarized in the following table:

Name of the Drug	Indication
Acetylcysteine	Tear deficiency, impaired mucus production.
Diclofenac sodium	Inhibition of intraoperative miosis during cataract surgery (but does not possess intrinsic mydriatic properties); postoperative inflammation in cataract surgery.
Hydroxyethylcellulose	Tear deficiency.
Lignocaine HCl	Local anesthetic.
Liquid paraffin	Tear deficiency.
Oxybuprocaine HCl	Local anesthetic.
Proxymetacaine HCl	Local anesthetic.
Zinc sulphate	Treatment of excessive lacrimation.

Chapter 10: Otic Preparations

A) DRUGS USED FOR OTITS EXTERNA

B) DRUGS USED FOR OTITIS MEDIA

C) DRUGS USED FOR EAR WAX

OTIC PREPARATIONS

Most patients that attend a clinic with an ear problem tend to be children. The most common diseases that affect the ears are otitis externa, otitis media and accumulation of waxy secretions in the external ear. Otitis media can further be subdivided into acute otitis media without effusion, acute otitis media with effusion, chronic suppurative otitis media, which implies a non-intact tympanic membrane with 6 weeks (some references say 2 weeks) or more of middle ear drainage.

Although viruses cause some ear infections, bacteria cause most. There have been increasing reports of resistance to antimicrobial agents that are used for the common bacterial causes for ear infections (*Strep. pneumoniae*, *H. influenzae* and *M. catarrhalis*). The rates of these are different between countries. Because of this, there have been various debates on use of antibiotics for treatment of ear infections (especially otitis media). Risks and benefits have to be outweighed for each case. *[BMJ. 1997(12 July);315:98-102].*

There is sufficient information to support encouragement of breast-feeding and avoidance of tobacco smoke so as to prevent occurrences of ear infections in children. Preliminary results suggest that multivalent pneumococcal conjugate vaccines that are immunogenic in infants and children older than 2 months are efficacious in preventing otitis media caused by serotypes of *Strep. pneumoniae* contained in this vaccine.

In this chapter, general treatments for the previously mentioned diseases will be discussed. Each category of agents; anti-infective agents, analgesics and earwax removers will be discussed within the disease of concern.

A) DRUGS USED FOR OTITS EXTERNA

Otitis Externa (OE): a disorder in which there is an infection or inflammation of the external ear and ear canal (auditory meatal skin). More commonly seen in teenagers and young adults. There is often a history of recent exposure to water (i.e. swimming in polluted water) or mechanical ear trauma from scratching or foreign objects in the ear.

The two most common presentations are otalgia (ear pain) that can range from pruritis to severe pain that is exacerbated by motion of the ear including chewing and by manipulation of the pinna and pressure on the tragus, and otorrhea (discharge in or coming from the external auditory canal). If the inflammation is severe it can cause aural fullness and loss of hearing. The most common cause of otitis externa is bacterial infection mainly *Pseudomonas aeuroginosa* but also *Staphylococcus aureus*, *Entorobacter* and other bacteria can cause it, fungal growth such as *Candida* and *Aspergillus* can cause 10% of the cases. It can also result from noninfectious dermatological cause such as eczema or psoriasis.

It is important to exclude an underlying chronic otitis media before treatment is commenced. Many cases recover after thorough cleansing of the external ear canal by suction, or dry mopping. A frequent problem in resistant cases is the difficulty in applying lotions and ointments satisfactory to the relatively inaccessible affected skin. The most effective method is to introduce a ribbon gauze dressing soaked with **corticosteroid** eardrops or with an astringent such as **aluminium acetate solution** or **2% acetic acid**. When this is not practical, the ear should be gently cleaned with a probe covered in cotton wool and the patient encouraged to

lie with the affected ear uppermost for ten minutes after the canal has been filled with adequate quantity of one of the above mentioned solutions.

A topical anti-infective is usually used for treatment that is not used systemically (such as **neomycin**), for only about a week (as excessive use may result in fungal infections; and these may be difficult to treat and require expert advice), unless the eardrum is perforated. **Chloramphenicol** may also be used. Solutions containing an anti-infective and a corticosteroid are used for treating cases where infection is present with inflammation and eczema.

When a resistant Staphylococcal infection (a boil) is present in the external auditory meatus, **flucloxacillin** is the drug of choice. The skin of the pinna adjacent to the ear canal is often affected by eczema, and topical corticosteroid creams and ointments are then required and should be applied five or six times daily. Prolonged use should be avoided.

Ear drops and ointments should be applied using 3-4 drops of a liquid preparation or a similar quantity of ointment, warmed if necessary, inserted into the affected ear four times daily except for fluoroquinolones which are applied twice daily. The duration is for 3 days beyond the cessation of symptoms (typically 5-7 days) but in severe cases 10-14 days may be required. . If discharge is profuse, eardrops applied directly may be washed away; in these circumstances the ear canal should be carefully cleaned and a 1 cm gauze wick impregnated with the eardrops should be introduced into it.

Note: *When OE is treated topically with preparations containing chlorhexidine, aminoglycosides (e.g. neomycin), or polymyxins, in patients who have a perforation of the tympanic membrane, there is* ***an increased risk of drug-induced autotoxicity*** *(deafness). It is therefore important to ensure that there is no perforation in such patients before prescribing these preparations.*

In the presence of a perforation, refer patient to a specialist, where there may be closer supervision if drops are needed in Otitis media.

B) DRUGS USED FOR OTITIS MEDIA

Otitis Media (OM): is an infection and/or inflammation of the middle ear (area behind the eardrum-typmanic membrane). OM is the second most prevalent disease of childhood after respiratory tract infections. It frequently occurs with respiratory infections.

Infants and children are at highest risk for OM with the peak between 6-13 months and incidence decreases with age with a marked decrease after 6 years. The incidence is higher in boys, children in large daycare setting, those exposed to second hand smoke, non-breast fed infants and those with HIV or biological sibling or parent with a significant history of OM, and those with craniofacial anomalies, and more in winter months.

The most commonly identified pathogens are S*treptococcus pneumoniae* (30-50%), non-typable *H. influenzae* (20-30%) and *Moraxella catarrhalis* (1-2%), viruses cause a minority of the disease.

Diagnosis of OM is based on clinical symptoms which are: otalgia, fever, hearing loss, generalized malaise and otoscopic findings which include a hyperemic, opaque bulging tympanic membrane with poor mobility, purulent otorrhea with perforated tympanic membrane may be present.

Local treatment of *acute otitis media* is ineffective and there is no place for drops containing a local anesthetic or an antibiotic. Culture of any discharge is helpful in selecting the appropriate

treatment; simple analgesics such as paracetamol are used to relieve pain.

Treatment: Some experts recommend watchful waiting for 24-48 hours after diagnosis of acute otitis media for patients older than 2 year and giving simple analgesia provided that close follow up is feasible since OM has high rate of spontaneous resolution in 60-80%of the cases. The recommendation of the American Academy of Pediatrics is to treat all cases of OM by giving a 5-7 days course of antimicrobial agents in certain children 2 years of age or older. Younger children and children with underlying condition such as craniofacial anomalies, chronic or recurrent OM or perforation of tympanic membrane should receive standard 10 day course *(Red Book, 2000)*.

Patients assessed at low risk for *Strep. pneumonia* resistance can be treated with usual dose amoxicillin 40-45 mg/kg/day in 3 divided doses.

Risk factor for resistance include: recent antibiotic exposure, age < 2 years, and day care attendance. For patients at high risk for resistance or with treatment failures when assessed after 3-5 days, suitable alternative drugs include: high dose amoxicillin 80-90 mg/kg/day in 2 or 3 divided doses is recommended (drug of choice) or high dose amoxicillin clavulanate (80-90 mg/kg/day) of amoxicillin component or cefuroxime axetil (30 mg/kg/day in 2 divided doses). For penicillin resistant cases erythromycin, erythromycin-sulfisoxazole and in severe cases or treatment failure clarythromycin can be given.

Even after the infection is cured, the middle ear fluid may persist for weeks or months, and in the majority of cases, clears spontaneously. Treatment is indicated if effusions persist for 3 months or more.

In *recurrent acute otitis media*, which is defined as 3 or more distinct and well documented episodes in 6 months or 4 episodes in 1 year, a daily dose of a prophylactic antibiotic (*sulfisoxaole 50mg/kg/day or amoxicillin 20mg/kg/day once daily) at bed time* during the winter months can be tried but routine use of prophylaxis has come into question due to emergence of many resistant bacteria so it should be reserved for selected cases.

Chronic suppurative otitis media implies a non-intact tympanic membrane (perforation or tympanostomy tube present) within 6 weeks or more of middle ear drainage *(BMJ 2000; 321:126-127)*. In other books it is defined if more than 2 weeks. Any acute ear infection may become chronic, and can be more dangerous than acute ear infection because if prolonged or repeated, it may cause permanent damage to the ear. Chronic infection may show less severe symptoms. The bacteria that cause chronic infection are often different from those that cause acute ear infection. Usually the causative agents are *Pseudomonas*, *Bacteroides*, *Staph. aureus* and *proteus.* Topical ear drops have been shown to be more effective than systemic antibiotics. Among the **topical drops quinolone** antibiotics have been shown to be more effective than aminoglycoside and less ototoxic. **Ofloxacin** drops are approved for children older than 1 year. If topical antibiotics fail, parenteral ceftazidime or imepenem should be used. Surgery is usually needed as well after control for infection. *(BMJ 2000; 321: 126-127)*. Such cases should be under specialist supervision. It is important that antibiotic treatment does not replace drying the ear. It is also important to teach how to wick, so as to dry the ear. **No cotton-tipped applicator or sticks should be used.** Repeated courses of antibiotics should not be given for draining ear. It is preferred to take culture before starting treatment to know the organism and the susceptibility to antibiotics.

C) DRUGS USED FOR EAR WAX

Ear Wax: Wax-block or cerumen-impaction is the blockage of the ear canal with cerumen (wax). The ear canal is lined with hair follicles and glands that produce a waxy oil called cerumen. This protects the ear by trapping dust, microorganisms, and foreign particles, and prevents them from entering and damaging the ear. The wax usually makes its way to the opening of the ear where it falls out or is removed by washing.

In some people, the glands produce more wax than can be easily excreted out the ear. This extra wax may harden within the ear canal and block the ear. More commonly, the ear canal may be clogged by wax when attempting to clean the ear causing blockage as it goes deeper into the canal. Wax blockage may cause perforated eardrum, otitis media, otitis external as well as hearing loss if not treated.

Wax may be removed by syringing with body temperature water (cold or hot water may cause a response consisting of brief but severe dizziness or vertigo). If necessary, wax can be softed before syringing with simple remedies such as **olive oil** or **almond oil**. The patient should lie with the affected ear facing upward for 5 to 10 minutes after a generous amount of the solution has been introduced into the ear. Some proprietary preparations containing organic solvents can cause irritation of the meatal skin, but they are not more effective than other indicated preparations that are less likely to cause irritation.

Note: *Syringing is best avoided in patients with a history of recurring otitis externa, a perforated eardrum, or previous ear surgery. A person who has hearing only in one ear should not have that ear syringed because even a very slight risk of damage is unacceptable in this situation.*

An available product in our market is **Cerumol®** , which contains chlorbutol 5%, paradichlorobenzene 2%, and arachis oil 57%.

Notes:

1) For detailed information about all the mentioned medication in the following table, refer to the related chapters, i.e. anti-infective preparations, analgesics and steroids.

2) Betamethasone and prednisolone sodium phosphate are both contra-indicated if an infection is present.

3) Sensitivity to the anti-infective or solvent may occur and resistance to antibacterials is a possibility with prolonged use.

*4) **Chloramphenicol eardrops** contain propylene glycol and cause sensitivity in about 10% of patients (the eye ointment can be used instead).*

Table-10.3 gives a summary of agents/ products that are used in ear problems in our market.

Table-10.3: The following table contains some of the drugs on the market for The Treatment of Otitis Media, Otitis Externa, and Ear Wax Accumulation.

Drug	Class	Indications	Administration	Cautions	Side effects
Amoxicillin	Anti-infective	Treatment for OM	Orally: 40-50 mg/kg/day, divided into t.i.d.	Be aware of bacterial resistance. May not be active against *Moraxella*.	*Refer to anti-infectives chapter.*
Co-trimoxazole	Anti-infective	Treatment for OM	Oral: 10 mg/kg/dose given b.i.d.	Do not administer in infants less than 1 month old who are premature or jaundiced.	*Refer to anti-infectives chapter.*
Erythromycin	Anti-infective	Treatment for OM, for penicillin sensitive patients	Orally: 50 mg/kg/day, divided q. 6 h., 4 times daily	Avoid prolonged use. May not be active against *H. Influenzae*.	*Refer to anti-infectives chapter.*
Chloram-phenicol	Anti-infective preparation	Bacterial infection in OE	Apply 2-3 times daily	Avoid prolonged use	High incidence of sensitivity reaction to vehicle.
Clotrimazole	Anti-infective preparation	Fungal infection in OE	Apply 2-3 times daily continuing for at least 14 days after disappearance of infection		Occasional skin irritation or sensitivity.
Gentamicin	Anti-infective preparation	Bacterial infection in OE	Apply 3-4 times daily and at night	Avoid prolonged use; risk of ototoxicity increased if perforated eardrum	Local sensitivity.
Neomycin Sulphate	Anti-infective preparation	Bacterial infection in OE and OM	Apply eardrops q. 2-3 h.; ear ointment 2-4 times daily. Reduce frequency of application when relief is obtained	Avoid prolonged use; slight risk of ototoxicity increased if perforated eardrum	Local sensitivity.
Tetracycline Hydrochloride	Anti-infective preparation	Bacterial infection in OE	Apply q. 2 h.	Avoid prolonged use	Local sensitivity; stains skin and clothing.
Beta-methasone Sodium Phosphate	Anti-inflammatory preparations	Eczematous inflammation in OE	Apply q. 2-4 h.; reduce frequency of application when relief is obtained	Avoid prolonged use.	Steroid glaucoma in predisposed patients.

Otic Preparations

Prednisolone Sodium Phosphate	Anti-inflammatory preparations	Aczematous inflammation in OE	Apply q. 2-3 h.; reduce frequency of application when relief is obtained	Avoid prolonged use.	Steroid glaucoma in predisposed patients.
Aluminum Acetate	Astringent preparations	Inflammation in OE	Apply drops, or use on a wick	-	Local sensitivity.
Cerumol (paradichloro-benzene, benzocaine, chlorobutanol , ol-terebinth)	Ear wax remover	Occlusion or Partial occlusion of external auditory Meatus due to Wax	Instill 5 drops into ear with cotton wool plug and leave for 10-30 min.	Avoid prolonged use	Local irritation, pain.
Warm purified water	Ear wax remover	Soft, little waxy ear	Applied once	Vertigo may occur rarely	Must be at body temperature
Oils (olive, almond)	Ear wax softners and remover	Hard wax-lubricant, alleviate itching	Applied once	-	Use 2-3 days only.

Chapter 11: DERMATOLOGICALS

A) EMOLLIENTS, HUMECTANTS
1. **Vaseline**
2. **Glycerin**

B) ANTIPRURITICS, ANTIHISTAMINES, LOCAL ANESTHETICS
1. **Zinc Oxide / Calamine**
2. **Lignocaine / Benzocaine**

C) ANTIFUNGALS
1. **Miconazole**
2. **Ketoconazole**
3. **Tolnaftate**

D) ANTIBACTERIALS
1. **Oxytetracycline**
2. **Neomycin/Gentamicin**

E) ANTIVIRALS
1. **Acyclovir**

F) ANTISEPTICS / DISINFECTANTS
1. **Ethyl Alcohol**
2. **Povidone-Iodine**
3. **Cetrimide**
4. **Chlorhexidine**

G) ANTIPARASITICS
1. **Scabicides: Benzyl Benzoate, Crotamiton**
2. **Pediculicides: Malathion, Lindane**

H) KERATOLYTIC AGENTS
1. **Salicylic Acid**
2. **Sulfur**

I) MISCELLANEOUS
1. **Topical corticosteroids: Betamethasone Valerate**
2. **Preparations for acne: Retinoic Acid/Tretinoin, Benzoyl Perxoide**
3. **Sunscreens**

Dermatological Preparations

A large number of drugs are available for topical skin therapeutics. **Many of the preparations available should be prescribed by dermatologists, to ensure expert advice and supervision.** The "vehicle" of a preparation refers to the carrier-base that brings the drug into close contact with the skin. Both the vehicle and the active ingredients are important in treating skin disease. Skin preparations may contain preservatives, anti-oxidants, perfumes and coloring agents that may give rise to adverse reactions. Before choosing a specific preparation, factors such as cosmetic acceptability to the patient, suitability for the condition, safety and stability should be considered.

- **Creams** are chosen for wet and weeping skin conditions. They are cosmetically acceptable and have proved good delivery systems for various drugs. Generally, creams are cosmetically more acceptable than ointments as they are less greasy and easier to apply.
- **Ointments** are greasy preparations, suitable for chronic dry skin lesions. They are more occlusive than creams, promoting hydration and the penetration of specific drugs, but are disadvantageous in oozing conditions.
- **Lotions** may be preferred to creams or ointments when it is intended to apply a thin layer of the preparation over a large or hairy area.
- **Powders** may contain one or more active ingredients with or without auxiliary substances. They are useful as adjunctive agents, intended to be applied to skin for therapeutic, prophylactic or lubricant purposes. They are used in folds where friction may occur between opposing skin surfaces. They should not be applied in areas that are very moist as they tend to cake and abrade the skin.

When there is skin irritation, the underlying cause of irritation should be always sought and appropriate antipruritic therapy instituted. Although ***topical antibiotic*** agents may be valuable in the management of some infected skin conditions such as impetigo and infected eczema, they should not be used indiscriminately, thus resulting in the emergence of resistant bacterial strains. As for ***topical steroids***, they are used frequently for the symptomatic relief and control of inflammatory and allergic skin conditions, and they are often prescribed without regard for the appropriateness of the indication, the potential for adverse effects or proper concern for the potency of the preparation. Topical corticosteroids should generally not be used in the presence of bacterial (including tuberculosis), fungal or viral infections of the skin.

Excessive drying and defatting of the skin should be avoided, e.g., hot baths, alcoholic skin preparations, detergents and alkaline soaps.

A) EMOLLIENTS & HUMECTANTS

Emollients/Barriers are occlusive agents or moisturizers used to prevent or relieve the signs and symptoms of dry skin. Emollients are used to rehydrate and soothe the skin, and are valuable in all conditions characterized by dryness, scaling and cracking of the skin. Frequent application is usually needed and continued prophylactic use is recommended.

The oily nature of these emollients promote water retention because the moisture of the skin cannot pass through the oily film. The frequency of application depends on the degree of dryness of the

skin. The most common emollients are petrolatum jelly (vaseline), lanolin, and liquid petrolatum (mineral oil). Lanolin and mineral oil are not very effectively used for the treatment of dry skin. However, combinations with other formulations are very common.

Humectants are hydrating agents that draw water into the stratum corneum to hydrate the skin. They are used in conjunction with emollients to treat and prevent dry skin. The difference between an emollient and a humectant is that an emollient **retains** the water that is already in the skin while a humectant **adds** water to the skin. The most common humectants available are: glycerin, propylene glycol, and phospholipids.

1) Vaseline

- ***DRUG SUMMARY:***

Vaseline or petrolatum jelly is one of the most effective emollients available. It is not very well tolerated by patients due to its greasiness and staining properties. It can also be used in conjunction with other products as an ointment base.

- ***INDICATIONS:***

For treatment and prevention of dry skin.

- ***CONTRAINDICATIONS:***

Hypersensitivity to petrolatum.

- ***DOSAGE FORMS:***

Ointment.

- ***RECOMMENDED DOSAGE:***

Directions: to be applied to affected area(s) as needed. Frequency of application depends on how dry the skin is. It can be used with hydrating agents like glycerin in order to hydrate the skin more effectively.
*In some cases it is recommended to advise the patient to hydrate the skin by soaking the affected area in water for 5-10 min., then patting it dry and applying vaseline to it.

- ***PRECAUTIONS AND WARNINGS:***

Petrolatum should not be applied over puncture wounds, infections, or lacerations because its high occlusive ability may lead to inflammations and infections. Excessive hydration should also be avoided. Use caution when applied around the nasal mucosa because it can obstruct breathing.

- ***ADVERSE EFFECTS:***

Adverse effects are rarely seen with the topical use of vaseline, however acne is possible.

- ***BRANDS:***

Petroleum Jelly, Vaseline.

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2) Glycerin

- ***DRUG SUMMARY:***

Glycerin is one of the most common hydrating agents. In addition to its hydrating effect, glycerin provides lubrication to the skin surface.
It is indicated for use in the treatment and prevention of dry skin. It can also be used as a skin protectant and as a solvent for different pharmaceutical agents. The only contraindication for use is hypersensitivity to glycerin.

B) ANTIPRURITICS, ANTIHISTAMINES & LOCAL ANESTHETICS

Pruritis or itching may occur with any type of systemic or skin disease. Pruritis can cause redness, local irritation and sometimes lesions if untreated. It can also be a form of dermatitis. Several pharmaceutical products are available for the treatment of pruritis depending on the cause of it. Most formulations are available as combined products. **The key in the treatment is to identify and then discontinue the aggravating factor of the itching before initiating therapy.** The mentioned drugs are some of the most common ingredients found in antipruritic products.

1) Zinc Oxide / Calamine [WHO,P]

- ***DRUG SUMMARY:***

Zinc oxide is an astringent with antipruritic properties. It is combined with ferric oxide to make calamine. Calamine is a pink colored powder that is not soluble in water. It has astringent, antiseptic, antibacterial, and antipruritic action. When applied to the skin, the evaporation of water produces a cooling effect and the oozing of watery discharge is reduced.

- ***INDICATIONS:***

It can be used in mild cases of dermatitis and poison ivy. In some cases calamine can be used to treat diaper rash and to relieve the itching caused by chicken pox. It is generally used as an antipruritic agent.

- ***CONTRAINDICATIONS:***

Hypersensitivity to any of the ingredients.

- ***DOSAGE FORMS:***

Lotion, ointment, cream.

- ***RECOMMENDED DOSAGE:***

To be applied to the affected area(s) as needed (3-4 times/day).

Directions: it is safe for use in infants, children and adults.

*Avoid contact with the eye(s). Flush with running water if contact with the eyes occurs.

- ***PRECAUTIONS AND WARNINGS:***

For external use only. It should not be applied to ulcers or infected skin lesions associated with pus.

- ***ADVERSE EFFECTS:***

Rare adverse effects are noted which include: local irritation, burning, and stinging.

- ***BRANDS:***

Adinol Ointment (Teva), Caladerm (JePharm), Calatrim Lotion (Trima), Dyprotex (Mediline), Calamine Lotion (Sam-On).

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2) Lignocaine / Benzocaine

- ***DRUG SUMMARY:***

Lignocaine is a topical local anesthetic that temporarily relieve pain by preventing the transmission of nerve impulses.

- ***INDICATIONS:***

For the temporary relief of pain, burning, itching, discomfort, and irritations in local skin disorders. It can also be used for local anesthesia of mucous membranes including oral, nasal and laryngeal membranes as well as anal pruritis and hemorrhoids.

- ***CONTRAINDICATIONS:***

Hypersensitivity to any of these products.

- ***DOSAGE FORMS:***

Ointment, cream, spray, lozenges, gel.

- ***RECOMMENDED DOSAGE:***

To be applied to the affected area as needed.

Directions: Use the minimal amount possible to avoid systemic side effects.

*Do not apply oint./creams/gel to the eyes.

*Lozenges should be sucked and not chewed for soothing laryngeal discomfort.

*When using the oral anesthetic applied to the mouth and throat (like the lozenges or spray), use caution while swallowing food. Ingestion of food should be delayed for 1

hour after using these products to prevent choking.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use when the benefits outweigh the potential hazards to the fetus, (Category C). Safety for use during pregnancy has not been established yet. One or two applications will not cause harm.

Lactation- Use caution. Sufficient data is not available.

Children- Not to be used in infant < 1 y. of age. Safe in children > 1 y., but decrease the dose depending on the age, body-weight and physical condition.

- ***PRECAUTIONS AND WARNINGS:***

- Use the minimal effective dosage to avoid systemic absorption and side effects.

- ***ADVERSE EFFECTS:***

Adverse effects are dose related. Local adverse effects might include: burning, stinging, and tenderness. Cutaneous lesions, urticaria, edema, contact dermatitis are also noticeable. Anaphylactic reactions and shock can also result from hypersensitivity.

- ***INTERACTIONS:***

Class I antiarrhythmic agents: caution should be exercised when using these agents together since the toxic effects are increased (synergistic action).

- ***OVERDOSE:***

Systemic absorption may occur due to overdosage with topical treatment. CNS (convulsions) and cardiovascular (hypotension) complications can occur. Refer to an emergency setting for symptomatic and supportive care.

- ***BTRANDS:***

Esracain (Rafa), Xylene.

C) ANTIFUNGALS

One of the most common skin diseases are fungal infections. They can occur anywhere in the body especially the areas that are mostly wet or sweaty. Such areas include the soles of the feet, between the toes, and the diaper area in infants/ children/ and even adults . . . etc.

In most cases, topical antifungals are used. Ideally, skin infections should be examined by a dermatologist to confirm diagnosis before the treatment is begun. The primary effect of most antifungal drugs is to prevent colonization of new tissue by the organisms. The crucial factor for the successful treatment of skin fungal infections is to understand the kinetics of turnover of epidermal cells. In some complicated cases oral antifungals are needed to treat the fungal infections.

There are a lot of products containing antifungal agents on the market. **Studies have not proven superiority of one product over the other in treating most localized infections of the skin.** Topical antifungal agents include the broad spectrum imidazoles and triazoles (i.e. butoconazole, clotrimazole [WHO,P], econazole, ketoconazole, miconazole [WHO,P], terconazole, nyastatin[P] (for candidal infections only), and tolnaftate.

Miconazole will be used as the prototype for the imidazole antifungal agents.

[For more information about the oral antifungal agents available, refer to the anti-infectives chapter.]

1) Miconazole [WHO,P]

- ***DRUG SUMMARY:***

Miconazole is an imidazole derivative broad spectrum antifungal agent. It inhibits growth of different vulvovaginal candidiasis (*Moniliasis* and vaginal yeast infections) and dermatophytes such as *Candida ablicans, Trichophyton rubrum* and active forms of *Tinea versicolor* . . . *etc.* It exerts fungicidal effect by altering the permeability of the fungal cell membrane.

- ***INDICATIONS:***

Tinea pedis (athlete's foot), *Tinea cruris* (jock itch), *Tinea corporis* (ringworm) and vaginal and cutaneous candidas.

- ***CONTRAINDICATIONS:***

Hypersensitivity to miconazole.

- ***DOSAGE FORMS:***

Cream, powder, lotion, oral gel; suppositories/ ovules and cream for vaginal use.

- ***RECOMMENDED DOSAGE:***

Directions: Apply to affected skin areas twice a day (morning and night) for 2 weeks. If treating *tinea pedis* use for 1 month.

*For vaginal use: use supp./ovules daily at bedtime for 3 days; cream twice a day, for 7 days.

*For external use only. Avoid contact with the eyes.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid unless clearly needed (Category B), **specially in first trimester**. There have been reports of birth defects (i.e. cardiovascular, oral clefts, spina bifida and hypospadias), observed when product was used vaginally during the first trimester, but no solid data is available to associate miconazole with congenital defects.

Lactation- Not enough clinical information is available, use caution when applying on a nursing mother.

- ***PRECAUTIONS AND WARNINGS:***

Discontinue if severe irritation occurs.

Vaginal products may interact with latex products including diaphragm and condoms. Warn patients.

- ***ADVERSE EFFECTS:***

Irritation, burning, and allergic contact dermatitis.

- ***INTERACTIONS:***

No drug interactions have been noted with topical use of miconazole.

- ***OVERDOSE:***

Refer to the anti-infectives chapter.

- ***BRANDS:***

Daktarin/Gyno-Daktarin (Abic/Janssen), Daktazole (JePharm), Fungazole (Pharmacare), Fungitirin (BPC).

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2) Ketoconazole

- ***DRUG SUMMARY:***

Ketoconazole is another imidazole broad-spectrum antifungal agent. It works by altering the permeability of the cell membrane of different types of fungus and yeast. It is significantly better absorbed after oral administration than other imidazoles, but has been associated with hepatotoxicity.

- ***INDICATIONS:***

Cream: for the treatment of *tinea corporis* (ringworm), *tinea cruris* (jock itch) and *timea pedis* (athlete's foot).

Shampoo: reduction of scaling due to dandruff, seborrhoic dermatitis and Pityriasis versicolor (*Tinea versicolor*).

- ***CONTRAINDICATIONS:***

Hypersensitivity to this group of antifungal agents.

- ***DOSAGE FORMS:***

Cream, shampoo (both 2%).

- ***RECOMMENDED DOSAGE:***

*Cream: Apply to affected area and surroundings once daily. Results can be seen as soon as treatment is initiated.

Use for at least 2 weeks to reduce the possibility of recurrence.

Tenia pedis may require 6 weeks of treatment.

When used to treat seborrheic dermatitis it should be applied twice a day for up to 4 weeks or when improvement is seen.

*Shampoo: Moisten hair and scalp thoroughly with water, then apply a sufficient amount to produce enough lather.

Massage throughout the scalp and hair for around one minute.

Rinse hair thoroughly with warm water.

Repeat as before but leave it on for an additional 3 minutes and rinse thoroughly. Dry hair with towel or warm airflow.
Shampoo hair twice a week for 4 weeks with at least 3 days between each shampooing.
For *Pityriasis versicolor* it should be used once daily for five days.
*For external use only. Avoid contact with the eyes.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only if the potential benefits outweigh the potential hazards on the fetus (Category C); sufficient studies are unavailable.
Lactation- Safety has not been established yet. Use caution when used in nursing mothers.
Children- Safety and efficacy in children has not been established yet.

- ***PRECAUTIONS AND WARNINGS:***

Discontinue if sensitivity reactions occur. The cream contains sulfites that might cause hypersensitivity reactions in susceptible individuals.
Shampoo might cause removal of the curls in permanently waved hair.

- ***ADVERSE EFFECTS:***

Cream: Severe irritation, pruritis, stinging, and allergic reactions.
Shampoo: increase in normal hair loss, abnormal hair texture, irritation, mild dryness of skin, itching, and dryness/ oiliness of hair and scalp.

- ***INTERACTIONS:***

Overview of Ketoconazole Drug-Drug Interaction	
Drug	**Interaction**
Astemizole and ***terfenidine***	These antihistamines should be avoided even with the topically administered ketoconazole. Severe cardiovascular adverse reactions may occur.

- ***OVERDOSE:***

Shampoo: if ingested, employ supportive measures; gastric lavage with sodium bicarbonate.

- ***BRANDS:***

Nizoral (Abic/Jennsen)

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3) Tolnaftate

- ***DRUG SUMMARY:***

Tolnaftate is effective in the treatment of superficial fungus infections of the skin. Because of its superficial action it might be administered with oral anti-fungal agents like Griseofulvin [*for more information refer to the anti-infectives chapter*], or Ketoconazole.

- ***INDICATIONS:***

It is effective for the treatment of *Tenia pedis* (athlete's foot), *Tenia cruris* (jock itch), and *Corporis* (ringworm). It can also be used for preventing superficial fungal infections. This agent is not suitable for deep infections of the nails or hair follicles.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug or product.

- ***DOSAGE FORMS:***

Cream, solution, gel, powder (all as 1%).

- ***RECOMMENDED DOSAGE:***

Directions: Apply to affected areas twice a day for 2 to 4 weeks. Only small quantities are required.
*Affected areas should be clean and dry before application of the product.
*For external use only.
*Avoid contact with the eyes.

- ***PRECAUTIONS AND WARNINGS:***

If no improvement is seen within 4 weeks, patient should be re-evaluated.

- ***ADVERSE EFFECTS:***

Mild irritation and allergic reactions might occur (rarely).

- ***OVERDOSE:***

Incidents of toxicity with topical use are very rare. If it occurs use symptomatic and supportive care.

- ***BRANDS:***

Athletes Foot (Scholl), Pitrex (Teva), Tinaderm (Shering), Tinasol (Fischer).

D) ANTIBACTERIALS

Antibacterials are used to treat and prevent topical infections. Different kinds of antibiotics are used depending on the type of organism. Since there are a lot of products on the market, remember these points:

- Although topical antibiotics are indicated for infective skin conditions, they **should not be used indiscriminately**, thus resulting in the emergence of resistant bacterial strains, which precludes future systemic use of the antibiotic. Mupirocin (Bactroban®) is an example of a commonly used broad spectrum topical antibiotic which is abused. Resistant *Staph. aureus* to mupirocin are emerging. Mupirocin should not be used as a first-line agent or in hospitals, and should be used when other topicals (i.e. tetracyclines) fail. When used, avoid use for longer than 10 days.
- Use of **combination products** of an antibiotic and corticosteroids should be **avoided** in bacterial infections.

1) Oxytetracycline

- ***DRUG SUMMARY:***

Oxytetracycline is a broad-spectrum tetracycline antibiotic that inhibits protein synthesis. It is usually used in combination with polymixin B. Its use may be limited because it oxidizes and turns the skin yellowish-brown.

- ***INDICATIONS:***

Used for infection prophylaxis in minor cuts, wounds, burns, and skin abrasions. It also aids in healing and treating superficial infections of the skin.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Ointment.

- ***RECOMMENDED DOSAGE:***

Directions: Apply to infected area(s) 1 to 4 times a day. Cover with sterile bandage if needed.

*For external use only. Not to be used on the eyes; there are special preparations for ophthalmic use.

- ***PRECAUTIONS AND WARNINGS:***

Long term use may lead to overgrowth of non-susceptible bacteria or fungi.

Discontinue if redness, irritation, swelling or pain persists or increases, or if secondary infections occur. The ointment might stain clothes.

- ***ADVERSE EFFECTS:***

Yellow to brown stains may occur on the skin as mentioned above. Skin irritation and rash might occur in some cases. Hypersensitivity reactions are very common.

- ***BRANDS:***

Jordacycline (Jordan), Oxycin (BPC), Tetracare (Pharmacare), Tetrapharm (JePharm), Teva-cycline Derm (Teva).

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2) Neomycin [WHO,P] or Gentamicin

- ***DRUG SUMMARY:***

Neomycin and Gentamicin are aminoglycoside antibiotics that are active against gram negative bacteria as well as *Staphylococcus* infections. They work by inhibiting protein synthesis, they are bactericidal. Resistance for neomycin is very common and limits its use. Because of the resistance factor it is mostly used in combinations with other antibiotics such as polymixin B and/or bacitracin. Use of these

agents on large areas of the skin should be avoided especially in children, in the elderly and in those with impaired renal function, due to risk of nephrotoxicity and ototoxicity. Patients sensitive to neomycin may be treated with gentamicin.

- ***INDICATIONS:***

Used for the prevention and the treatment of infections secondary to minor cuts, wounds, burns, and skin abrasions.

- ***CONTRAINDICATIONS:***

Hypersensitivity to drug.

- ***DOSAGE FORMS:***

Cream, ointment.

- ***RECOMMENDED DOSAGE:***

Directions: Apply to infected area(s) 1 to 4 times a day. Covering the infected area(s) with sterile bandage is possible.

- ***PRECAUTIONS AND WARNINGS:***

-Hypersensitivity reactions are very common.

-Chronic use of topical aminoglycoside antibiotics increases the possibility of sensitization. Discontinue use if symptoms of hypersensitivity appear.

-Use with care in treating burns and trophic ulceration because it can lead to systemic absorption and systemic adverse effects, especially in children and in renal impaired patients.

- ***ADVERSE EFFECTS:***

Ototoxicity and nephrotoxicity are common especially if applied to large areas for long periods of time for this group of drugs. Possible photosensitization with gentamicin has been reported.

- ***BRANDS:***

Garamycin (Schering), Gentatrim (Trima), Garamine (Jordan Chemical Lab).

E) ANTIVIRALS

Antiviral drugs should be only prescribed by a specialist. Cases of recurrent labial and genital herpes simplex should be treated as early as possible.

[*For more information about systemic antivirals, refer to the anti-infectives chapter.*]

1) Acyclovir

- ***DRUG SUMMARY:***

Acyclovir (*also written as aciclovir*) is an antiviral that inhibits the viral DNA replication. It is only effective if started at onset of infection. Some decrease in the duration of viral shedding has been noted.

- ***INDICATIONS:***

It is used for the management of initial and recurrent episodes of herpes genitalis and in genital and labial cases of herpes simplex viral infections as injection.

Acyclovir is not a cure for herpes simplex infections, it might benefit in treating recurrent attacks.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Cream, ointment.

- ***RECOMMENDED DOSAGE:***

Directions: Apply to infected area(s) every 3 hours (or 6 times a day) for 7 days. **Application should start as early as possible** (as soon as the signs and symptoms occur).

*Use rubber gloves when applying to lesions to prevent the spreading of the lesions to other area(s) in the body or transmitting the virus to other individuals.

*The ointment should thoroughly cover all lesions.

*For external use only. Avoid use on the eyes; special preparation available for eyes.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use only if the potential benefits outweigh the potential hazards on the fetus (Category C). Well-controlled clinical studies on pregnant women have not been done.

Lactation- It is not known whether it is excreted in the breast milk. Use caution when used on nursing mothers.

- ***PRECAUTIONS AND WARNINGS:***

Dose should not be exceeded. No data is available that proves that acyclovir prevents the transmission of the infections to other people, or prevent recurrence infections when applied in the absence of signs and symptoms. Not to be used to prevent recurrent HSV infection.

- ***ADVERSE EFFECTS:***

Mild pain, burning/stinging, pruritis, rash, and vulvitis.

- ***BRANDS:***

Virax (BPC), Zovirax (GlaxoWellcome).

F) ANTISEPTICS/ DISINFECTANTS

Antiseptics and disinfectants are generally used to destroy and inhibit the growth of pathogenic micro-organisms. There is no clear difference between them.

The term **antiseptic** is used to a chemical agent that destroys or inhibits micro-organisms on living tissues having the effect of limiting or preventing the harmful results of infection.

However a **disinfectant** is a chemical agent that destroys microorganisms, but it does not necessarily kill all the micro-organisms, but reduces them to a level that is not harmful. It can be applied to the living tissues as well as inanimate objects.

1) Ethyl Alcohol (Ethanol) [P]

- ***DRUG SUMMARY:***

It is a widely used antiseptic and a disinfectant that exerts bactericidal and fungicidal action in concentrations at 70%. In concentrations above 80% its bactericidal effect is low. It has virucidal action at 90%. It is less effective against HBV viruses.

Used as an antiseptic agent before injections to prevent topical infections. It is not a desirable wound antiseptic because it causes irritation in already damaged tissues, and may delay healing.

- ***CAUTION:*** The solution is flammable.

Avoid use on broken skin and the eyes. Intended for external use only.

- ***ADVERSE EFFECTS:*** may include local irritation, burning and stinging especially in cases when it is used on open wounds or on broken skin.

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2) Povidone-Iodine [WHO,P]

- ***DRUG SUMMARY:***

A disinfectant and antiseptic that is active against bacteria, fungi, viruses, protozoa, and cysts. Concentrations of 4-10 % are available in the market.

- ***INDICATIONS:***

As an antiseptic and disinfectant for the treatment and prevention of contaminated wounds and for pre-operative preparation of the skin and mucous membranes. It also acts as a disinfectant for the equipment used in the operation.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug, should not be used on patients with non-toxic nodular colloid goiter.

- ***DOSAGE FORMS:***

Solution, powder, ointment (10% povidone iodine=1% iodine).

- ***RECOMMENDED DOSAGE:***

<u>Directions</u>*:* To be applied on the skin or mucous membrane. Ointment maybe applied to affected area 2-4 times daily.
*Disinfecting the equipment should be done according to regular protocols taken by the institution.
*For external use only, not to be applied on open skin. Avoid contact with the eye(s).

- ***PRECAUTIONS AND WARNINGS:***

Avoid use in pregnancy and lactation. Neonatal hypothyroidism has been reported.

- ***ADVERSE EFFECTS:***

Local irritation, itching, and pruritis are possible but rare. When applied to severe burns or to large areas systemic adverse reactions might occur.

- ***BRANDS:***

Betadine (Rafa), Iodocare (Pharmacare), Iodo-Vit (Vitamed), Polydine (Fischer).

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3) Cetrimide

- ***DRUG SUMMARY:***

Cetrimide is an antiseptic with great bacterial activity against gram-positive bacteria. In higher concentrations it is active against gram-negative bacteria. It has variable activity against fungus and viruses.

- ***INDICATIONS:***

It is used as an antiseptic for cleansing skin, wounds, and burns. It is mainly used in combination with other agents like chlorhexidine (explained below). It is also a component of some shampoos to remove scales in seborrhea.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Solution: 0.1-1% (further dilution is required before use), cream: 0.5%

- ***PRECAUTIONS AND WARNINGS:***

For external use only. Avoid contact with the eyes. It is susceptible to contamination with micro-organisms therefore precautionary measures should be taken. Avoid use in body cavities.
Hypersensitivity reactions are common after repeated use.

- ***ADVERSE EFFECTS:***

Irritation is possible but rare. It usually occurs after several applications. There have been rare reports of burns due to concentrated solutions of cetrimide.

- ***OVERDOSE:***

If ingested, cetrimide causes nausea, vomiting, esophageal damage and necrosis. It can also cause cyanosis, depression of the CNS, hypotension, coma, and it might lead to death. Treat ingestion by treating the symptoms, avoid emesis and lavage.

- ***BRANDS:***

Capillon (Gramse), Cetrimide (Vitamed).
(*refer to the price list for other products*)

---

4) Chlorhexidine [WHO,P]

- ***DRUG SUMMARY:***

It is an antiseptic and a disinfectant effective against a wide range of bacteria (excluding bacteria that cause tuberculosis), fungi, and viruses. It is available as a gluconate and an acetate salt.

- ***INDICATIONS:***

Used to disinfect the skin, wounds, burns, and to clean instruments and hard surfaces. It is used as a surgical scrub, hand rinse and wipes. The chlorhexidine wipes are used as a cleanser for acne vulgaris. It is also used as a mouthwash to prevent gingivitis and to prevent plaque.
It is found in combinations with other antiseptics especially cetrimide (*refer to cetrimide*).

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Solution, mouthwash, dental gel, cream.

- ***RECOMMENDED DOSAGE:***

**As a disinfectant:* for emergency disinfection of clean instruments, emerse the instruments in a 0.5% solution of the gluconate or the acetate mixed with 70% alcohol. For storage and disinfection emerse for 30 minutes in 0.05% solution.

**As an antiseptic:* chlorhexidine gluconate (0.05% aqueous solution) is used to disinfect wounds, burns, and other damaged skin disorders.

**As a mouthwash:* 0.2% chlorhexidine gluconate is used twice a day after brushing and flossing.

**As a dental gel:* 1% chlorhexidine gluconate is used after brushing with the normal tooth paste twice a day.

*For external use only.

*Keep out of the eyes and ears (when using the topical solution).

*Avoid exposing it to excessive heat.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use with caution. No data is available about the use of chlorhexidine in pregnant women.

Lactation- Use with caution. There has been some reports about the excretion of chlorhexidine in breast milk. Use only when the benefit of its use outweighs the risk on the infant.

- ***PRECAUTIONS AND WARNINGS:***

-Do not use on a regular basis on wounds involving more than the superficial layer of the skin. It might cause deafness if applied in the middle ear.

-When using the mouthwash do not swallow solution, only use it as a gargle.

- ***ADVERSE EFFECTS:***

Irritation, dermatitis, photosensitivity, and deafness.

- ***BRANDS:***

Bactosept concentrate/ Bactroscrub (Vitamide), Uniscrub (Seton).

G) ANTIPARASITICS

Scabies: It is a parasitic skin infestation caused by *Sarcoptes scabiei*. It burrows itself beneath the stratum corneum. It does not bite or sting, but it is characterized by secondary inflammation and intense itching. It is usually associated with poor hygiene, crowded conditions, and venereal disease. It is usually transmitted through bodily contact with an infested host, clothing, bedding or toilet use.

Pediculosis: is an infestation with lice. There are three types: *Pediculosis capitis* caused by head louse, *Pediculosis corporis* caused by body louse and *Pediculosis pubis* caused by crab louse.

In treating infected patients it is important to examine contacts for evidence of infection and treat accordingly. Emphasis on proper hygiene (i.e. changing sheets and towels) for preventing reinfestation is essential. It may be recommended to treat family members in close contact for preventive measures.

Scabicides and Pediculicides are used for therapy of these infections.

1) SCABICIDES

a) Benzyl Benzoate [WHO,P]

- ***INDICATIONS:***

It is used in the eradication of scabies. It is also used as a pediculicide.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Lotions and emulsions.

- ***RECOMMENDED DOSAGE:***

Apply to the whole body from the neck down after a bath.

Directions: *The concentrated lotion is applied to adults, while the diluted lotion is required for infants and children (other products are preferred for their use).

Individual product instructions should be followed. Another coat may be applied when the first application dries up.
*The residue should be washed off after 24 hours.
*A second application may be required after 5 days.
*Clothing and bedding should be cleaned in boiling water to prevent re-infestation.

- ***PRECAUTIONS AND WARNINGS:***

For external use only. Avoid contact with the eye(s) and face.
Safety for use in pregnancy (Category C) and lactation is not established. Use only if clearly needed.

- ***ADVERSE EFFECTS:***

It might irritate the skin, mucous membrane and the eye(s).

- ***OVERDOSE:***

If ingested, it stimulates the CNS and causes convulsions.
Treatment involves gastric lavage and symptomatic measures.

- ***BRANDS:***

Benzocide (Trima), Scabicide (BPC), Scabiex (Rekah).

---

b) Crotamiton

- ***DRUG SUMMARY:***

It is used as an antipruritic for itch due to scabicides, however, it is not really known how it exerts its effect.

- ***INDICATIONS:***

Used for the eradication of scabies and symptomatic treatment of pruritis due to scabies.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug.

- ***DOSAGE FORMS:***

Cream, lotion.

- ***RECOMMENDED DOSAGE:***

Directions: After bathing, apply to the whole body from the neck down. A second application is advisable in 24 hours. A cleansing bath is required after 48 hours after the last application.
*Change clothing and linen the next morning to prevent reinfestation.
*For external use only.

- ***USE IN SPECIAL CASES:***

Pregnancy- Avoid use. It is not known whether it can cause fetal harm, use on pregnant women only if clearly needed (Category C).
Lactation- Use caution. No clinical studies are available concerning the use of it in breast-feeding mothers.
Children- Safety and efficacy for use in children have not been established.

- ***PRECAUTIONS AND WARNINGS:***

Do not apply to acutely inflamed skin, the eyes or mouth. If severe irritation occurs discontinue use. Do not apply near the eyes, mouth, and mucous membrane.

- ***ADVERSE EFFECTS:***

Local irritation and allergic sensitivity reactions might occur.

- ***OVERDOSE:***

If ingested it can cause convulsions, nausea, vomiting, abdominal pain, burning and irritation of oral esophageal and gastric mucousa. Do not induce vomiting. Take to the hospital for supportive and symptomatic care. When applying large amounts of it topically to children it might cause cyanosis.

- ***BRANDS:***

Crutex (BPC), Eurax (Novartis C.H.), Scabicin (Fischer).

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2) PEDICULICIDES

a) Malathion

- ***DRUG SUMMARY:***

Malathion is a lousicidal and ovicidal that is dispensed by prescription only. The advantage of its use is that it is less toxic than other products because it rapidly hydrolyzes and detoxifies.

- ***INDICATIONS:***

Treatment of head lice and their ova.

- ***CONTRAINDICATIONS:***

Sensitivity to it or any of its products.

- ***DOSAGE FORMS:***

Lotion 0.5%.

- ***RECOMMENDED DOSAGE:***

Directions: Apply to dry hair and rub gently until the scalp moistens. Allow it to dry naturally. **Do not cover or use any heat to dry it up.** After 8 to 12 hours rinse hair and apply a non-medicated shampoo. Rinse, then comb hair with a fine toothed comb to remove dead lice and eggs. Repeat within 7 to 9 days if required.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use during pregnancy only if clearly needed (Category B).

Lactation- Exercise caution when using in nursing mothers. It is not known whether it is excreted in breast milk.

Children- Safety and efficacy in children < 2 years of age have not been established. However the use of it in children between the ages of 2 and 11 years of age had shown no documented problems.

- ***PRECAUTIONS AND WARNINGS:***

-It **contains flammable alcohol**. The lotion should not be exposed to open flames or electric heat. Do not smoke while applying lotion or while hair is wet.

-For external use only. Avoid contact with the eyes. If it gets in the eye accidentally, flush immediately with running water.

- ***ADVERSE EFFECTS:***

Irritation of the scalp has occurred. Other adverse effects are rare.

- ***INTERACTIONS:***

Exposure to carbamate or organo-phosphate-type insecticides or pesticides when using malathion may increase the possibility of systemic absorption. Advise patients using malathion to protect themselves from these insecticides or pesticides. Other interactions are possible if percutaneous absorption of malathion occurs.

- ***OVERDOSE:***

Oral ingestion of malathion may cause systemic adverse reactions. These reactions are delayed reactions that can occur 12 hours after ingestion.

Symptoms of overdose include- Abdominal cramps, anxiety, unsteadiness, confusion, diarrhea, labored breathing, dizziness, watery eyes, pinpoint pupil, seizures and bradycardia.

Treatment- Induce vomiting promptly or lavage the stomach with 5 % sodium bicarbonate solution.

Severe respiratory distress is one of the most serious overdose symptoms, requiring artificial respiration and doses of IV or IM atropine.

Patient should be observed continuously for signs of deterioration due to delayed absorption.

- ***BRANDS:***

Nouryl (Chefaro), Prioderm (NAPP/Rafa).

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b) Lindane

- ***DRUG SUMMARY:***

Lindane (Gamma Benzene Hexachloride) is an ectoparasiticide and an ovicide; kills scabies and their eggs. It is not used for prevention. It is a 2nd line treatement for those who cannot tolerate other safer agents, or treatment with other products has failed.

- ***INDICATIONS:***

Treatment of *Pediculus capitis* (head lice) and *Pediculus pubis* (crab lice) and their ova. The cream and lotion are also indicated for scabies.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the active ingredient or the product. It is also contraindicated in neonates since it is easily absorbed from their skin, and in patients with known seizures disorders.

- ***DOSAGE FORMS:***

Lotion, cream, shampoo (all as 1%).

- ***RECOMMENDED DOSAGE:***

Rubber gloves should be worn during the application of lindane products.

***Cream and lotion: *Scabies*-** Apply a thin layer to dry skin, to the whole body from the neck down, rub thoroughly. Leave on for 8 to 12 hours then wash thoroughly with warm water (not hot). One application should be curative.

***Lotion: *Pediculosis Pubis*-** Apply a sufficient quantity to cover the hair and the skin in the pubic area and other infested areas like the thighs, trunk and axillary region. Leave in place for 12 hours then wash thoroughly. Reapplication is not necessary unless living lice is found. It can be reapplied after 7 days. Sexual partner should be treated concurrently.

***Lotion: *Pediculosis Capitis*-** Apply a sufficient quantity to cover the affected areas. Rub into the scalp and hair and leave in place for 12 hours then wash thoroughly. Reapplication is not necessary unless living lice is found. It can be reapplied after 7 days.

***Shampoo: *Pediculosis Capitis and Pubis*-** Apply a sufficient quantity to dry hair. Work thoroughly into the hair and keep in place for 4 minutes. Add small amounts of water until a lather forms. Rinse hair and then towel dry. Comb hair with a fine toothed comb, to remove the nits and nit shells.

- ***USE IN SPECIAL CASES:***

Pregnancy- It should not be used more than once during pregnancy. There are no adequate studies in pregnant women, but use is not contraindicated (Category B).

Lactation- Lindane is secreted in breast milk in low concentrations when applied. The low concentrations make it unlikely that it will cause serious adverse reactions. If necessary, advise the patient to use an alternative method of feeding for 2 days.

Children- Contraindicated in neonates. In young children, lindane tends to get absorbed from the skin more than in adults. There is a potential of CNS toxicity when it is applied topically. Seizures have occurred after excessive use or ingestion of lindane. It should not be used prophylactically.

- ***PRECAUTIONS AND WARNINGS:***

For external use only as directed.

Use extreme caution in elderly or patients weighing less than 50 kg (110 lbs).

Avoid contact with the eyes or face, if it occurs flush eyes or face with water immediately. Avoid use on open cuts or broken skin.

Oils and creams used simultaneously with lindane can enhance its absorption. If an oil based product is used on the hair, it should be washed out and hair should be dried before using lindane.

- ***ADVERSE EFFECTS:***

Adverse reactions include: CNS adverse effects ranging from dizziness to seizures/convulsions and death (especially after misuse of the product).

Irritation from lindane can cause eczematous eruptions.

Itching, redness, swelling, burning or skin rash may occur, and must not be confused with ineffective treatment.

- ***OVERDOSE:***

As mentioned above, CNS adverse reactions occur after extensive use or oral ingestion of lindane causing seizure attacks and even death.

Treatment of the overdose includes gastric lavage, or speed gastric emptying by using

saline cathartics. Treat seizure attacks with phenobarbital or diazepam.

- ***BRANDS:***

Bicide (Fischer), Parazine (Al-Razi).

H) KERATOLYTIC AGENTS

A keratolytic agent is an agent used to dissolve or break down keratin. These agents are used for several skin conditions including warts, corns, seborrhea, and even used in some anti-dandruff products.

1) Salicylic Acid WHO

- ***DRUG SUMMARY:***

A keratolytic agent that is considered safe and effective. It produces desquamation of the horny layer of skin, while not affecting the structure of the epidermis. It causes the epithelium to swell, soften, macerate and then desquamate.

- ***INDICATIONS:***

Salicylic Acid is used as an aid in the removal of extra keratin in hyperkeratotic skin disorders, such as plantar warts, psoriasis, calluses and corns. It is also used alone or in combinations to treat dandruff, seborrheic dermatitis, acne, and tinea infections.

- ***CONTRAINDICATIONS:***

Hypersensitivity to salicylic acid or any of its components.

It is also contraindicated in infants, diabetics, and patients with impaired circulation. It should not be used for birthmarks or warts with hair growing from them, genital or facial warts, or warts on mucous membranes. It should not be used on broken, irritated or infected skin.

- ***DOSAGE FORMS:***

Solution 17%, ointment 3%, cream 2%, gel 17%.

- ***RECOMMENDED DOSAGE:***

For specific instructions for use of these products, refer to individual product labeling by the manufacturer.

Directions: For external use only.

*Soak the affected area with warm water for 5 minutes before application to enhance the effect. Then apply to affected area. Remove any loose tissue with brush or cloth then dry thoroughly.

*If treating warts, improvement should occur in 1 or 2 weeks and maximum results should be expected in 4 to 6 weeks. Some warts might take up to 12 weeks to go away. Apply only on the wart or affected area. Avoid application to the skin surrounding it.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use during pregnancy if the potential benefits outweigh the potential risks on the fetus (Category C). There are no adequate studies in pregnant women.

Lactation- Use with caution. No well-controlled studies have been performed to prove if topical salicylic acid is excreted in breast milk.

- ***PRECAUTIONS AND WARNINGS:***

Avoid contact with the eyes, mucous membranes, and normal skin surrounding the warts. If contact with eyes or mucous membranes occurs, immediately flush with water for 15 minutes.

Avoid inhaling salicylic acid vapor.

Prolonged use over large areas especially in young children and patients with hepatic or renal impairment may cause salicylate toxicity (*for more details refer to overdose*).

- ***ADVERSE EFFECTS:***

Local irritation may occur from contact with normal skin surrounding the affected area. If irritation occurs, temporarily discontinue then resume use with caution.

- ***INTERACTIONS:***

Interactions have been reported with the use of topical salicylates.

[*Refer to the NSAIDs chapter for more details.*]

- ***OVERDOSE:***

Salicylate toxicity may occur with prolonged use especially in young children or with patients with renal or hepatic impairment.

Be aware of the symptoms of salicylate toxicity that includes: nausea, vomiting, dizziness, loss of hearing, tinnitis, lethargy, hyperpnea, diarrhea, and psychic disturbances. Discontinue use of the drug.

- ***BRANDS:***

Oxy-clean (SK-Beecham), Salatac (Dermal Labs), Zino Pads (Scholl), Salisol-2 (Rekah).

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2) Sulfur

- ***DRUG SUMMARY:***

Sulfur is a keratolytic agent that provides peeling and drying actions. It is also a mild antiseptic, a mild antifungal and a parasiticide. Because of these properties this agent is found in many preparations combined with other drugs for the treatment of acne, dandruff, seborrhoeic conditions, scabies, and superficial fungal infections. It is also used in some creams for oily skin.

It can cause hypersensitivity reactions as well as discoloration of certain metals, so use caution when applied.

I) MISCELLANEOUS

a) PREPARATIONS FOR ECZEMA:

Eczema is a superficial skin disorder characterized by redness, edema, oozing, crusting, scaling and itching. Eczema and dermatitis are usually used interchange-ably. Causes of eczema/dermatitis include: allergens, irritants, infections and in some cases the cause is unknown.

The treatment of such conditions depends on the cause and the type of eczema the patient has. In the initial stages, before starting the treatment, one should find out the cause of these conditions. Then **the first step is to avoid the causative agent.**

Agents that can be used in treating the dermatitis include:

1. Bath products/oatmeal baths and oil baths (mineral or vegetable oil)
2. Emollients and moisturizers (vaseline, petrolatum or lanolin)
3. Astringents (witch hazel)
4. Antipruritics and protectants (zinc oxide and calamine)
5. Keratin-softening agents (urea and alpha hydroxy-acid/ lactic acid).

Patients with moderate to severe conditions should be referred to a dermatologist for initiation of appropriate therapy. **Avoid use of topical cortico-steroids at the primary care level, especially in infants and children.**

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b) PREPARATIONS FOR PSORIASIS:

Psoriasis is a chronic recurrent disease characterized by dry silvery scaling plaques of various sizes. Under these plaques there are flat topped pink/red lesions. Lesions appear in small areas of the body for short periods of time with unpredictable remissions and exacerbations. **Since there are several types of psoriasis, this skin disorder is better managed by a dermatologist, to avoid misdiagnosis and further complications.**

The duration of psoriasis is variable. Lesions may last a lifetime or may disappear quickly causing either hypo-pigmentation or hyper-pigmentation.

The most important factor in the treatment of psoriasis is to relieve its symptoms. **The agents available do not cure psoriasis, they only reduce its severity and its symptoms.** The most common symptom of psoriasis is dry skin

accompanied with pruritis. Gentle rubbing of emollients with or without hydrating agents, or oatmeal baths might help ease the itching and remove the scales.

Each stage of the disease is treated differently. Acute psoriatic onset, characterized by severe erythematous lesions, calls for soothing local therapy with emollients. Tars, salicylic acid, and aggressive UV radiation therapy must be avoided at this stage because of potential irritant effect. As the acute process subsides and the usual thick-scaled plaques appear, more potent therapy with agents such as keratolytics may be used.

c) PREPARATIONS FOR SEBORRHEA:

Seborrhea is a form of dermatitis characterized by a group of eruptions occurring in the areas of the greatest sebaceous gland (i.e. the scalp, face, and trunk).

Seborrhea usually occurs in hairy areas especially in the scalp; it appears like a dull yellowish-red lesion with oily appearing scales. Pruritis is very common. There are many different kinds of seborrhea including seborrhea capitis; which is the most common type of seborrhea. Seborrhea might occur in newborns and infants during the first 12 weeks of life and it is called cradle cap. It often clears up by 8-12 months of age. Seborrhea is sometimes considered as an extension of dandruff. However, dandruff is considered as a stable condition while seborrhea fluctuates in severity.

The treatment of seborrhea is generally the same as dandruff but with some exceptions. **Frequent cleansing with a non-medicated shampoo should be tried first.** If there is no response, seborrhea should be treated with shampoos containing pyrithione zinc, selenium sulfide, salicylic acid and coal tar.

Topical steroids are used for the management of seborrhea in cases when all the other shampoos did not work. Hydrocortisone lotion for example should be applied once daily until the symptoms decrease then used intermittently to avoid exacerbation. Long term use of hydrocortisone is not recommended. A more potent topical steroid is sometimes indicated when hydrocortisone fails to work.

1) TOPICAL CORTICOSTEROIDS

- ***DRUG SUMMARY:***

Topical corticosteroids are a group of agents used for their anti-inflammatory activities. They act against most causes of inflammation including mechanical, chemical microbiological and immuno-logical. When applied to an inflamed site it causes a decrease in edema, erythema and pruritis. Most available products used contain Betamethasone.

Betamethasone Valerate [WHO,P]

- ***INDICATIONS:***

Betamethasone is used in relieving inflammations and pruritis for different forms of dermatitis, eczema, psoriasis, and first- and second-degree burns. It can be used alone or as adjunctive treatment depending on the case.

Corticosteroids in combination with antifungals to relieve yeast infections, and with antibiotics to relieve secondary dermatoses are marketed. But combination products of these should be avoided unless clearly indicated.

Different bases (like ointment, cream, lotion, gel ...etc.) might change the potency and the indication of the agent (refer to table-11.1).

- ***CONTRAINDICATIONS:***

Hypersensitivity to any corticosteroid. Monotherapy in primary bacterial infections such as impetigo, paryonchia,

erysipelas, cellulitis, angular cheilitis, erythrasma, treatment of rosacea, perioral dermatitis or acne; use on the face, groin or axilla; and prolonged ophthalmic use.

- ***DOSAGE FORMS:***

Refer to table-11.1.

- ***RECOMMENDED DOSAGE:***

Directions: To be applied sparingly to affected areas 2 to 4 times a day.

*For external use only. Avoid contact with the eyes unless indicated.

*Some studies show that applying corticosteroids once or twice a day is as effective as three or more. Some researches advise applying it twice a day until clinical response is achieved and then only as frequently as needed to control the condition.

*Short term or intermittent therapy (every other day, or once a week, or 3 to 4 consecutive days per week) may be more effective and cause fewer adverse effects than continuous regimens using lower potency products.

*Use low potency agents in children, on large areas, and on body sites especially prone to steroid damage such as face, scrotum, axilla, flexures and skin folds. Reserve higher potency agents for areas and conditions resistant to treatment with milder agents.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use in pregnancy only if the potential benefits outweigh the potential hazards on the fetus (Category C). Corticosteroids are teratogenic in animals when administered systemically at relatively low dosages. The more potent corticosteroids are teratogenic after dermal application in animals. No well-controlled studies have been done on pregnant women.

Lactation- Exercise caution. It is not known whether topical corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk.

Children- Children may be more susceptible to topical corticosteroid-induced HPA axis suppression and Cushing-syndrome. Limit administration to the least amount compatible with effective therapy. Chronic corticosteroid therapy may interfere with the growth and development of children.

- ***PRECAUTIONS AND WARNINGS:***

-Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, Cushing's syndrome, hyperglycemia and glycosuria. Conditions that increase systemic absorption include: application of potent corticosteroids, use over large areas, prolonged use, and occlusive dressings.

-Local irritation may occur and requires discontinuation of the agent. Allergic contact dermatitis might develop especially when applied to dry skin or open wounds.

Avoid using potent corticosteroids on the face, groin and axillae. It might result in atrophic changes.

-Do not use topical corticosteroids as sole therapy on widespread plaque psoriasis. It has been reported that withdrawal of the treatment of psoriasis with corticosteroids may provoke pustular psoriasis.

-The use of corticosteroids on infection sites might worsen the infection. Discontinue the use of corticosteroids and apply an antifungal or an antibacterial agent.

-Occlusive dressings might increase the chance of bacterial infections. Use appropriate measures.

- ***ADVERSE EFFECTS:***

Local burning, itching, irritation, erythema, dryness, pruritis, hypopigmentation, allergic contact dermatitis, numbness of fingers, stinging, cracking, skin atrophy, secondary infections, maceration of the skin.

Prolonged application around the eyes can cause cataracts, and glaucoma.

(Systemic adverse reactions are common. Refer to Chapter 1: anti-inflammatories drugs for more details.)

Table–11.1: Relative Potency of Selected Topical Corticosteroidal Products		
DRUG	**DOSAGE FORM**	**CONCENT-RATION**
I. Very High potency		
Augmented betamethasone dipropionate	Ointment	0.05%
Clobetasol propionate	Cream, Ointment	0.05%
Diflorasone diacetate	Ointment	0.05%
II. High potency		
Augmented betamethasone dipropionate	Cream	0.05%
Betamethasone dipropionate	Cream, Ointment	0.05%
Bethamethasone valerate	Ointment	0.1%
Diflorasone diacetate	Cream, Ointment (emollient base)	0.05%
Fluocinonide	Cream, Ointment, Gel	0.05%
Fluocinolone acetonide	Cream	0.2%
Triamcinolone acetonide	Ointment	0.1%
Desoximetasone	Cream, Ointment	0.25%
	Gel	0.05%
III. Medium potency		
Betamethasone dipropionate	Lotion	0.05%
Betamethasone valerate	Cream	0.1%
Fluocinolone acetonide	Cream, Ointment	0.025%
Triamcinolone acetonide	Cream , Ointment	0.025%
	Lotion	0.1%
	Cream, Ointment	0.5%
Fluticasone propionate	Lotion	0.05%
	Cream, Ointment	0.005%
Desoximethasone	Cream, Ointment	0.05%
	Cream	
IV. Low potency		
Desonide	Cream	0.05%
Dexamethasone sodium phosphate	Cream	0.1%
Fluocinolone acetonide	Cream, Solution	0.01%
Hydrocortisone	Lotion	0.25%
	Solution	1%
	Cream, Ointment	0.5%, 1%,
Hydrocortisone acetate	Lotion	2.5%
	Cream, Ointment	0.5%, 1%

* *Drug Facts and Comparisons, 2000:1633-34.*

2) PREPARATIONS FOR ACNE

Acne vulgaris is the most common adolescent skin disorder. It is an inflammatory pilosebaceous disease that involves oil glands and hair follicles of the skin, primarily on the face and trunk. Acne occurs due to an interaction between hormones, keratinization, sebum, and bacteria which determines the severity of the acne. **Acne is rarely cured, but its symptoms can be controlled. Agents will reduce symptoms and minimize permanent scarring.**

The management of acne depends on its severity. Some researches indicate that acne can be aggravated by different kinds of food such as peanuts, chocolate, fats and carbohydrates in an indirect way. So dietary restrictions can be the first step in the management of acne. The skin should be cleansed from excess sebum, the ducts should be unblocked, and the pilo-sebaceous orifice should not be closed. The patient should avoid any cosmetics that are oil based. The agents that can be used can be either topical or oral agents depending on the severity of the lesions.

There is another kind of acne called 'deep' acne, which causes deep lesions and requires vigorous treatment. In these cases a referral to a dermatologist is required to decrease scarring and help prevent further lesions. Oral antibiotics and isotretinoin might be required.

The treatment of acne depends on the severity of the condition. Superficial acne may be treated with washing the affected areas at least twice a day with medicated or non-medicated soap. For more complicated cases or in cases of superfacial pustular acne refer the patient to a dermatologist.

In this section the most used products for the treatment of acne are discussed.

Retinoic Acid (Tretinoin)

- ***DRUG SUMMARY:***

Retinoic acid is a vitamin A acid with an unknown mode of action. It is reported that it increases the turnover of follicular epithelial cells and stimulates mitotic activity.

- ***INDICATIONS:***

Used for topical treatment of acne vulgaris. It can also be used to improve spots and wrinkles.

- ***CONTRAINDICATIONS:***

Hypersensitivity to it or any of its metabolites.

- ***DOSAGE FORMS:***

Cream, gel, solution.

- ***RECOMMENDED DOSAGE:***

Directions: Apply once a day, before bedtime, to the entire affected area. Hands should be washed thoroughly after applying.

*If irritation occurs after application, apply every other day to minimize the irritation. Local erythema and peeling might occur at the application site.

*During the early weeks of therapy, exacerbation of inflammatory lesions may occur due to the action of the medication on deep, previously undetected lesions; which is not a reason to discontinue therapy.

*Therapeutic results should be seen after 2 to 3 weeks, but in some cases it might take up to 6 weeks.

*Patients may use cosmetics, but the face should be washed out and cleansed before applying Tretinoin.

*Keep away from the eyes, mouth, angles of the nose, and mucous membranes.

- ***USE IN SPECIAL CASES:***

Pregnancy- Elevated serum concentrations of retinoic acid in early gestation are considered teratogenic in humans. Because topical preparation administration (*if occlusive dressings are not used*) has relatively poor systemic absorption, it is thought not to be of significant risk to the fetus. Congenital

malformations have rarely been reported following topical use, but without conclusive evidence. Use should be avoided (Category C).

Lactation- Exercise caution. It is not known whether topical corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. The minimal absorption that could result precludes any clinically significant amounts in breast milk. It is preferably to avoid use.

- ***PRECAUTIONS AND WARNINGS:***

-Avoid excessive application since it might worsen the condition. Application of a thin layer on the affected area should be enough to give good results.

-Sun exposure should be minimized or avoided when applying tretinoin. Sunscreen products are recommended to avoid sunburns and irritation.

- ***ADVERSE EFFECTS:***

Sensitive skin may become red, inflamed, and blistered. Discontinuation of tretinoin is advised until the skin improves.

Decreasing the frequency of application might be helpful.

Temporary hyper- or hypo-pigmentation is possible. **All adverse effects have been reversible upon discontinuation.**

- ***INTERACTIONS:***

Significant skin irritation might occur when using other anti-acne topical products such as ***sulfur*****,** ***benzoyl peroxide*****, or** ***salicylic acid***.

Medicated soaps, cleansers, and astringents containing high percentage of ***alcohol***, might have an extensive drying effect which might increase irritation and interact with tretinoin.

- ***OVERDOSE:***

Oral ingestion of tretinoin may lead to the same side effects as those of vitamin A oral intake. *(for more details refer to the vitamins & minerals chapter.)*

- ***BRANDS:***

Locacid (Fabre/Mediline), Retavit (CTI/CTS), Retin-A (Cilag/JC Health Care).

Benzoyl Perxoide

- ***DRUG SUMMARY:***

Benzoyl peroxide is an antibacterial agent. It removes excess sebum, reduces fatty acids and lipids produced by the causative bacteria, and causes peeling and drying.

- ***INDICATIONS:***

Treatment of mild to moderate acne vulgaris and oily skin. It might be used in severe acne as an adjunct with other agents such as antibiotics, sulfur/salicylic acid preparations.

- ***CONTRAINDICATIONS:***

Hypersensitivity to the drug. Patients allergic to benzoic acid or its derivatives might be allergic to benzoyl peroxide.

- ***DOSAGE FORMS:***

Liquid: 2.5%, 5%, 10% (used as wash).

- ***RECOMMENDED DOSAGE:***

Directions: Prior washing of the affected area with medicated or non-medicated soap is required.

*For external use only. Avoid contact with the eyelids, lips, mucous membranes and damaged skin.

*When used as a cleanser, wash once or twice a day, rinse thoroughly and pat dry.

*Control the amount of drying and peeling by modifying dose frequency or concentration.

*When used as the primary treatment of acne: apply once daily; gradually increase to 2-3 times a day if needed. If excessive dryness occurs, dosage should be reduced.

*In some cases severe irritation might develop causing discontinuation of therapy until the irritation clears. Resume therapy with less frequent application.

- ***USE IN SPECIAL CASES:***

Pregnancy- Use in pregnant women only if clearly needed. It is not known whether

benzoyl peroxide can cause fetal harm when used by pregnant women (Category C). Regular use should be avoided.

Lactation- It is not known whether benzoyl peroxide is excreted in breast milk. Administer with caution to nursing mothers.

Children- Safety and efficacy in children under 12 yrs. have not been established.

- ***PRECAUTIONS AND WARNINGS:***

-Benzoyl peroxide is an oxidizing agent that might bleach the hair or colored fabric.

-Some of these products contain sulfites, which might cause allergic reactions in susceptible patients. **Use caution or avoid its use in patients allergic to sulfites.**

-Some studies indicate that it is a tumor promoter, however, there is no evidence that the drug is a carcinogen in humans.

- ***ADVERSE EFFECTS:***

Excessive drying, peeling, erythema, and possible edema. Allergic contact dermatitis has occurred in some cases.

- ***INTERACTIONS:***

Tretinoin use with benzoyl peroxide might cause excessive skin irritation.

- ***OVERDOSE:***

Symptoms include: excessive scaling, erythema or edema.

Treatment of overdose starts by discontinuing of application. Reinstate application at reduced dosage after signs and symptoms disappear. To increase the healing of the irritation, use emollients and cool compresses or topical corticosteroids in severe cases.

- ***BRANDS:***

Acne Mask (Neutrogena/Lapidot), Akneroxid (Hermal Chemie), OXY (SK-Beecham).

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3) SUNSCREENS

Ultraviolet (UV) light is the most energetic and thus potentially the most damaging to human skin. UV light is differentiated into UVC (200-290 nm), UVB (290-320), and UVA rays (320-400 nm). Traditional thinking has long held that UVA was much safer than UVB. UVB was known as tanning vs. UVB which was burning. Now, it is realized that UVA is just as damaging. UVB radiation is absorbed primarily by the epidermis, while the longer wavelengths of UVA penetrate the skin more deeply-into the dermis-where they may damage underlying structures including blood vessels.

Protection from UV rays can be achieved by three means: avoiding exposure to sunlight; by remaining out of the sun, covering the skin with protective clothing, and using chemical agents on the skin to absorb or block solar rays.

Chemical agents that block or absorb UV rays have been categorized traditionally as physical (inorganic) sunblocks or chemical organic sunscreens (see table 11.2). This is based on their mechanism of action in protecting the skin against UV radiation.

Physical sunscreens are opaque formulations that reflect, scatter, absorb, and/or physically block radiation. They are important because they block the entire UV spectrum. They are best used in protecting localized, sun sensitive areas such as the nose, lips, nasal mucosa, and shoulder. Their effectiveness depends on the thickness of application. They can be messy and cosmetically unappealing for application over large areas of the body. *Chemical sunscreens* work by absorbing and thus blocking the transmission of UV radiation to the epidermis. These are more varied in characteristics than physical sunscreens. They can be useful for daily application over a prolonged period and most are cosmetically acceptable preparations.

Products available contain combinations of these agents to cover most UV radiation.

Sunscreens are divided into different kinds or strengths depending on the **Sun Protection Factor (SPF).** The SPF is the sunscreen's effectiveness in protecting against sunburn; the SPF value is the length

of time an individual may be exposed to UV radiation when a sunscreen is applied, compared to when it is not, and not get burned (minimal erythema). The range extends from a value of 2 (minimal) to (45 ultra-high protection). An SPF-15 sunscreen absorbs 93% of UV radiation, while increasing the SPF to 30 raises it to 96.7%.

Skin types differ from person to person. That is why there are different types of sunscreens to suit these different types of skin. Also, certain medication use (table 11.3) can cause photosensitivity (photo-allergy or phototoxicity) that one should caution patients about, and advise use of protective sun measures.

Sunscreen products maybe used safely on infants younger than 6 months of age when adequate clothing and shading are not available.

It is also important to note that products are labeled as water-resistant or water-proof (very water-resistant), depending on the ability to bind to the skin, and their resistance to removal by sweating, exercise or swimming (substantivity). Water-resistant products remain effective in water for at least 40 minutes, while water-proof last 80 minutes.

Advise people to use sunscreens correctly, since many use an insufficient quantity resulting in less than expected protection. Application should be 15-30 min before going into the sun, and reapplied 3-4 times if exercising outdoors or swimming. Cotton clothes provide best protection as long as they don't become wet. Protection is needed even on cloudy days because 60-80 % of UV rays can pass through clouds.

Topical sunscreen products are considered complementary drugs in the WHO essential drug list, without any specific agents listed.

Table 11.2: Available Physical (Inorganic) and Organic Sunscreens *		
Physical Agents	**Range of protection**	**Special notes**
Titanium dioxide	290-700 nm	Provide best protection against UV light from reaching the skin. They can cause folliculitis, acne, and may stain clothing.
Zinc Oxide	290-700 nm	
Organic Sunscreen Agents		
Aminobenzoic acid (PABA)	260-313 nm	Provide acceptable efficacy against UVB, but transmits most UVA.
PABA esters: Padimate O	290-315 nm	Esters are more acceptable products because they are less irritating and can be more substantive.
Cinnamates: Octylmethoxycinnamate Cinoxate	 280-310 nm 270-328 nm	Their effectiveness depends mainly on the properties of the vehicle used. May cause or aggravate eczema or acne.
Salicylates: Homosalicylate Octyl salicylate Triethanolamine salicylate	 290-315 nm 260-310 nm 296-320 nm	They are week sunscreens, therefore must be used in higher concentrations. They do not bind well to the skin and maybe removed easily by sweat.
Avobenzone (Parasol 1784)	310-400 nm	Block long wave UVA.
Benzophennones: Oxybenzone Dioxybenzone Sulisobenzone	 270-350 nm 206-380 nm	They are often combined with other sunscreens to provide broader UVA protection. They are reported to aggravate eczema or acne.
Anthranilites: menthyl anthranilate	 322-350 nm	Weak UV blocker, so it is combined with other sunscreen agents.

** Kim HI, Ghalai FE, Tennessen WW. Here comes the sun. Contmp Pediatr. 1997;14:41-69.*

Table-11.3: A Partial List of Drugs that May Cause Photosensitivity	
Medications	**Examples**
Antihistamines	cyproheptadine, diphenhydramine
Anti-infectives	tetracycline, nalidixic acid, sulfonamides
Antipsychotic agents	phenothiazines, haloperidol
Diuretics	thiazides, acetazolamide, amiloride
NSAIDs	phenylbutazone, ketoprofen, naproxen
Miscellaneous	captopril, carbamazepine, quinidine, oral contraceptives, amiodarone, coal tar

(For more information about these agents, refer to each individual agent in previous chapters)

Chapter 12: VITAMINS AND MINERALS

A) VITAMINS

1. Fat-Soluble Vitamins

Vitamins A, D, E, K

2. Water-Soluble Vitamins

Vitamins B_1, B_6, B_{12}, Folic acid, Niacin, Ascorbic acid

B) MINERALS

1. Ca

2. Fe

3. F

4. I

5. K

A) VITAMINS

Vitamins are potent non-caloric, organic compounds that are essential in small quantities for the specific body functions of growth, maintenance, and reproduction. Because most vitamins (with the exception of vitamin D) cannot be synthesized by the body in sufficient quantities to meet metabolic needs, they must be supplied by food or supplementation. **The only disease a vitamin can cure is the one caused by a deficiency of that vitamin.** The best vitamin sources are the natural ones (i.e. vegetables and fruits). However, the way the food is prepared, served and stored have major influence on its nutritional value. Guidelines for the clinical assessment of nutritional status include: evaluation of growth, development, fitness, medical and dietary history observations of signs consistent with deficiencies.

The Recommended Dietary Allowances (RDAs) are levels of daily intake of essential nutrients that, based on scientific knowledge, the Food and Nutrition Board Judges approved to be adequate to meet the known nutrient needs of most healthy persons. They are not requirements, they are recommended daily intakes of certain essential nutrients. Based on available scientific knowledge, they are considered to be adequate. They vary for age and sex, with extra allowances for women during pregnancy and lactation, as well as from one country to another. They also don't apply to cover therapeutic nutritional requirements in cases of disease or other abnormal states (i.e., metabolic disorders, weight reduction, drug therapy . . .).

Although it is generally believed that vitamins are harmless, there are real dangers related to the use of some of them. **Excessive use of one or more vitamins may causes toxicity** (i.e. Vitamin D)**, or may cause relative deficiencies of other essential micro-nutrients** (i.e. salts and minerals)**.**

Vitamins are classified in 2 categories: fat soluble vitamins and water-soluble vitamins.

Fat soluble vitamins (i.e. A, D, E, K) generally occur in fats and oils of foods. Once absorbed they are stored in the liver and fatty tissue until the body needs them. Since they are stored and excess can be taken in, especially in the form of supplements, toxicity can occur. For example, high dose of vitamin A, can produce loss of appetite, itching, loss of weight and enlarged liver and spleen *(refer to toxicity symptoms of other vitamins*).

All other vitamins are *water soluble vitamins* (i.e. B, C,...). Cooking and over-washing can take them out of the foods. The body absorbs them easily, and just as easily excretes them in the urine, so adverse effects are diminished. Nonetheless some water-soluble vitamins can still cause diarrhea by irritating the intestines (i.e. doses of vitamin C > 1 gm/d), or interfere with common laboratory results (also vitamin C).

Access to **good nutrition should be the priority** for public health in all countries. Encouraging individual and government spending on unnecessary vitamin preparations does not contribute to the public health need. It is wrong to suggest that a capsule or tablet can replace the nutrients in foods, and it diverts efforts to solve problems of hunger, malnutrition and vitamin imbalances.

Table 12.1: Fat Soluble Vitamins

Vitamin (other names)	Natural Sources	Deficiency Symptoms	Toxicity Symptoms	Comments
Vitamin A [WHO] (Retinol, retinal, carotene)	Fortified dairy products, eggs, liver, spinach and other dark leafy greens, deep orange fruits and vegetables.	Impaired growth, painful joints, cracked teeth, depression, night blindness, spots, and possibly anemia (microcytic).	Red blood cell breakage, nose bleeds, bone pain, headaches, abdominal cramps and pain, vomiting, diarrhea, over-reactivity of immune system, blurred vision, loss of appetite, dry skin, liver and spleen enlargement as well as bone and joint pain.	In cases of deficiency; Adult dose: 10000-20000 IU/d for 2 months. Child (1-8 y): 5000-10000 IU/d for 2 months. RDA=child: 400-700 mcg RE, adult males: 1000 mcg, female: 800 mcg.
Vitamin D (Calciferol, chole-calciferol)	Self-synthesis with sunlight, fortified milk, eggs, liver, and sardines.	Rickets; (Ca abnormalities), abnormal growth, misshaped bones (bowing of the legs), joint pain, malformed teeth, muscle spasm, osteomalacia.	Raised blood calcium, excessive thirst, headaches, irritability, loss of appetite, kidney stones, mental and physical retardation. * Effectiveness of supplements depends on adequate Ca intake.	Supplements containing > 100 IU are not advisable. * Doses of 400 IU (10 mcg of cholecalciferol) are not advisable unless there is a specific disease state. * Dose for Rickets is 1000-4000 IU. Avoid use of supplements in infants and children who have adequate exposure to sunlight or a normal diet. RDA=10 mcg cholcalciferol (100 IU).
Vitamin E (Alpha-tocopherol)	Polysaturated plant oils (margarine, salad dressings), green and leafy vegetables, wheat germ, nuts and seeds.	Red blood cell breakage, anemia, degeneration of nervous and muscular systems, weakness, leg cramps, fibrocystic breast disease.	Nausea, headache, blurred vision, flatulence and diarrhea. With doses of ≥ 1000 IU/ 24h chronic use it augments the effects of anti-clotting medication.	300-400 IU/24 hours prescribed for deficiencies. There is no evidence that it is protective against arterio-sclerosis, cancer, pulmonary damage, heart disease, peptic ulcer, burns, or inflammation of skin disorders. RDA= child: 10 IU, males and pregnant females: 15, females:12, lactating females: 16-18.
Vitamin K (Phylloquinone, phytona-dione)	Bacterial synthesis in the digestive tract, liver, green leafy vegetables, cabbage type vegetables, milk.	Deficiency is always associated with pathologic conditions; may be due to malabsorption syndrome or liver disease. Hemorrhaging is the most common symptom.	Interference with anti-clotting medication, vitamin K analogues may cause jaundice. Hemolytic anemia, hyperbilirubinemia have been reported with large doses in newborns.	Vitamin K supplementation will not counteract the anticoagulant effect of heparin, but it counteracts the effects of warfarin. RDA=child: 15-45 mcg (according to age) Adult males: 65-80 mcg Adult females: 45-65 mcg.

Table 12.2: Use in Special Cases				
Vitamin	**Pregnancy**	**Lactation**	**Renal Disease**	**Liver Disease**
A	Safety of amounts > 5000 IU/d during pregnancy has not been established. Avoid use in excessive doses, animal reproduction studies have shown fetal abnormalities.	RDA for nursing mothers is 6000 IU. Human milk supplies sufficient Vit. A for infants unless maternal diet is grossly inadequate.	Vit. A toxicity and elevated plasma Ca and alkaline phosphatase concentrations have been reported in chronic renal failure patients.	It is stored and metabolized in the liver. In liver cirrhosis Vit. A deficiency can occur, and supplementation is recommended.
D	Safety in amount > 400 IU/d is not established. Avoid larger doses, animal studies have shown fetal abnormalities.	Vit. D is excreted in breast milk in limited amounts. Monitor infants' serum Ca concentration if mother is taking large doses to avoid hypercalcemia in the child.	The kidney of uremic patients might not be able to adequately synthesize calcetriol (the active hormone formed form precursor of Vit. D). Hypocalcemia and secondary hyperparathyroidism that can lead to metabolic bone disease of renal failure.	Elevated liver enzyme tests can occur with high doses. Use caution.
E	Safety is not established. No reported teratogenicities in human or animal studies.	No harmful effects have been noted.	No harmful effects have been noted.	Use caution with high doses.
K	It crosses the placenta, but not reported to cause harm to the fetus, or affect the reproduction capacity.	It is excreted in breast milk. Use only when clearly needed.	Use caution with high doses.	Repeated large doses of Vit. K may further depress liver function.

Table 12.3: Selected Water Soluble Vitamins				
Vitamin (other names)	**Natural Sources**	**Deficiency Symptoms**	**Toxicity Symptoms**	**Comments**
Vitamin B_1 (Thiamin, thiamine)	Pork, ham, liver, whole grains, legumes, nuts.	Beriberi, edema, enlarged heart, abnormal heart rhythms, wasting, weakness, difficulty walking, loss of reflexes, mental confusion, and paralysis.	No symptoms reported with doses of up to 500 mg.	Alcoholism and high carbohydrate diet may be causes of thiamin deficiency. Dose for Beriberi is 25 mg b.i.d. or t.i.d. for 5 days, followed by daily dose of 5 mg for 1 month. RDA= child: 0.7-1.3 mg, adult males: 1.5 mg, adult females: 1.1 mg.
Vitamin B_6 **WHO** (Pyridoxine, pyridoxal)	Milk, yogurt, meat, banana, leafy green vegetables, lentils, whole-grain, or enriched breads and cereals.	Cracks at corners of mouth, hypersensitivity to light, reddening of cornea, and skin rashes. Severe cases include convulsions, sideroblastic anemia, and peripheral neuropathy.	No toxicity has been reported. High doses of 200-600 mg have been shown to inhibit prolactin.	For deficiency, a dose of 50-200 mg/24 hours may be required RDA= child: 1-1.7 mg, adult males: 2 mg, adult females: 1.5 mg.
Vitamin B_{12} (Cyano-cobalamin)	Animal products: meat, fish, milk, cheese, eggs, . . . etc.	Anemia (large-cell type-macrocytic anemia), smooth tongue, fatigue, hypersensitivity reactions of the skin, neurological abnormalities: ataxia, parasthesia, hyporeflexia, Babinski, clonus and coma.	No toxicity symptoms known.	Anemia can be due to lack of intrinsic factor necessary for absorption. Supplementation is of no use. May mimic folate deficiency. ***Need to exclude folate deficiency anemia before starting to supplement with B_{12} therapy***. RDA= child: 0.7-2 ug, adult males and females 2 ug.
Niacin **WHO** (nicotinic acid, nicotin-amide, vitamin B) three	Milk, eggs, meat, poultry, fish, whole grain and enriched breads and cereals, and all protein-containing foods.	Pellagra, diarrhea, black-smooth tongue, irritability, loss of appetite, dizziness, mental confusion progressing to psychosis or delirium, flaky skin rash on areas exposed to sun.	Diarrhea, heartburn, ulcer irritation, vomiting, dizziness, painful flush and rash (niacin rush), sweating, abnormal liver function, low blood pressure.	Dose for Pellagra: 300-500 mg/d, in divided doses. For hyperlipidemias, in doses of 1-2 g t.i.d. RDA= child: 9-17 mg, adult male: 20 mg, adult female: 15 mg.

Vitamin (other names)	**Natural Sources**	**Deficiency Symptoms**	**Toxicity Symptoms**	**Comments**
Folic acid [WHO] (folate, folacin, pteroyl-gutamic acid)	Leafy green vegetables, legumes, seeds, liver, yeast, lean beef.	Anemia (macrocytic or megaloblasitic), GI disorders, suppression of immune system, smooth red tongue, depression, mental confusion, irritability and forgetfulness, fainting (masks vitamin B_{12} deficiency).	No toxicity reported. *** Folic acid in doses > 0.1 mg daily may obscure pernicious anemia in that hematological remission can occur while neurologic manifestations remain progressive.**	(Food canning, long exposure to heat, and extensive refining may destroy 50-100% of naturally occurring folic acid.) Correction of deficiency is usually 1 mg/24 hrs. *****Rule out pernicious anemia before administration of Folic acid.***** In populations with moderate to high prevalence anemia dose is **0.5 mg/24 hours** (WHO recom-mendations). Doses > 1 mg are not necessary except in some life-threatening hematological disease. RDA= child: 50-150 ug, adult male: 200 ug, adult female: 150-180 ug **In pregnant women:** The RDA for folate is 0.4 mg/24 hrs, and 0.8 mg/24 hrs if clinical symptoms are present. Studies have proved that folic acid supplementation can decrease the incidence of neural tube defect; it should be started before conception and continued until 12 weeks of pregnancy. The dose 0.4 mg, and 4 mg in those with previous history of neural tube defect.
Vitamin C [WHO,P] (Ascorbic acid)	Citrus fruit, cabbage type vegetables, dark green vegetables, strawberries, peppers, lettuce, tomatoes, potatoes, and mangos.	Scurvy, anemia (microcytic), pinpoint hemorrhages, suppression of immune system, bleeding gums, loosened teeth, muscle degeneration and pain, hysteria, bone fragility, rough skin, failure of wounds to heal.	Nausea, abdominal cramps, diarrhea, excessive urination, fatigue, insomnia, rashes, interference with medical tests, aggravation of gout symptoms.	Claims for use as prevention of common cold have been unsupported by well designed-controlled studies. Doses of > 200 mg are rarely indicated, even though most products on the market contain > 500 mg! High doses of 1 g/24 hours, increase side effects. RDA= child: 40-50mg, adult: 60mg.

Table 12.4: Use in Special Cases				
Vitamin	**Pregnancy**	**Lactation**	**Renal Disease**	**Liver Disease**
B_1	Safe. Studies have not shown an increased risk of fetal abnormalities.	It is not known if the drug is excreted in breast milk. No harmful effects have been reported.	Excess thiamin is excreted in the urine. No harmful effects have been reported.	In patients with liver disease (cirrhosis, encephalopathy) there is an increased need for thiamin use.
B_6	Requirements are increased during pregnancy and lactation to 2.0-2.5 mg/d. Do not use excessive amounts during lactating (> 10 mg/tablet) since pyridoxine may inhibit lactation by prolactin suppression.		It is metabolized in the liver and excreted in the urine. Use caution if using doses larger than RDAs.	
B_{12}	Requirements are increased during pregnancy and lactation to 2.6 mcg/24 hours. No harmful effects were reported. (Max. amount absorbed from a single oral dose is 1-5 mcg.)		No reports of harmful effects in these cases. Use caution in severe cases.	
C	It is not known whether it can cause fetal harm or can affect reproduction capacity. Do not take very large doses.	Ascorbic acid is excreted in breast milk, but no harmful effects have been reported.	No reports of toxicity.	
Folic Acid	Safe. Pregnant women are more prone to develop folate deficiency, leading to complications of pregnancy and fetal abnormalities. Studies in pregnant women have not shown any harmful effects with the increased dose recommendations. *(See table 12.3)* **> 1 mg doses are not necessary.**	Folic acid is excreted in breast milk, without any harmful effects to the nursing child. RDAs during lactation are 0.26-0.28 mg/day.	No reports harmful effects.	
Niacin	Use of doses larger than RDAs in pregnancy and lactation have not been studied for safety. Use only when clearly needed.		Use caution. 1/3 of the dose is excreted unchanged in the urine.	Prolonged use of very high doses (> 6 g/24 hrs.) can cause liver damage.

Minerals constitute about 4% of body weight. Minerals are present in the body in a diverse array of organic compounds such as phosphoproteins, phospholipids, hemoglobin, and thyroxin, in inorganic compounds such as sodium chloride, potassium chloride, calcium and phosphate as free ions. They are involved in regulating cell membrane permeability, osmotic pressure, and acid-base and water balance in the body.

Unlike vitamins, minerals exist in plants in varying amounts, according to the composition of the soil in which the plant is grown.

Vitamins and minerals, particularly iron, are regularly prescribed or taken during pregnancy. The belief that because they are 'natural' substances and are harmless, causes a lot of overuse. The need for iron supplementation in pregnant women, is a controversial subject. It is important to note that international agencies such as WHO and UNICEF strongly promote and support the routine iron supplementation during pregnancy. That is especially done in those countries where pregnant women are more likely to be or become anemic due to poverty, malaria epidemics and/or high prevalence rates of intestinal parasites. However, many industrialized countries have abandoned this policy preferring a selective iron supplementation according to the patient's need.

Most pregnant women have a lower iron level in the blood since the mother's blood volume is increased in order to supply the growing baby. The human body, if not malnourished, has large reserves of iron in the liver and bone marrow, and during pregnancy these stores are used. But the demands made on women's bodies from blood loss due to early, frequent and closely spaced pregnancies make them vulnerable to nutritional deficiencies, especially anemia.

WHO definition of anemia for pregnant women is when hemoglobin blood level is **below 11 g/100 ml** (hemoglobin > 80%). The WHO has suggested that all pregnant women in high-risk areas receive iron supplements (due to the large numbers who suffer iron-deficiency anemia), especially during the last four to five months of pregnancy. Iron supplementation, however, is a curative approach, and emphasis should be on prevention.

Administration of combination preparations of iron with folate, B_{12} or cobalt has little justification in a pregnant woman unless clearly indicated. It is better to **identify type of anemia of the patient before prescribing** or recommending supplementation when possible. Furthermore, when supplementation is implemented, it should not keep out further regular Hb-level tests and follow-ups of antenatal visits to assure efficacy, better compliance in taking the treatment and giving proper dietary counseling.

The major mineral content of the skeleton consists of calcium and phosphorous. Ca is another element that requires special attention in women's health. Since women are 6-8 times more likely to get osteoporosis (often known as brittle bone disease) than men, it is important to start prevention measures including education to all women at high risk *(refer to the RDAs table for needs at the different stages)*.

There are no sufficient studies or data on our region that records prevalence of nutritional deficiencies. The primary health care provider's role is to screen and prevent such cases when possible. The improvement of general nutrition is the most important in all, whether children or women before and during pregnancy, as well as giving supplementation when needed.

Table 12.5: Summary of Selected Minerals				
Mineral	**Natural Sources**	**Deficiency Symptoms**	**Toxicity Symptoms**	**Comments**
Ca [WHO,P] **(calcium)**	Milk and milk products, small fish (canned sardines with bones), bean curd, broccoli, beets, greens and legumes.	Stunted growth in children, adult bone loss (osteoporosis).	Excess Ca is excreted except in hormonal imbalance states. * It has not been shown that Ca causes fetal harm when taken as supplements.	Absorption of supplements varies between Ca salts. Ca carbonate has the highest content of elemental Ca. Side effects include GI disturbances such as nausea and constipation. RDA= child: 800 mg, adult: 800 mg-1200 mg.
Fe [WHO,P] **(iron)**	Red meat, fish, poultry, shellfish, eggs, legumes, dried fruits, green leaves. *** People with normal Fe levels should not take Fe supplements chronically.**	Fatigue, weakness, iron deficiency (pernicious) anemia, split or spoon-shaped nails, sore tongue, dyspnea on exertion, palpation.	Acute overdose of 200 mg/kg may be fatal. **Iron overload:** infections, liver injury, possible increased risk of heart attack, acidosis, bloody stools, and shock.	Supplements may cause GI discomfort, nausea, diarrhea or constipation, and dark stool. Advise patient to eat foods rich in fiber to prevent diarrhea or constipation. * Sustained release or enteric-coated preparation reduce the amount of available iron, since they transport iron beyond the place of absorption, the duodenum. RDA= child: 10 mg, adult male: 10-12 mg, adult female: 15 mg. Pregnant: 30 mg.
F [WHO] **(fluorine)**	Municipal water (not to exceed 2-8 parts per million), mouthwash. (Each city should test their water supply for F levels).	Dental decay, increased risk of osteoporosis as the person gets older.	Salivation, abdominal pain, vomiting, diarrhea, dehydration, thirst, tremor, mental irritability, dental fluorosis (molting of tooth enamel) with chronic over dosage of Ca & F.	F supplements can be given to children as a preventive measure for dental decay in areas with low F level in the water. RDA= child: 0.7-2 mg, adult male: 4 mg, adult female: 3 mg.
I [WHO] **(iodine)**	Salt water, fish, vegetables produced in soil with high content of iodide.	Hypothyroidism (goiter), cretinism.	Depressed thyroid activity. Chronic intoxication (iodism), include unpleasant taste burning in mouth or throat, soreness of the teeth and gums, swelling of eyes lids.	Iodine supplements should be only administered under direct medical supervision. Iodide (the reduced form of iodine) crosses the placenta readily. RDA= 70-150 ug, adult: 150ug
K (potassium)	All whole/fresh foods: meats, milk, fruits (especially bananas), vegetables, grains, legumes.	Deficiency accompanies dehydration, causes muscular weakness, paralysis and confusion. Can cause death.	Muscular weakness, triggers vomiting, irregular heart beats in susceptible patients. In patients with renal failure do not use to avoid hyperkalemia or cardiac arrest!	GI discomfort (i.e. nausea, diarrhea, etc.) are common side effects of supplements. Can decrease by taking the potassium supplements with meal.

Table 12.6: Significant Drug Interactions		
Vitamin/ Mineral	**Drug involved**	**Description**
A	Cholestyramine	Absorption of Vit. A is reduced.
	Mineral Oil	Use of mineral oil interferes with the intestinal absorption of Vit. A.
	Oral contraceptives	These significantly increase plasma Vit. A levels.
B_6	Levodopa	Pyridoxine (B_6) reduces effectiveness of levodopa. Avoid supplementation that contain > 5 mg pyridoxine/24 hours in such patients.
	Phenobarbital, phenytoin	Serum levels of these drugs maybe decreased, leading to sub-therapeutic levels. Advise patients taking these drugs not to take high dose supplements.
B_{12}	Aminosalicylic acid	The biologic and therapeutic action of Vit. B_{12} may be reduced. There is no need to administer aminosalicylic acid to patients with B_{12} deficiency (megaloblastic anemia), who are taking supplementation. An abnormal Schilling test and false symptoms of Vit. B_{12} deficiency may also occur.
	Alcohol	Excessive alcohol intake (longer than 2 weeks) may cause malabsorption of vitamin B_{12}.
C	Oral estrogen	Ascorbic acid increases serum levels of estrogen contained in oral contraceptives or estrogen replacement therapy, leading to increased adverse effects. Warn patient against intake of high doses of Vit. C supplements.
	Warfarin	The anticoagulant action of warfarin may be reduced. Do not co-administer Vit. C in large doses.
	Glucose lab. tests	Doses of ≥ 500 mg Vit. C, will cause false negative urine glucose tests. Advise patient against intake of this vitamin supplementation 48-72 hours before conducting blood/urine tests.
D	Antacids/Mg containing	Hypermagnesemia may develop in patients with chronic renal disease.
	Digitalis Glycosides	Hypercalcemia in patients on digitalis may precipitate cardiac arrhythmias. Patients on Digoxin should avoid use of high doses of Vit. D supplements.
	Mineral oil, Cholestyramine	Reduce absorption of Vit. D, especially with prolonged use. Monitor patients who are taking these drugs chronically, for signs of deficiency.
E	Oral anticoagulants	High doses of Vit. E increases the effect of anticoagulants, so it increases the risk of bleeding.
K	Anticoagulants	Anticoagulant effects are antagonized by Vit. K. Physicians should warn patients against taking supplements while on this medication.
Folic Acid	Aminosalicylic acid	Decreased serum folate levels may occur during concurrent use. Avoid concomitant use unless clearly needed.
	Hydantoins	If folic acid is required *(refer to drug interactions)*, need to monitor serum hydantoin (i.e. phenytoin) levels to avoid lower therapeutic levels of the anticonvulsant, and adjust dosage as needed.
Niacin	Lovastatin	It has been reported that co-administration of niacin have resulted in rhabdomyolysis (a fatal disease marked by destruction or degeneration of skeletal muscles). Avoid co-administration.
	Sulfinpyrazone	Uricosuric effect may be inhibited by nicotinic acid. Advise patient against taking large dose supplementation if using this medication.

Ca salts	Atenolol	Bioavailability of atenolol may be decreased, resulting in decreased beta blockade. Warn patients against large dose supplementation.
	Caffeine	High intake of beverages containing caffeine (> 10 cups/day of coffee) increases loss of Ca though the urine.
	Iron Salts	GI absorption of iron may be reduced. If both minerals are indicated for use, space out their administration time, or use Ca carbonate and not another Ca salt.
	Tetracyclines	The absorption and serum levels of tetracyclines may be decreased, decreasing its anti-infective response. Do not co-administer. Warn patients.
	Verapamil	High doses of Ca supplements increase the toxicity of verapamil. This can be reversed by discontinuing the Ca salts (supplement).
Fe Salts	Antacids Cimitidine	GI absorption of iron is reduced. Do not administer at the same time interval.
	Ascorbic acid	Ascorbic acid may enhance the absorption of Iron from the GI, but this increase may not be significant.
	Levodopa, Penicillamine, Quinolones	Marked reduction of the absorption of this medication , may be due to chelation or complex formation with iron. Do not co-administer.
	Tetracyclines	Co-administration decreases absorption of both drugs, due to complex formation. Do not co-administer, and warn the patient.
	Coffee, tea	Consumption of these with a meal or 1 hour after the meal, may significantly inhibit the absorption of dietary iron. Warn your patients.
F	Dairy products	Do not administer fluoride supplements with dairy products. Calcium fluoride is formed, which is poorly absorbed.
I	Lithium carbonate	Concomitant use may result in hypothyroidism. Do not co-administer.
K	ACE Inhibitors	Concurrent use may result in hyperkalemia. Do not use concomitantly.
	Potassium-sparing diuretics	These diuretics will increase potassium retention and can produce severe hyperkalemia. Do not use concomitantly.
	Digitalis	Use caution in these patients. *Potassium* antagonizes digitalis preparations. A decrease in K level favor digoxin binding, increasing the likelihood of digitalis toxicity. Increased K levels decreases digitalis binding and decreases digitoxin effect. Be very careful.

Table 12.7: Possible Drug Induced Nutritional Deficiencies With Chronic Use		
Drug Group	**Drug**	**Nutrient Depleted**
Diuretics	Thiazides Furosemide	Potassium, zinc, magnesium Calcium, potassium, magnesium
Antihypertensives	Hydralazine	Vitamin B6 (Peripheral neuropathy)
Anticonvulsants	Phenytoin	Vitamin D (Rickets, osteomalacia) Folate (megaloblastic anemia)
Anticoagulants	Warfarin	Vitamin K
Anti-ulcer	Cimetidine, ranitidine (with long-term use)	Vitamin B_{12} (pernicious anemia)
Antibiotics	Tetracycline	Calcium, Vitamin K
Anti-tubercular	Isoniazid	Vitamin B_6, niacin, vitamin D
Antihyperlipidemic	Cholestyramine	Fat Vitamin A, Vitamin K, B_{12} and folate.
Analgesics	Aspirin	Ascorbic acid, potassium, iron.
Anti-inflammatory	Colchicine Sulfasalazine	Fat, Vitamin B_{12}. Folate
Antineoplastic, antipsoriatic	Methotrexate	Folate, Vitamin B_{12}, fat.
Laxatives	Mineral oil Phenolphthalein (bisacodyl)	Vitamins A, D, E, K, Calcium & phosphorus. Vitamin D, calcium, potassium.

Chapter 13: VACCINES

1) **BCG (Bacille Calmette-Guerin)**
2) **OPV / IPV (Oral and Inactivated Poliomyelitis Vaccines)**
3) **Tetanus Vaccine**
4) **DPT Vaccine (Diphtheria, Pertussis and Tetanus)**
5) **Measles Vaccine**
6) **MMR Vaccine**
7) **Hepatitis B Vaccine**
8) **Influenza Vaccine**
9) **Hib Vaccine (Haemophilus Influenza Type B)**

VACCINATION AND IMMUNIZATION

The vaccination and immunization terms are often used interchangeably.

Vaccination is a term that denotes the administration of any vaccine. **Immunization** is a more inclusive term denoting the process of inducing or providing immunity artificially by administering a vaccine. Immunization can be active or passive. *Active immunization* is protection produced by the person's own immune system, as response to the administration of a vaccine or toxoid. This type of immunity is usually permanent. *Passive immunization* means protection by products produced by an animal or human, that are transferred to another human as a vaccine. This protection usually disappears over time. (CDC, 1995).

There are three sources of antibody used in passive immunization vaccines:
[1] homologous pooled human antibody-immune globulin, [2] homologous human hyperimmune globulin, [3] heterologous hyperimmune serum- antitoxin.

Vaccines are classified into two basic types: *Live attenuated vaccines* that can be viral or bacterial (i.e., measles, mumps, oral polio, BCG), and *inactivated vaccines* that are composed of either whole or fraction, protein-based or polysaccharide-based, of either viruses or bacteria (i.e., influenza, pertussis, hepatitis B, tetanus, haemophilus influenzae type b).

Vaccines may come from different sources of pharmaceutical companies, and it is important to follow the directions of the manufacturer for administration, storage …etc, for each product. Vaccines have different inert (non-active) ingredients/ additives that can vary not only between different active material, but also from one manufacturer to another. If the recipient is sensitive to one of these additives, allergic reactions can occur. Some of the terms that we should be familiar with include:

Suspending fluids: These may be sterile water or saline or complex fluids containing small amount of protein or other constituents derived from the medium or biologic system in which the vaccine is produced (e.g. serum proteins, egg antigens, cell-culture-derived antigens).
Preservative, stabilizers, and antibiotics: These components of vaccines, antitoxins, and globulins are used to inhibit or prevent bacterial growth in viral cultures of the final product or to stabilize the antigens or antibodies. Allergic reactions can occur if the recipient is sensitive to one of these additives (e.g. phenols, albumin, glycine, and neomycin).
Adjuvants: Many antigens evoke insufficient immunologic responses when given in the natural state. Efforts to enhance immuno-genicity include mixing antigens with a variety of substances or adjutants (e.g. aluminum phosphate or hydroxide). Vaccines containing adjuvant must be injected deep into the muscle mass; they should not be administered subcutaneously or intradermally because this can cause local irritation, inflammation, granuloma formation, or necrosis.

Route of Administration:
It is important to refer to each product label for the proper site of administration. *Subcutaneous (SC) injections* are usually administered into the thigh of infants and in the deltoid area of older children and adults. *Intradermal (ID) injections* are generally given on the volar aspect of the forearm, except for human diploid-cell-rabies-vaccine, with which reactions are less severe in the deltoid area. The preferred sites for *Intra-muscular (IM) injections* are the anterolateral aspect of the upper thigh and the deltoid muscle of the upper arm. The buttock should not be used routinely as

a vaccination site for infants, children, or adults because of the risk of injury to the sciatic nerve.

Administration in Special Cases:

Vaccination During Pregnancy: There is no evidence that any live vaccine (including Rubella) causes birth defects. The concern of infecting the fetus is theoretical. However, since there is a theoretical possibility, live vaccine should not be given to pregnant women (except OPV in some cases).

There is no convincing evidence of risk from vaccinating pregnant women with inactivated virus or bacteria vaccines, toxoids, or IG preparations; therefore, in high risk areas the vaccine should be given. Tetanus and diphtheria toxoids are the only immunobiologic agents routinely indicated for susceptible pregnant women. Hepatitis B, influenza and pneumococcal vaccines are recommended for women at high risk for infection and for complication of influenza and pneumococcal disease.

Vaccination of Preterm Infants: Infants born prematurely, regardless of birthweight, should be vaccinated at the same chronological age and according to the same schedule and precautions as full-term infants and children. Birthweight and size are not factors in deciding if a child is to be vaccinated or not, except in hepatitis B vaccine as first dose should be given when the infant is 2 kg as seroconversion rate were lower in those less than 2 kg (*Red Book, 2000*).

Vaccination and Breast-Feeding: neither live or killed vaccines affect the safety of breast-feeding for mothers or infants. Breast-feeding does not adversely affect immunization and is not contraindicated for any vaccine. Breast-fed infants should be vaccinated according to routine recommended schedules.

Vaccinating Immunocompromized Persons: Severe complications have followed vaccination with live, attenuated virus vaccines and live bacterial vaccines among these patients. Killed or inactivated vaccines do not cause danger to such patients, and can be administered as recommended for healthy persons.

In general patients with asymptomatic-HIV, or limited immune system (i.e. asplenia or renal failure) should not receive live vaccines, expect for measles, mumps and rubella. For persons with symptomatic-HIV infection, MMR can be administered since there are accumulating evidence of its safety.

Vaccination during chemotherapy or radiation therapy should be avoided because antibody response is poor. Patients with leukemia in remission whose chemotherapy has been terminated for 3 months may receive live-virus vaccines.

Vaccines that are contraindicated for use in patients with severe immunocompromized states that are symptomatic-HIV infected persons or not HIV-related (i.e. leukemia, lymphoma) include: BCG, OPV, and yellow fever. Such patients who are exposed to measles should receive immune globulin (IG) regardless of prior vaccination status.

Vaccination of Persons with Hemophilia: People with bleeding disorders such as hemophilia are at risk of hematomas if given intramuscular injections. In such patients using the subcutaneous or intradermal route for the vaccines should be done. Some products may only be given intramuscularly; therefore, the manufacturer should be contacted for clear guidelines.

Spacing and Timing of Vaccines:

Some vaccines require administration of more than one dose for development of an adequate antibody response, and some vaccines require booster doses to maintain protection. Intervals between doses that are

longer than those recommended do not lead to a reduction in the final antibody levels. Therefore, it is not necessary to restart an interrupted series or add extra doses of vaccine (except oral typhoid). In contrast, giving doses of a vaccine at less than recommended intervals may lessen the antibody response and should be avoided. Doses given at less than recommended intervals should not be counted as part of a primary series.

Many vaccines can safely and effectively be given simultaneously (on the same day, not at the same site). [See tables-13.1 & 13.2].

1. Simultaneous administration:

In general, an inactivated vaccine can be given either simultaneously or at any time before or after a different inactivated or a live vaccine. They can be administered at separate sites. Simultaneous administration of the most widely used live and inactivated vaccines has not resulted in improved antibody response or increased rates of adverse reactions. Simultaneous routine administration of MMR, DPT, OPV and IPV is recommended. There are no contra-indications to simultaneous administration of any vaccine except with cholera and yellow fever vaccines.

2. Non-simultaneous administration:

When vaccines commonly associated with local or systemic side effects are given simultaneously, the side effects may be increased or exaggerated. Whenever possible, these vaccines should be given on separate occasions.

-Live-virus vaccines can interfere with the response of a tuberculin test. Tuberculin testing can be done either on the same day that the live-virus vaccines are administered or 4-6 weeks afterwards.

-If administration of an IG preparation becomes necessary because of imminent exposure to disease, live-virus vaccines can be given simultaneously with the IG product, with the recognition that vaccine-induced immunity might be compromised. The vaccine should be administered at a site remote from that chosen for the IG inoculation. Vaccination should be repeated about 3 months later unless serologic testing indicates that specific antibodies have been produced.

-Live attenuated vaccine viruses might not replicate successfully, and antibody response could be diminished when the vaccine given after IG preparations. killed vaccines can be given simultaneously or at any time before or after an IG product is used.

Table–13.1: Guidelines for Spacing Live and Killed Antigen Administration

Antigen combination	Recommended minimum interval between doses
≥ 2 killed antigens	No spacing. May be given simultaneously or at any interval between doses.
Killed and live antigens	No spacing required.
≥ 2 live antigens	4 wk minimum interval if not administered simultaneously

If a child is not up-to-date on his or her vaccination, it may be necessary to "accelerate" the normal schedule in order to catch up. In this situation it is important to know how closely the doses can be spaced and still be effective for that specific case.

Table - 13.2. Guidelines for Spacing the Administration of IG Preparations and Vaccines		
Simultaneous administration: immunobiologic combination		**Recommended minimum interval between doses**
IG and killed antigen		None. Given at different sites or at any time between doses.
IG and live antigen		Should generally not be given simultaneously. If unavoidable to do so, give at different sites and revaccinate or test for seroconversion in 3 months.
Non-simultaneous administration: immunobiologic administration		**Recommended minimum interval between doses**
First	***Second***	
IG	Killed antigen	None
Killed antigen	IG	None
IG	Live antigen	6 weeks and preferably 3 months. (*3 mon. for measles*)
Live antigen	IG	2 weeks.

The WHO Expanded Program of Immunization (EPI) has established recommendations for immunizing infants, children, and adults that are based on characteristics of vaccines, scientific knowledge about the principles of active and passive immunization, and judgments by public health officials and specialists in clinical and preventive medicine. Each country would modify the list according to its needs. Recommendations for immunizations practice scientific evidence of benefits, costs, and risks to achieve optimal levels of protection against infectious diseases.

[See EPI diseases, vaccine types and recommendations in tables-13.3, 4 & 5, and Palestinian recommendations in table-13.6].

Table – 13.3: Epidemiology of the EPI Target Disease							
Disease	**Agent**	**Reservoir**	**Spread**	**Transmissible Period**	**Subclinical Infection**	**Duration of Natural Immunity**	**Risk Factors for Infection**
Tuberculosis	Mycobacerium tuberculosis	Humans	Airborne droplet nuclei from sputum positive person	As long as sputum acid fast Bacilli positive	Common but not important in transmission	Not known. Reactivation of old infection commonly causes disease	Low access to care, Immunodeficiency Malnutrition Alcoholism Diabetes
Diphtheria	Toxin producing bacterium (*C. diphtheria*)	Humans	Close contact; respiratory or cutaneous	Usually < 2 wks. Some chronic carriers	Common	Usually lifelong	Crowding Low socioeconomic status
Tetanus	Toxin producing bacterium (*Cl. Tetani*)	Animal intestines soil	Spores enter body through wounds/ umbilical cord	No person-person transmission	No	No immunity induced by infection	Contamination of umbilical cord Agricultural work
Pertussis (Whooping-cough)	Bacterium (*B. Pertussis*)	Humans	Close respiratory contact	Usually < 3 wks. (starts before whoop is apparent)	Mild illness common may be not be diagnosed	Usually lifelong	Young age Crowding
Poliomyelitis (Polio)	Virus (serotypes 1,2 and 3)	Humans	Fecal-oral, close respiratory contact	Few days before and after acute symptoms	100-200 sub-clinical infections for each paralytic case	Type-specific immunity, lifelong	Poor environmental hygiene
Measles	Virus	Humans	Close respiratory contact and aerosolized droplets	4 days before, until 2 days after rash	May occur	Lifelong	Crowding Low socioeconomic status
Yellow fever	Virus	Humans Monkeys	Mosquito-borne infections	Common in endemic areas	-	Lifelong	Mosquitoes Occupation
Hepatitis B	Virus	Humans	Perinatal; child-child; blood; sexual spread	Chronic carriers > 30 yrs.	Common, especially in infants	If develops, lifelong	HbeAg+ mother Multiple sex partners; IVDU, working with blood products.

Table – 13.4: Characteristics of EPI Vaccines						
Disease	**Nature of vaccine**	**Minimum potency per dose**	**Form**	**Contains Additives/Adjuvants**	**No. of doses* and route**	**Heat stability**
Tuberculosis	Attenuated bovis	50,000 to one million live particles	Freeze dried	None	1 ID	Medium in dried form, low in reconstituted form
Diphtheria	Toxoid	At least 30 IU	Fluid	$Al(OH)_3/AlOP_4$ / Usually thimerosal (merthiolate)	3 IM	High
Tetanus	Toxoid	At least 40 IU in TT and 60 IU for T-component in DPT when tested in mice	Fluid	$Al(OH)_3/AlOP_4$ / Usually thimerosal	3 IM	High
Pertussis	Killed whole cell pertussis bacterium	At least 4 IU	Fluid	$Al(OH)_3/AlOP_4$ / Usually thimerosal	3 IM	Medium
Poliomyelitis	Attenuated live viruses of 3 types	Type 1 > 1 million Type 2 > 100,000 Type 3 > 600,000 infectious units	Fluid	None/ Stabilizer; Magnesium chloride or sucrose	4 Oral	Low
Measles	Attenuated live virus	At least 1000 infectious units	Powder for injection	Small amount of antibiotic & stabilizers	1 S/C	Medium in dried form, low in reconstituted form
Yellow fever	Attenuated live virus	At least 1000 mouse LD_{50} or the equivalent in PFU	Powder for injection	Stabilizing substances	1 S/C	Medium in dried form, low in reconstituted form
Hepatitis B	HbsAg	2.5 to 20 mcg of HbsAg	Fluid	$Al(OH)_3/AlOP_4$ / Usually thimerosal	3 IM	High

***** *Refer to individual drug monographs for scheduel and doses.*

Table – 13.5: Reported Vaccine Efficacy and Duration		
Vaccine	**Vaccine efficacy**	**Duration of immunity after primary series**
BCG	20-80% vs. TB 75-86% vs. meningitis and miliary TB.	Unknown; some evidence that immunity wanes with time.
Diphtheria Toxoid	97% clinical efficacy.	Antitoxin levels decrease after 10 years from the last dose. A booster administered every 10 years (as Td) may be administered.
Tetanus Toxoid	A complete tetanus toxoid series provides 100% efficacy.	3 doses are protective for 5 yrs; 5 doses may provide >20 years of protection. Boosters are recommended every 10 years.
Pertussis	71- 84% protection. Estimate vary widely; efficacy higher against severe disease.	Unknown; evidence that it wanes with time.
IPV	> 90% of recipients develop protective antibodies to all three poliovirus types after 2 doses, and at least 99% are immune following 3 doses. Less local GI immunity is produced.	Duration of immunity not known with certainty but provides protection for many years after a complete series.
OPV	A single dose produces about 50% of immunity. Three doses produce immunity to all 3 poliovirus types in > 95% of recipients. Produces local GI-intestinal and pharyngeal immunity.	As with other live virus vaccines, immunity is probably life-long.
Measles	> 95% at 12 months of age: 98% at 15 months of age (approx. 2-5% of children fail to respond to MMR 1st dose).	Lifelong if boosted by wild virus circulating.
Rubella	95% aged 12 months and older after a single dose.	> 90% of vaccinated persons have protection for at least 15 years. Some studies indicted that one dose confers lifelong protection.
Hepatitis B	80-100% effective in preventing infection or clinical hepatitis in those who receive the complete course (3) of vaccine. (90-95% adequate antibody response in healthy adults, infants and adolescents. 75-95% effective in newborns from HepaAg+ mothers. 90% respond after age 40, 75% develop protection by the age of 60.)	> 13 years; further follow-up is ongoing.
Influenza	90% protection from illness of healthy young adults. 30-40% effective in preventing illness among frail elderly persons, and 80% effective in preventing death.	Immunity following inactivated influenza vaccination rarely exceeds 1 year, depending on the vaccine starin(s).

Table – 13.6: Palestinian Immunization Schedule						
Vaccine	**Dose**	**Route**	**Site**	**Course**	**MOH Ages**	**UNRWA Ages**
BCG	0.05 ml	Intradermal	Left upper arm	-Primary	-On first registration	-At birth
OPV	2 drops	Oral	Mouth	-Primary series -Booster -Booster	-At 2,4,6 mon. of age -At 12 mon. of age -At school entry	-At 2,4,6 of age -At 12 mon. of age
IPV	1 ml	Subcutaneous	Left upper arm	-2 doses	-At 1&2 mon. of age	-At 1&2 mon. of age
DPT	0.5 ml	Intramuscular	Lateral aspect of the thigh	-Primary series -Booster	-At 2,4,6 mon. of age -At 12-15 month of age -At school entry	-At 2,4,6 mon. of age -At 12 months.
Measles	0.5 ml	Subcutaneous	Left upper arm	-3 doses	-At 9 mon.	-At 9 mon.
Hepatitis B	0.5 ml	Intramuscular	Lateral aspect of the thigh	-Primary	-At 0, 1,6 mon. of age	-At birth, 1,6 mon. of age
MMR	0.5 ml	Subcutaneous	Left upper arm	-Primary	-At 15 mon. of age	-At 15 mon. of age
TT	0.5 ml	Intramuscular	Left upper arm	-Booster -During pregnancy	-For 3rd prep. or 9th grade -For primigravida & 5 yrs. later	-At first pregnancy * -After 5 years of the first pregnancy
Td	0.5 ml	Intramuscular	Left upper arm	-Booster	-Every 10 years, persons ≥ 7 yrs of age. -Wound management	-At 15 yrs of age, ninth grade

*In case documentary evidence could be provided that full coverage has been attained, 3 primary series plus one booster and 2 doses of TT at school age (no need for additional boosters).

1) BCG [WHO,P]
(Bacille Calmette-Guerin)

- ***VACCINE SUMMARY:***

BCG is a strain of tubercle bacillus that is used to prepare the vaccine against TB. BCG vaccine, a live attenuated vaccine, gives good protection in children, mainly against miliary and meningeal tuberculosis. EPI recommends that all countries with high incidence of TB infection should immunize with a single dose of BCG at or soon after birth.

- ***INDICATIONS:***

Vaccine used for immunization against TB.

- ***CONTRAINDICATIONS:***

In patients with symptomatic HIV infection, or other severe immune deficiency disease including high doses of corticosteroids or chemotherapy drugs.

- ***RECOMMENDED DOSAGE:***

Refer to tables-4, 5 & 6.

Always follow direction for reconstitution by the manufacturer.

Once reconstituted, the vaccine must be protected from light, kept cold and discarded at the end of the day.

- ***USE IN SPECIAL CASES:***

Refer to introduction.

Immunization of asymptomatic HIV infants is advised when the risk of tuberculosis is high.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-When given properly, this vaccine is extremely safe.

A small red tender swelling about 10 mm may appear at the site of injection within about 2 weeks (since BCG bacteria grow slowly), which may also become an ulcer. The ulcer heals by itself, and leaves a small scar, which is a good indicator that the child has had the vaccine later on. If no scar develops, the dose must be repeated.

-Multiple repeat doses of BCG are not recommended.

-Patients on long-term systemic high doses of corticosteroids will have reduced immune response. Physicians should use caution in such patients; administer the vaccine not less than 3 weeks after discontinuation of the steroid therapy.

- ***ADVERSE EFFECTS & OVERDOSE:***

Simple swelling and ulceration at the site of injection may occur, as well as cold abscess. Lymphatic glands swelling is most likely to occur if the needle used was not sterile, the needle was injected too deep, or the dose was large or there is a problem in the manufactured vaccine. In such cases refer the child for symptomatic treatment.

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2) OPV / IPV [WHO,P]
Oral Poliomyelitis Vaccine/
(Inactivated Poliomyelitis Vaccine)

- ***VACCINE SUMMARY:***

Polio is almost eradicated; therefore, measures are implemented to assure that all the population must continue to be covered with vaccination. Two kinds of vaccines exist; OPV (the oral-live virus) and IPV (the inactivated-injectable virus). OPV is made of a weakened live polio virus. IPV is made of polio virus that has been killed. It cannot cause polio. IPV is more expensive, but may be recommended for pregnant women, people with an impaired immune system, and adults who have not been immunized previously. Immunization against polio forms a part of the WHO's EPI.

- ***INDICATIONS:***

An immunization against poliomyelitis (for prevention of permanent crippling, paralysis, and sometimes even death).

- ***CONTRAINDICATIONS:***

In patients with history of hyper-sensitivity reaction to the vaccine, and immuno-compromized patients. OPV should not be given to anyone in a family with a known family history of immunodeficiency until the immune status of all family members is documented.

- ***DOSAGE FORMS:***

OPV-liquid bottle with dropper. IPV-vial.

- ***RECOMMENDED DOSAGE:***

Refer to tables 13.4, 5 & 6.

-The OPV bottle dropper should not touch the child's tongue/mouth. If the child spits the drop out, give another dose.

-Doses may vary between different manufacturers; instruction on the label of the vaccine should always be checked.

-If child misses the usual time for a dose, the next dose can be given as soon as possible. Immunity will be good, even if there is a delay. There is no need to repeat earlier doses.

-A single dose of IPV does not result in significant protection, therefore at least 2 doses of IPV must be given.

-The minimum interval between the first 3 doses of IPV, OPV, or any combination of IPV and OPV is four weeks.

-If ≥ 2 doses of OPV have been given, there is little benefit in switching to IPV.

- ***USE IN SPECIAL CASES:***

Refer to introduction.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-The presence of a minor infection is not a contraindication. In patients with acute fever, persistent vomiting or diarrhea, the vaccine should be postponed. If the child has diarrhea when OPV is given, the vaccine may not work so well, because the organism that causes diarrhea may interfere. An extra dose of OPV may be given four weeks after the normal course is administered.

-When children in the household receive OPV, immunocompromised household contacts or adults who are not adequately vaccinated against polio are at small risk of contracting polio disease.

-OPV can be given simultaneously with any other childhood vaccines.

-Under no circumstances should OPV administered by injection.

-Administration of OPV to patients receiving corticosteroids or radiation therapy, may result in insufficient response to OPV. IPV may be administered in such cases.

- ***ADVERSE EFFECTS & OVERDOSE:***

Usually there are no side effects with OPV. Vaccine-associated paralytic polio (VAPP) is extremely small (~ one case/1.4 million first dose receivers). VAPP is more likely to occur in persons ≥ 18 years of age than in children.

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3) Tetanus Vaccine [WHO,P]

- ***VACCINE SUMMARY:***

Tetanus vaccines stimulate the production of the protective antitoxin. Complete and appropriate times vaccination is nearly 100% effective in the prevention of tetanus. The vaccine is usually given to children as a combination with diphtheria and pertussis vaccines. Immunization against tetanus forms a part of the WHO's EPI.

- ***INDICATIONS:***

Vaccine used as active immunization against tetanus (prevention of muscles to spasm or lockjaw).

- ***CONTRAINDICATIONS:***

Acute febrile illness, history of severe hypersensitivity or convulsions.

- ***DOSAGE FORMS:***

Vial.

- ***RECOMMENDED DOSAGE:***

Refer to tables-15.4, 5 & 6.

-Always follow directions for recon-stitution by the manufacturer.

Immunization of women can start at any stage of pregnancy. Tetanus toxoid (TT) does not harm the fetus. See table 15.7 on schedule of TT for women of child-bearing age.

-The need for tetanus vaccine in wound management depends on both the condition and the patient's immunization history. A dose of tetanus is only recommended if the risk of infection is considered high. If more

than 10 yrs. have passed, a reinforcing dose should be given.

- ***USE IN SPECIAL CASES:***

Refer to the introduction.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-Vaccination should be postponed in patients with acute febrile illness.

-Booster doses should not generally be given at intervals of less than 10 years because of increased risk of severe local reactions.

- ***ADVERSE EFFECTS & OVERDOSE:***

Pain, redness and swelling at the site of the injection may occur; this should go away by itself and needs no treatment. Anaphylaxis and neurological reactions have rarely occurred.

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4) DPT WHO,P

(Diphtheria, Pertussis, and Tetanus Vaccines)

- ***VACCINE SUMMARY:***

These vaccines are available as combinations so as to be given simultaneously.

The DPT (or DTP) vaccine is a "3-in-1" vaccine that protects against diphtheria (which may lead to pneumonia, heart failure, and paralysis), pertussis (whooping cough which could lead to pneumonia or bronchitis), and tetanus. It can be given to children less than 7 years old.

The DT vaccine is a "2-in-1" vaccine that does not contain pertussis, can be given to children less than 7 years old.

The Td vaccine is the "adult" vaccine. It is a "2-in-1" vaccine that protects against tetanus and diphtheria. It contains a slightly different dose of diphtheria vaccine than the DT vaccine. It can be given to anyone older than 7 years old.

- ***INDICATIONS:***

DPT vaccine is used for active immunization against the bacterial infections of diphtheria, pertussis, and tetanus. TT or Td may be given to an adult as prevention of tetanus from wound or injury that breaks the skin.

- ***CONTRAINDICATIONS:***

In patients with severe hypersensitivity history to the vaccine; history of convulsion or shock in the following three days after the vaccination, encephalopathy within 7 days for P component of DPT.

- ***DOSAGE FORMS:***

Vial.

- ***RECOMMENDED DOSAGE:***

Refer to table 13.4,5&6. In general DPT is administered in four doses, and a booster. Booster is given every 20 years as Td.

-Table 13.7 shows the duration of the immunity of different schedules for DPT vaccination.

-Always follow direction for administration by the manufacturer.

-If child misses a dose of DPT, the next dose can be given at any time after four weeks of the first dose. There is no need to repeat earlier doses.

Table – 13.7: Expected Duration of Immunity after Different Immunization Schedules

Schedule	Duration of immunity (age)
A) 3 DPT in infancy	5 years
B) 4 DPT infancy and 2nd year	8 years
C) As in B plus one DT at school entry	18 years
D) As in C plus one DT at school leaving	40 years
E) Two DT at School (if no A→D)	10 years
F) 3 DT at school (if no A→D)	15 years
G) 5TT as recommended by EPI	40 years

- ***USE IN SPECIAL CASES:***

Refer to introduction.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-For children above 10 years or adults a specially diluted adsorbed vaccine is used.
-DPT should not be used in persons with a history of neurologic disorders.
-Use caution in children who had symptoms of: collapse or shock-like state within 48 hours of previous dose, elevated temp. of 40.5 or more within 48 hours of dose, and persistant inconsolable cry for more than 3 hrs.

- ***ADVERSE EFFECTS & OVERDOSE:***

Slight fever and crying may occur but of no significance. Fever that does not resolve within one day, or starts 24 hours after a dose of DPT is not due to the vaccine. Local mild reaction such as swelling, redness or tenderness at the injection site may occur. Rarely convulsions have been reported due to the pertussis part of DPT.

---

5) Measles Vaccine [WHO,P]

- ***VACCINE SUMMARY:***

This vaccine is available as a single vaccine or as a combination. In most countries, including Palestine, measles vaccine is used as a combination with mumps and rubella- (MMR) vaccine.

- ***INDICATIONS:***

Measles vaccine is used as active immunization against measles.

- ***CONTRAINDICATIONS:***

In patients with history of anaphylactic reactions or systemic hypersensitivity to neomycin, acute febrile illness including active untreated TB, and within 3 months of administration of IG, whole blood, or other blood products containing antibodies.

- ***DOSAGE FORMS:***

Vial.

- ***RECOMMENDED DOSAGE:***

Refer to table-4, 5 & 6.

- ***USE IN SPECIAL CASES:***

Refer to introduction.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-Use extreme caution in patients with mild hypersensitivity to eggs or neomycin.
-Always follow direction for reconstitution by the manufacturer.
-Administration to children less than 9 months of age makes only 50% of the vaccine effective. If a 6 month old baby is seriously exposed to measles, then the vaccine may be given as long as another dose is administered when the child is nine months old.
-There are conflicting reports about effect of vitamin A supplementation on reducing the response to the measles vaccine.

- ***ADVERSE EFFECTS:***

Mainly fever and rash may occur. A fever may develop 5-10 days after the vaccination, and may last 1-2 days; a simple analgesic may be administered if the fever is high.

---

6) MMR Vaccine [WHO,P]

(Measles, Mumps and Rubella)

- ***VACCINE SUMMARY:***

The MMR vaccine is a "3-in-1" vaccine that protects against measles, mumps, and rubella. MMR should be given irrespective of previous measles vaccine, or history of measles, mumps, or rubella infection.

- ***INDICATIONS:***

The vaccine is used for active immunization against measles, mumps and rubella.

- ***CONTRAINDICATIONS:***

Patients with anaphylactic reactions to eggs, gelatin or neomycin. Children who have received another live vaccine by injection within 3 weeks.

- ***DOSAGE FORMS:***

Freeze-dried vial.

- ***RECOMMENDED DOSAGE:***

Refer to table-4, 5 & 6.

Dose should be reconstituted with the diluent as indicated by the manufacturer, and used within one hour.

- ***USE IN SPECIAL CASES:***

Refer to introduction.

Women known to be pregnant should not receive the vaccine. Pregnancy should be avoided for 2 months following receipt of the measles vaccine, and 3 months following MMR vaccine.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-Use caution in patients with history of hypersensitivity to eggs, gelatin, or neomycin streptomycin.

-In children with untreated malignant disease or altered immunity, and those receiving immunosuppressive drugs or radiotherapy, or high dose corticosteroids.

-MMR vaccine should not be given within three months of an injection of IG.

-If MMR is to be given to adult women, pregnancy should be avoided for 3 month (as for rubella vaccine).

-MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression.

- ***ADVERSE EFFECTS:***

As with measles; malaise, fever, and/or rash may occur, most commonly after vaccination and lasting about 2-3 days. Parotid swelling may occur usually in the third week; children with post vaccination symptoms are not infectious.

---

7) Hepatitis B Vaccine WHO,P

- ***VACCINE SUMMARY:***

Hepatitis B vaccine contains inactivated hepatitis B virus (HBV) surface antigen (HbsAg) adsorbed on aluminum hydroxide adjuvant. It is made biosynthetically from yeast cells using recombinant DNA techniques. EPI recommends this vaccine in high incidence areas of Hepatitis B infections.

- ***INDICATIONS:***

Hepatitis B vaccines are used for active immunization against HBV infections in persons at high risk of contracting the disease.

- ***CONTRAINDICATIONS:***

Serious allergic reaction to a prior dose of of this vaccine, or a vaccine component. Such allergic reactions are rare.

- ***DOSAGE FORMS:***

Vial.

- ***RECOMMENDED DOSAGE:***

Refer to table-15.4, 5 & 6. Hepatitis B vaccine is given as a series of three injections (shots).

-There are 2 different manufacturers that produce Hep. B vaccines. Vaccines made by different manufacturers are inter-changeable as long as the manufacturer's dosage recommendations are always followed. *{Note that Recombivax HB dose is 5 ug (0.5 ml), while Engerix-B dose is 10 ug (0.5 ml) for persons < 20 years of age.}*

-Most preparations are intended for intramuscular use only. Do not administer intravenously or intradermally unless there are clear directions from the manufacturer.

-The vial should be stored at 2 – 8 ºC, and not freezed.

- ***USE IN SPECIAL CASES:***

Refer to introduction. No information is available about the safety of the vaccine in pregnant women. However, because the vaccine contains only particles that do not cause HBV infection, there should be no risk. Since the vaccine does not contain a live virus, it may be used in cases of immunodeficiency. However, response to the vaccination in such persons may be suboptimal.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-It takes 6 months to confirm if there is adequate protection from the vaccine.

-The vaccine should be used with caution in patients with severely compromised cardiopulmonary status.

- ***ADVERSE EFFECTS & OVERDOSE:***

When given properly the vaccine is extremely safe. The most common side effect observed is soreness at the injection site.

If the vaccine is administered too deep, local reaction, ulcers and regional lymphadentitis may occur.

There have been rare reports of myalgia or arthralgia, neurological, abnormal liver function and dermatological side effects.

---

8) Influenza Vaccine WHO

- ***VACCINE SUMMARY:***

Inactive influenza vaccines are used for active immunization against influenza. Because of the periodic changes in the surface antigens of influenza virus, the WHO makes annual recommendations concerning the antigenic nature of this vaccine. Medical personals need to be updated every year with the changes. This vaccine is listed in the WHO 10th EDL for use in specific groups of individuals.

Influenza vaccine comes as whole-virus, split-virus, or purified surface antigen. Only split-virus or purified surface antigen vaccine should be used in children because these forms of the vaccine do not cause as much fever as whole-virus vaccine.

- ***INDICATIONS:***

As a measure to prevent influenza infection, specially in high risk groups such as elderly, persons with chronic disorder of the cardiovascular, pulmonary, and/or renal system, severe anemia, compromised immune function, that are at risk of severe complications or dying after an influenza infection.

- ***CONTRAINDICATIONS:***

Persons with a history of any signs and symptoms of anaphylactic reactions (hives, swelling of the mouth and throat, difficulty breathing, hypotension or shock) after eating eggs or egg products.

- ***DOSAGE FORMS:***

Vials.

- ***RECOMMENDED DOSAGE:***

For adults and children > 3 years; 0.5 ml given IM or deep SC (0.25 ml to children < 3 yrs). Vaccination produces immunity after about 14 days, lasting for about 6 months to 1 year, therefore vaccine is administered annually during October-November. Children aged 6 mon. - 9 yrs. receiving the vaccine for the first time, should get 2 doses at 1 mon. interval.

- ***USE IN SPECIAL CASES:***

Refer to introduction.

Babies as young as 6 months can get influenza vaccine. Children may have more side effects with influenza vaccine compared to adults *(See Vaccine Summary).* Only the split-virus vaccine should be used in children.

Administration to pregnant women is considered safe, but may be administered after the first trimester as a precaution to minimize any concern of theoretical risk.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

-Persons with acute febrile illnesses normally should not be vaccinated until their symptoms have cleared.

-Use caution in patients with allergy to thimerosal or sulfite additives.

-Certain drugs activity has been reported to be enhanced with administration of influenza vaccine: the anticoagulant warfarin, phenytoin and theophylline. Use vaccine with caution.

- ***ADVERSE EFFECTS & OVERDOSE:***

Local reactions such as pain, erythema, swelling or/and itching at the site of injections have been reported. Mild systemic reactions such as headache, abdominal pain, muscle aches and dizziness have occurred. Rarely neurologic symptoms have occurred.

---

9) Hib Vaccine
(Haemophilus Influenzae Type B)

- ***VACCINE SUMMARY:***

Hib vaccine is used for active immunization against *Haemophilus influenzae* type b infections, a gram (-) bacteria, one of the major causes of meningitis and other severe systemic illness in young children (< 5 yrs). This polysaccharide (or related oligasaccharide) vaccine is linked to a protein carrier to form a conjugate vaccine, so as to enhance immunogenicity effect compared with non-conjugated vaccine. At this time, the EPI has not adopted routine use of this vaccine until full cost data analysis would be available.

- ***INDICATIONS:***

Vaccination against *Haemophilus influenzae* type b infections.

- ***CONTRAINDICATIONS:***

In immunocompromized individuals.

- ***DOSAGE FORMS:***

Freeze dried preparation.

- ***RECOMMENDED DOSAGE:***

-There are different schedules for vaccination according to the product. Always refer to the manufacturer's directions. In general, the conjugate vaccine is given by deep subcutaneous or intramuscular injection in doses of 0.5 ml, for 3 to 4 doses. The vaccine may be given at 2-4 months, 4-6 months and 12-15 months of age.

Hib vaccination schedule:

-HibTITER: 3 doses, 2 months apart, starting at 2 months of age, with a booster at 12-15 months of age.

-PedvaxHIB: 2 doses, 2 months starting at 2 months of age, with a booster at 12-15 months of age.

-ProHIBIT: 1 dose at 15 months to 5 years of age, no booster needed.

-Children aged 13-48 months should be given a single dose since they are at lower risk and the vaccine is effective after a single dose in this age group. Routine use in older children > 5 years or adults is not recommended.

-Vaccine may be given simultaneously with DPT, measles, BCG or Hep B, as well as with IG.

- ***USE IN SPECIAL CASES:***

The safety of the vaccine for pregnant women has not been established. On theoretical grounds, avoid vaccination unless there is a substantial risk of infection of the women.

- ***PRECAUTIONS AND WARNINGS, INTERACTIONS:***

Use caution in patients with hypersensitivity to eggs, diphtheria toxoid, and thimerosal additive.

- ***ADVERSE EFFECTS & OVERDOSE:***

These are very mild, and may include headache, myalgia, low grade fever (1 out of 100 doses) or other minor symptoms. Very rarely encephalitis has followed vaccination, generally in infants under 9 months of age.

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Appendix A – Price List

This list of drugs is based on the September 2002 cost price list from Palestinian drugstores and pharmacies. Drug prices constantly change in the Palestinian market so this information is to be used only as a guide for health professionals.

ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY, AND ANTIGOUT DRUGS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFAC-TURER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
A) Analgesics, Antipyretics, and Non-Steroidal Anti-Inflammatory Agents					
Acetylsalicylic Acid (ASA)	***ACETOSAL***	300mg 500mg	Tab. Tab.	Rekah	9.00/40 10.00/20
	ALKA SELTZER	324mg	Efferv. Tab.	Agis	8.00/10
	ASCRIPTIN ***(ASA with antacid)***	ASA 325mg AlOH 75mg MgOH 75mg	Tab.	RP Rorer	21.00/100
	ASPIRIN 81 ***ASPIRIN***	81mg 100mg	E.C. Tab. Tab.	Bayer	16.00/30 10.00/30
	BABY ASPIRIN	100mg	Chew. Tab.	JCL	6.00/20
	CARTIA	100mg	Tab.	SK Beecham	16.00/28
	MICROPIRIN	75mg	Tab.	Dexxon	30.00/10
	TEVAPIRIN	100mg	E.C. Tab.	Teva	11.00/30
Paracetamol	***ABROL***	500mg	Tab.	Rekah	5.00/30
	ABROLET	150mg 250mg	Supp.	Rekah	10.00/12 14.00/5
	ACAMOL	500mg	Tab.	Teva	11.00/20
	ACAMOLI	80mg 150mg 125mg/5ml	Chew. Tab. Supp. Syr. (Stwbry)	Teva	13.00/50 12.00/12 13.00/100ml
	ALDOLOR	500mg 100mg/ml 120mg/5ml	Tab. Drops Syp. Sugar free	CTI	14.00/50 13.00/20ml 8.00/110ml
	DEXAMOL	500mg	Cap.	Dexxon	27.00/50
	DEXAMOL KID	250mg 125mg/5ml	Chew. Tab. Syp (Stwbry or Cola)	Dexxon	12.50/20 12.00/115ml
	FEBRAMOL	500mg 120mg/5ml 150mg 300mg	Tab. Syp (Stwbry) Supp. Supp.	BPC	5.00/20 7.00/100ml 5.00/6 7.00/6
	OTAMOL	500 mg 120mg/5ml 300mg	Tab. Syp (Stwbry) Suppository	JePharm	5.00/20 9.00/120ml 5.00/5
	PAMOL	150mg 300mg 500mg 125mg/5ml	Supp. Supp. Supp. Syrup	Eastern Chem.	5.00/5 5.00/5 8.00/5 7.00/100ml
	PARACARE	500mg	Tab. Syrup	Pharmacare	4.00/20 7.50/100ml

	PARAMOL	500mg 125mg/ml 150mg 300mg 500mg 30mg	Tab. Syrup Supp. Supp. Supp. Chew. Tab.	JCL	5.00/20 7.00/100ml 3.00/5 3.50/5 6.50/5 10.00/20
Ibuprofen	***ADEX 200*** ***ADEX 400***	200mg 400mg	Cap.	Dexxon	13.60/30 22.00/30
	ARTOFEN	200mg 400mg 600mg	Tab. Tab. Tab.	Teva	12.00/20 22.00/50 22.00/30
	BRUFEN 400	400mg	Tab.	Boots	16.00/30
	IBUFEN	400mg 600mg	Cap. Cap.	Dexxon	13.00/30 18.30/30
	ISOFEN	200mg 400mg	Tab.	JCL	7.00/20 15.00/20
	NUROFEN	200mg	Tab.	Boots	16.00/12 24.00/24
	TRUFEN	200mg 400mg 600mg 100mg/5ml	Tab. Tab. Tab. Susp. (Orange)	JePharm	5.00/20 10.00/20 8.00/20 15.00/100ml
Naproxen	***APO-NAPROXEN***	250mg 500mg	Tab.	Apotex	33.00/30 65.00/30
	NAPREX	250mg 500mg 500mg	Tab. Tab. Supp.	BPC	20.00/20 12.50/10 18.50/12
	NAPROXI	250mg 500mg	Tab. Tab.	Gerard	29.00/5 29.00/5
	NAXYN	250mg 500mg 500mg	Tab. Tab. Supp.	Teva	59.00/50 26.00/30 38.30/12
Diclofenac	***ABITRENE***	25mg 50mg 100mg	Tab. Supp. S.R. Tab.	Abic	8.00/20 19.00/10 12.00/10
	BETAREN	25mg 50mg	Tab. Tab.	Dexxon	13.00/30 27.00/30
	BETAREN S.R.	100mg	S.R. Tab.	Dexxon	16.00/10
	DICLOFEN	25mg 50mg 100mg 12.5mg 75mg 100mg 1%	Tab. Tab. S.R. Tab. Supp. Supp. Supp. Gel	JePharm	16.50/30 23.00/30 15.00/10 11.00/6 28.00/10 42.00/15 14.00/30g
	RHUMACARE	50mg 1%	Tab. Gel	Pharmacare	22.00/30 18.00/50gm

	RUFENAL	25mg 50mg 100mg 100mg 1%	Tab. Tab. S.R. Tab. Supp. Gel	BPC	12.00/30 20.00/30 12.00/10 27.00/12 13.50/30g
	VOLTAREN	25mg 50mg 1%	Tab. Supp. Gel	Novartis	52.00/30 28.00/10 18.00/20g 34.00/50g
	VOLTAREN S.R.	100mg	S.R. Tab.	Novartis	54.50/10
	VOLTIN	50mg 100mg	Supp.	Eastern Chem.	18.00/10 26.00/12
Indomethacin	***INDOCAPS***	25mg 100mg	Cap. Supp.	JCL	10.00/24 13.00/10
	INDOCIN	25mg 100mg	Cap. Supp.	Eastern Chem.	9.00/20 15.00/12
	INDOLIN	25mg 100mg	Cap. Supp.	BPC	8.50/20 17.00/12 7.00/6
	INDOMED	25mg 100mg	Cap. Supp.	Assia	18.00/30 20.00/12
	INDOMED S.R.	75mg	S.R. Caps	Assia	37.00/10
	INDOPHARM	25mg 75mg 100mg	Cap. S.R. Cap. Supp.	JePharm	7.50/20 17.50/16 18.00/12
	INDOTARD	75mg	S.R. Cap.	CTI	35.50/10
	INDOVIS	25mg	Cap.	CTI	15.00/30
Piroxicam	***FELCOL***	10mg 20mg	Cap.	Eastern Chem.	21.00/20 29.00/20
	FELDENE	20mg 20mg 0.5%	Cap. Suppository Gel.	Pfizer	121.0040/30 51.00/12 26.00/25gm
	PIROX	20mg 20mg 0.5%	Cap. Supp. Gel	JePharm	33.00/20 24.00/6 17.00/30g
	Antigout Agents				
Allopurinol	***ALLORIL***	100mg 300mg	Tab.	Dexxon	35.50/50 35.50/20
	ZYLOL	100mg 300mg	Tab.	Teva	43.00/50 43.00/20
	URICNASE	100mg	Tab.	BPC	Not in private market /20
Sulfin-pyrazone	***ANTURAN***	100mg 200mg	Tab.	Novartis	124.00/100 93.00/50
	PYROCARD	100mg	Tab.	Trima	88.00/100
Colchi-cine	***COLCHICINE***	0.5mg	Tab.	Rafa	10.00/30

CARDIOVASCULAR DRUGS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
	Diuretics				
HC-THZ	***DISOTHIAZIDE***	25mg	Tab.	Dexxon	28.00/50
	ESIDREX	25mg	Tab.	Novartis	23.00/20
Furosemide	***DIASIX***	40mg	Tab.	JCL	8.50/20
	FUROVITE	40mg	Tab.	Vitamed	12.50/25
	FUSID	40mg 100mg	Tab.	Teva	34.00/50 131.00/100
	LASIX	40mg	Tab.	HMR	24.00/20
	MIPHAR	40mg	Tab.	Pharbita	13.00/50
	URIX	40mg	Tab.	BPC	13.00/20
Sirpnol-actone	***ALDACTONE***	25m 100mg	Tab.	Searle	29.00/20 46.00/10
	ALDOSPIRONE	25mg 100mg	Tab.	Teva	18.00/20 61.00/20
	Beta-Blockers				
Propranolol	***BLOCADRIL***	10mg 40mg	Tab.	BPC	6.50/20 9.50/20
	DERALIN	10mg 40mg	Tab.	Abic	8.00/30 11.00/30
	PROLOL	10mg 40mg	Tab.	Dexxon	5.50/50 14.00/50
	SLOW DERALIN	80mg 160mg	S. R. Cap.	Abic	61.00/30 114.00/30
Atenolol	***ATENI***	50mg 100mg	Tab.	Generics	43.00/30 60.00/30
	COROTENOL	50mg 100mg	Tab.	JePharm	52.00/50 20.00/50
	NORMALOL	25mg 50mg 100mg	Tab.	Dexxon	9.00/30 13.00/30 18.00/30
	NORMITEN	25mg 50mg 100mg	Tab.	Abic	11.00/30 11.00/30 11.00/30
	Angiotensin Converting Enzyme Inhibitors				
Captopril	***CAPOTEN***	12.5mg 25mg 50mg	Tab.	BMS	255.00/100 261.00/90 455.00/90
	CARDIOPRIL	25mg 50mg	Tab.	BCP	10.00/20 15.00/20
	INHIBACE	12.5mg 25mg 50mg	Tab.	Pharma-Best	40.00/100 45.00/90 84.00/90

	Calcium Channel Blockers				
Nifedipine	***ANGILAT***	10mg 20mg 10mg	Tab. Tab. Soft gel Cap.	BPC	20.00/30 40.00/30 35.00/75
	MEGALAT	10mg	Cap.	Agis	66.00/90
	OSMO-ADALAT	30mg 60mg	S.R. Tab.	Pharma-Clal	138.00/30 209.00/30
	PRESSOLAT	10mg 20mg	Tab.	Agis	40.50/20 51.00/20
Verapamil	***IKACOR***	40mg 80mg 120mg	Tab.	Teva	15.00/50 25.00/50 36.00/50
	IKAPRESS	180mg 240mg	S.R. Tab.	Teva	90.40/30 35.50/30
	VERACOR	40mg 80mg 120mg	Tab.	Dexxon	17.00/60 29.00/60 44.00/60
Diltiazem	***DILAPRESS***	120mg	S.R. Tab.	Abic	78.00/30
	DILATAM	30mg 60mg 120mg 240mg	Tab. Tab. S.R. Tab. S.R. Tab.	Abic	11.00/30 20.00/30 82.00/30 112.50/30
	LEVOZEM	30mg 60mg 90mg	Tab.	Dexxon	33.50/30 38.00/20 45.00/20
	Other Cardiac Agents				
Amiod-arone	***AMIODACORE***	200mg 150mg	Tab. Amp.	CTI	24.00/30 /6
	PROCOR	200mg	Tab.	Unipharm	34.00/30
Isosorbide Dinitrate	***CORDIL***	2.5mg 5mg 10mg 20mg 40mg	Subling. Tab. Subling. Tab. Tab. Tab. S.R. Tab.	Dexxon	5.50/40 6.00/40 9.00/50 12.00/50 46.00/25
	ISOCARDIDE	2.5mg 5mg 10mg 20mg 30mg	Subling. Tab. Subling. Tab. Tab. Tab. Tab.	Sam-On	5.00/40 7.00/40 7.00/40 8.00/40 10.00/40
	ISORDIL	10mg	Tab.	Wyeth Ayerst	46.00/100
	ISOTARD	20mg 40mg 60mg	S.R. Cap.	CTI	14.00/20 22.50/20 32.00/20
Warfarin	***COUMADIN NA***	5mg	Tab.	Taro	19.00/20

Digoxin	***DIGOXINZORI***	0.25mg	Tab.	Teva	12.00/40.
	LANOXIN	0.25mg 0.05mg/ml	Tab. Elixir	GSK	27.72/100 55.00/50ml
	LIPID LOWERING DRUG **Fibric Acids**				
Bezafibrate	***BEZALIP***	200mg	Tab.	Boehringer	91.00/100
	BEZALIP RETARD	400mg	Long Acting Tab.	Boehringer	52.00/30
	NORLIP	100mg 200mg	Tab.	Unipharm	75.00/100 73.20/50
	Bile Acid Sequestrants				
Cholestyramine	***CHOL-LESS***	4 gram	Sachets	Rafa	94.00/50
	QUESTRAN	4 gram	Sachets	Mead-Johnson	144.00/5
	HMG-CoA Reductase Inhibitors				
Simva-statin	***SIMOVIL***	5mg 10mg 20mg 40mg	Tab.	Assia/ Riesel	148.00/30 98.00/30 142.00/30 768.00/30
Fluvsa-statin	***LESCOL***	20mg 40mg	Tab.	BMS	108.00/28 145.00/28

GASTROINTESTINAL DRUGS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
Antacids & Ulcer-Healing					
Mg/Al Salts	***MAALOX***	Al-hydroxide 225mg Mg-hydroxide 200mg/5ml	Suspension	Rorer	24.00/355ml
	MAALOX NO.1	Al-hydroxide 200mg, Mg-hydroxide 200mg/5ml	Tab.	Rorer	25.00/100
	MAALOX PLUS	Al-hydroxide 225mg Mg-hydroxide 200mg/5ml Simethicone	Suspension Tab.	Rorer	27.00/355ml 25.00/50
	MAGNAGEL	Al-hydroxide 6.0% Mg-trisilicate 7.5%	Suspension	JePharm	17.00/355ml
	MAGNAGEL	Al-hydroxide 200mg Mg-trisilicate 300mg	Chewable Tab.	JePharm	63.00/400
	STOMAGEL	Al-hydroxide 500mg Mg-trisilicate 750mg/ 15 ml	Suspension	JCL	Not produced any more.
Ranitidine	***GI-CARE***	150 mg	Tab.	Pharmacare	14.00/20
	RANDIN	150mg	Tab.	JePharm	14.50/20
	RATIDINE	150mg 300 mg	Tab.	BPC	16.00/20 34.00/20
	ZANTAB	150mg 300 mg	Tab.	Teva	14.00/20 14.00/10
	ZANTAC	150mg 300mg	Efferv. Tab.	GSK	90.00/20 85.00/10
	ZANTAC	150mg 300 mg	Tab.	GSK	81.00/20 75.00/10
Omeprazole	***LOCID***	20 mg	Cap.	JePharm	49.00/14
	LOSEC	10mg 20mg	Cap.	Abic	284.90/30 224.00/14
	MARIAL	10mg 20mg	Cap.	JCL	30.00/14 55.00/14
	MEPRAL	20 mg	Cap.	BPC	50.00/14
	PEPTICUM	20 mg	Cap.	Pharmacare	60.00/15

	Antispasmodics/Anticholinergics				
Hyocine N-Butyl Bromide	***KOLIK***	Hyosciamine Sulfate 0.125 gm, alcohol 0.3ml/ml	Drops	JCL	9.00/10ml
	SCOBUTYL	Hyocine N-butyl bromide 10 mg	Tab.	JePharm	9.00/20
	Anti-Emetics				
Metaclopramide	***EMESTOP***	10 mg 5mg/5ml	Tab. Syrup	BPC	12.00/20 6.00/30ml
	NOVOMIT	10 mg 5mg/5ml	Tab. Syrup	JePharm	9.00/20 8.00/60ml
	PRAMIN	10 mg 5mg/5ml 5mg 20 mg	Tab. Syrup Supp. Supp.	Rafa	19.00/30 8.00/60ml 11.00/6 11.00/6
Meclizine/ Meclozine	***ANCOZINE***	Meclozine 15mg Pyridoxine 30mg	Supp.	BPC	9.00/6
	ANCOZINE	Meclozine 25mg Pyridoxine 50mg	Tab.	BPC	12.00/20
	PARAVOMINE	Meclozine 25mg Pyridoxine 50mg	Tab.	JCL	14.00/20
	Anti-Diarrhoeal				
Oral Rehydration Salts	***ELECTRO-SUBS***	NaCl 3.50g Na Bicarbonate 2.50g KCl 1.50g Glucose 20g	Sachet	BPC	4.00/sachet
	HYDRAN	NaCl 2.00g Trisodium- Citrate 2.58g KCl 1.49g Dextrose 30g	Sachet	Teva	23.00/3 sachets
	ORSET L.S.	Glucose 140mmol/L Na+ 56 mmol/L K+ 0 mmol/L Citrate 30 mmol/L Cl- 46 mmol/L	Efferv. Tab.	Novartis	24.00/10
Loperamide	***DIACARE***	2 mg	Caps	Pharmacare	10.00/8
	IMODIUM	2 mg	Caps	JanssenCilag	26.00/10
	IMODIUM CAPLET	2 mg	Cap.	JanssenCilag	20.00/10
	IMODIUM SOLUTION	2 mg	Solution	JanssenCilag	22.00/100ml
	STOPIT	2 mg	Caps	Rafa	16.00/10

	Laxatives				
Bisaco-dyl	***BISALAX***	5mg 10 mg	Supp.	JCL	5.50/5 8.00/5
	LAXADIN	5 mg	E.C. Tab.	Teva	15.00/50
Glyce-rin	***GLYCERINE***	Glycerin 2.7g Glycerin	Supp. adult Supp. child	Rekah	11.00/20 7.00/5
Psyll-ium	***METAMUCIL***	Psyllium	Powder	Searle	13.00/100g
	Anti-Hemorrhoids				
Different Preparations	***ANUSOL***	Bismuth subgalate 59mg, Bismuth ox. 24mg, Balsam peru 49mg, ZnO 296 mg.	Supp.	Park Davis	18.00/12
	ANUSOL	Bismuth sub-galate 2.25g, Bismuth ox 0.875g, Balsam peru 1.875g, ZnO 10.75g/100g.	Ointment	Park Davis	17.00/25g
	HEMORAL H.C.	Hydrocortisone acetate 0.5%, Lidocaine HCl 1.5%, ZnO 3% Bismuth subgalate 4%	Supp.	JCL	13.00/6
	HEMORAL H.C.	Hydrocortisone acetate 0.5%, Lidocaine HCl 1.5%, ZnO 5%, Bismuth subgalate 2%	Ointment	JCL	13.00/30g
	PROCTOCARE	Fluocinolone Acetonide 0.1%, Lidocaine HCL 20 mg	Ointment	Pharmacare	15.00/15g
	PROCTOCEDYL	Hydrocortisone 0.5% Cinchocaine-HCl 0.5%	Ointment Supp.	HMR	11.00/15g 11.00/12
	PROCTO-GLYVENOL	Tribenosid 400mg Lindocain 40mg	Cream Supp.	Novartis	26.00/30g 29.00/10

RESPIRATORY DRUGS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
	COLD PREPARATIONS				
	Antihistamines				
Chlorpheniramine	***AHISTON***	2mg	Tab.	Teva	7.00/20
	ALLERGON	3mg/5ml 2mg	Syrup Tab.	JCL	10.00/100ml 7.00/20
	ANAPHYL	3mg/5ml 2mg	Syrup Tab.	Sam-On	8.00/120ml 5.00/20
	CLOROYATE	3mg/5ml 2mg	Syrup Tab.	Pharmacare	Not in market
	DISORAMIN	2mg	Tab.	Dexxon	4.00/20
Astem-izole	***HISMANAL*** ***(No longer available in market.)***	10mg 1mg/ml	Tab. Syrup	Janssen	60.00/20 38.00/100ml
	LAHISTAN	10mg	Tab.	BCP	34.00/20
	Nasal Decongestants				
Oxymetazoline	***ALRIN***	0.05%	Nasal Drops Nasal Spray	Teva	7.50/10cc 10.00/15cc
	NASIVIN	0.025% 0.05%	Nasal Drops Nasal Drops Nasal Spray	Merck	9.00/10cc 12.00/10cc 14.00/10cc
	RHINOCLIR	0.05%	Nasal Spray	Agis	11.00/20ml
	NOSACARE	0.05%	Nasal Spray	Pharmacare	7.50/15cc
Pseudo-ephedrine	***OTRINOL***	120mg SR	Retard Cap.	Novartis	22.00/10
	SINUFED	30mg/5ml 60mg	Syrup Tab.	Trima	19.00/115ml 15.00/20
	TAROPHED	30mg/5ml	Syrup	Taro	18.00/120ml
	Expectorants				
Guaif-enesin	***ROBITUSSIN***	100mg/5ml	Syrup	A.H.Robins	20.00/20ml
	RESYL (sugar free)	100mg/5ml	Syrup	Novartis	17.00/100ml
	Antitussives / Cough Suppressants				
Codeine Phosphate	***CODEINE PHOSPHATE***	20mg	Tab.	Rekah	9.00/10
	CODICAL	20mg	Tab.	Sam-On	9.00/10
	PARACOD	20mg codeine 325mg APA	Tab.	Pharmacare	12.00/20
Dextromethorphan HBr*:* Available only in combinations products in the market.					

	Mucolytics				
Acetylcysteine	***AGISOLVAN***	200mg	Granules (Sachets)	Agis	12.00/12
	MUCOMYST	200mg	Granules (Sachets)	Mead-Johnson	101.48/3
	SIRAN 200	200mg	Powder Sach. Effervs. Tab.	Temmler Pharma	40.00/30 40.00/30
	BISOLVAN	8mg 4mg/5ml	Tab. Elixir	Boehringer	19.00/20 24.00/100ml
Brom-hexine	***MUCOCARE***	8mg 2mg/1ml	Tab. Elixir	Pharmacare	15.00/20 18.00/50ml
	SOLVEX	8mg	Tab.	Teva	19.00/20
	BRONCHODIALATORS AND ASTHMA MEDICATIONS				
Theophylline	***GLYPHYLLIN***	Theoph. Na Glycinate 250mg	Tab.	Teva	17.00/60
	THEO-DUR	Theoph. Anhy. 200mg 300mg	S.R. Tab.	Key Pharm.	 44.00/100 53.00/100
	THEOTARD	Theoph. Anhy. 50mg 75mg 100mg 200mg 300mg	S. R. Cap.	CTI	 12.50/30 13.00/30 13.00/30 20.50/50 23.00/30
	THEOTRIM	Theoph. Anhy. 100mg 200mg 300mg	S.R. Tab.	Trima	 10.00/30 19.00/30 24.00/30
	THEOPHARM	Theoph. Anhy. 100mg 200mg 300mg	S. R. Tab.	JePharm	 13.00/50 19.00/50 25.00/50

Salbutamol / Albuterol	***VENTOCARE***	2mg 2mg/5ml	Tab. Syrup	Pharmacare	4.00/20 10.00/180ml
	VENTOLIN	2mg 2mg/5ml 100mcg/inhal.	Tab. Syrup Aero. Spray	GSK	32.00/100 14.00/150ml 18.00/200doses
	VENTOLIN RESPI-RATOR SOLUTION	5mg/ml	Solution for Nebulizer	GSK	29.00/20cc
	VOLMAX	4mg 8mg	Tab.	GSK	30.00.50/14 36.00/14
	FEDRAL	4mg 2mg/5ml	Tab. Syrup	Eastern Chem.	5.00/20 7.00/100ml
Cromolyn Sodium (Na Cromoglycate)	***CROMUNAL***	1mg/inhal.	Inhaler	Agis	
	LOMUDAL	20mg	Gelatin Caps	Fisons	68.00/30
	LOMUDAL NEBULISER SOLUTION	20mg	Solution	Fisons	144.00/48ml
	NALCROM	100mg	Cap.	Fisons	156.00/100
	VICROM	1mg/inhal.	Inhaler	Fisons	
Beclomethasone Dipropionate	***BECLOFORTE***	250mcg/inhal.	Inhaler	GSK	43.70/200 metered doses
	BECONASE	50mcg/inhal.	Nasal Aerosol	GSK	
	BECOTIDE	50mcg/inhal.	Inhaler	GSK	58.00/200 metered doses
	RHINOCORT	50mcg/spray	Nasal Spray	Agis	50.00/200 sprays
	VIAREX	50mcg/inhal.	Inhaler	Schering	49.00/200
Prednisone	***PREDNITAB***	5mg 20mg	Tab.	BPC	14.00/40 25.00/20
	PREDNITONE	5mg 20mg	Tab.	Vitamed	 33.00/30
	PREDNISONE	5mg 20mg	Tab.	Rekah	14.00/10 45.00/30

	Widely Used Combination Products				
MULTI-INGREDIENTS	***ACTIFED SYRUP***	Pseudoeph. 60mg Triprolidine 2.5mg	Syrup	GSK	18.00/100ml
	ACTIFED EXPECTORANT	Pseudoeph. 30mg Triprolidine 1.25mg Gauifenasin 100mg	Syrup	GSK	19.00/100ml
	ALCINAL	Dextromethorph. 7.5mg Guiaphen. 105mg Chlorphenar. 1mg Phenylprop. 12.5mg	Syrup Cap.	Rekah	14.00/115ml 17.00/20
	COLDEX	Caffeine 30mg Chlorphenar. 2mg Phenylepher. 10mg Paracetamol 300mg	Tab.	Teva	12.00/20
	COLDEX-NIGHT	Dextromethor. 10mg Ephedrin. 8mg Chlorphen. 1mg Paracetamol 600mg	Elixir	Teva	18.00/60 ml
	DEXAMOL COLD (Day care)	Dextromethor. 10mg Guiaphen. 200mg Pseudoeph. 25mg Paracetamol 325mg	Cap.	Dexxon	19.50/30
	DEXAMOL COLD (Night care)	Dextromethor. 10mg Chlorphenar. 2mg Pseudoeph. 25mg Paracetamol 500mg	Cap.	Dexxon	6.50/10
	DEXAMOL SINUS	Pseudoeph. 25mg Paracetamol 500mg	Cap.	Dexxon	40.00/
	FEBRACOLD S.R.	Pseudoeph. 120mg Chlorphenir. 8mg	S.R. Cap.	BPC	10.00/8
	FLU	Chlorphenir. 2.5mg Phenyleph. 10mg Paracetamol 300mg Ascorbic Acid 100mg Caffeine 30mg	Tab.	JePharm	12.00/20
	FLU	*Each 5ml contain:* Chlorphenir. 1mg Phenylephrine 2mg	Syrup	JCL	12.00/60ml

MULTI-INGREDIENTS	***FORMULA 444***	*Each 5ml contains:* Dextromethor. 10mg Phenylpropan. 12.5mg Glycerly guaicolate 100mg	Syrup	JePharm	12.50/120ml
	HISTADEX	*Each 5ml contain:* Dexchlorphenir. 1mg Pseudoeph. 25mg	Syrup	Vitamid	15.00/115ml
	HISTAFED	Pseudoeph. 60mg Triprolidine 2.5mg	Drags Syrup	Trima	16.00/20 18.00/115ml
	NUSSIDEX	Pseudoephe. 25mg Dexchlorphen. 1mg	Tab. Syrup	Teva	15.00/20 15.00/115ml
	PARAFLU	Chlorphenir. 2.5mg Phenyleph. 10mg Paracetamol 300mg Ascorbic Acid 100mg Caffeine 30mg	Tab.	JCL	9.50/20
	PARAFLU	*Each 5ml contain:* Chlorphenir. 1mg Phenylephrine 2mg	Syrup	JCL	14.00/60ml
	PULMADRIN	*Each 5ml contain:* Pseudoeph. 30mg Triprolidine 1.25mg	Syrup	BPC	10.00/100ml
	TRICOLD	Paracetamol 350mg Phenlephr. 10mg Dextrometh. 7.5mg	Cap.	Agis	14.00/20
	TUSSIBAL EXPECTORANT	*Each 5ml Contain:* Guaifenesin 100mg Pseudoeph. 30mg Triprolidine 1.25mg	Syrup	JePharm	13.50/100ml
	TUSSIBAL HONEY	*Each 5ml contain:* Pseudoeph. 30mg Dextrometh. 10mg Triprolidine 1.25mg	Syrup	JePharm	14.00/100ml

ANTI-INFECTIVES

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
	ANTI-BACTERIALS				
	Penicillins				
Phenoxymethylpenicillin	***RAFAPEN V-K***	250mg 500mg 125mg/5ml 250mg/5ml	Tab. Tab. Susp. Susp.	Rafa	12.20/40 22.00/30 4.00/60ml 8.00/60ml
	RAFAPEN MEGA	990mg	Cap.	Rafa	32.00/20
	ORACILLIN	250mg 500mg 125mg/5ml 250mg/5ml	Tab. Tab. Susp. Susp.	JePharm	7.00/20 14.00/20 7.00/100ml 11.00/100ml
	BEPEN V.K.	250mg 500mg 250mg/5ml	Tab. Tab. Susp.	BPC	6.00/20 13.50/20 10.00/100ml
Cloxacillin	***LOXAVIT***	250mg 500mg	Cap.	Vitamed	6.50/10 20.00/10
	ORBENIL	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Syrup Syrup	Teva	8.70/12 12.00/10 14.00/60ml 21.30/60ml
Ampicillin	***PENIBRIN***	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	Teva	5.30/12 8.20/10 4.10/60ml 8.50/60ml
	PENTREXYL	125mg/5ml 250mg/5ml	Susp.	BMS	4.00/60ml 5.00/60ml
	BROADA-CILLIN	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	BPC	8.00/16 12.00/16 5.50/60ml 8.00/60ml
	AMPIPHARM	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	JePharm	7.00/16 12.00/16 5.00/60ml 8.00/60ml
Ampicillin + Flucoxacillin	***MAGNICILLIN***	250+250mg 250+500mg	Caps	BCP	20.00/16 30.00/16
	MEGACARE	500+250mg 250+125 mg/5ml	Cap. Susp.	Pharmacare	30.00/16 18.00/60ml 23.00/100ml

Amoxicillin	***AMOXICARE***	250mg 500mg 125mg/5ml 250mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp. Susp.	Pharmacare	9.00/16 14.00/16 9.00/100ml 12.00/100ml 9.00/60ml
	AMOXITID	250mg 500mg 750mg 125mg/5ml 250mg/5ml	Cap. Cap. Cap. Susp. Susp.	BPC	8.50/16 13.50/16 14.50/12 8.50/60ml 8.50/60ml
	HICONCIL	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	Mead-Johnson	11.00/12 12.00/12 8.00/60ml 11.00/60ml
	MOXYPEN	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	Teva	13.00/12 10.00/10 8.00/60ml 10.00/60ml
	MOXYVIT	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	Vitamed	15.00/10 20.00/20 8.10/60ml 10.00/60ml
	MOXEPHARM	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	JePharm	9.00/16 13.50/16 9.00/100ml 10.00/100ml
Amoxicillin & Clavulinic Acid	***AUGMENTIN***	250-125mg 500-125mg 875-125mg 457-75mg 250-62.5mg/5ml 125-31.25mg/5ml	Tab. Tab. Tab. Susp. Susp. Susp.	GSK	85.00/20 128.00/20 128.00/14 70.00/70ml 70.00/100ml 46.00/100ml
	AUGMENTIN-Duo	400-57mg Sugar Free	Susp.	GSK	46.00/35ml
	CURAM 625	500-125 mg 125-31.25mg /5ml	FC Tab. Susp.	Sandoz	50.00/20 26.00/100ml
	OGMIN	250-62.5mg/5ml 125-31.25mg/5ml	Susp. Susp.	BPC	50.00/100ml 35.00/100ml

	Cephalosporins				
Cephalexin	***CEFORAL***	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	Teva	19.00/12 38.10/12 14.60/60ml 27.60/60ml
	CEFACARE	500mg 250mg/5ml	Cap. Susp.	Pharmacare	29.00/16 16.00/60ml
	CEFALEX	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	BPC	18.00/16 29.00/16 10.00/100ml 21.00/100ml
	CEFOVIT	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	Vitamed	11.00/10 22.00/10 12.00/60ml 19.00/60ml
Cephalexin	***KEFLEX***	500mg 125mg/5ml 250mg/5ml	Cap. Susp. Susp.	Lilly	71.00/20 27.00/100ml 37.00/100ml
	JEFLEX	250mg 500mg 125mg/5ml 250mg/5ml	Cap. Cap. Susp. Susp.	JePharm	18.00/16 30.00/16 10.00/60ml 15.50/60ml
Cefaclor	***CECLOR***	250mg 500mg 750mg MR* 125mg/5ml 250mg/5ml	Cap. Caps Cap. Susp. Susp.	Lilly * (modified release)	48.00/12 62.00/12 73.00/12 36.00/60ml 54.00/60ml
Cefadroxil	***CEFADROX***	500mg 125mg/5ml 250mg/5ml	Tab. Susp. Susp.	BPC	31.00/12 12.00/60ml 20.00/60ml
	BIODROXIL	500mg	Cap.	Sandoz	43.00/12
	Tetracyclines				
Tetracycline	***TEVA-CYCLINE***	250mg	Cap.	Teva	6.00/20
	BRIMO-CYCLIN	250mg 500mg	Cap.	BPC	5.50/16 10.00/16
	TETRA-PHARM	250mg 500mg	Cap.	JePharm	5.00/16 10.00/16
	Macrolides				
Erythromycin	***ERYC*** (Erythromycin base)	250mg	Cap.	Taro	26.00/20
	ERYTHROCIN FILMTAB (Erythromycin stearate)	250mg	Tab.	Abbott	59.50/100ml

	ERYTHRO-TEVA (Erythromycin Stearate)	250mg 500mg 125mg/5ml 200mg/5ml 400mg/5ml	Tab. Tab. Susp. Susp. Susp.	Teva	11.00/12 21.40/10 11.00/60ml 13.40/60ml 25.00/60ml
	ERYTHROTAB (Erythromycin Stearate)	250mg	Tab.	BPC	18.00/24
	ERYTHRO-PHARM (Erythromycin Ethylsuccinate)	125mg/5ml 200mg/5ml	Susp. Susp.	JePharm	8.00/60ml 12.00/60ml
	ERYTHROLET (Erythromycin Ethylsuccinate)	25mg/5ml 200mg/5ml	Susp. Susp.	BPC	8.00/60ml 11.50/60ml
	ERYTHROCARE (Erythromycin Ethylsuccinate)	200mg/5ml 400mg/5ml	Susp. Susp.	Pharmacare	10.50/60ml 20.00/60ml
	Trimethoprim & Sulphonamindes				
TMP/SMX (Strength written as TMP/SMX)	***DISEPTYL***	80mg/400mg 40mg/200mg, 5ml	Tab. Susp.	Rekah	10.00/20 11.00/100ml
	RESPRIM	80mg/400mg 160mg/800mg 40mg/200mg, 5ml	Tab. Tab. Susp.	Teva	13.10/20 10.90/10 10.90/100ml
	SULFATRIM	80mg/400mg 160mg/800mg 40mg/200mg, 5ml	Tab. Tab. Susp.	Vitamed	6.20/20 21.80/20 10.00/100ml
	SULPRIM	80mg/400mg 160mg/800mg 40mg/200mg, 5ml	Tab. Tab. Susp.	JePharm	10.50/20 10.50/10 10.00/100ml
	Antibacterials for UTI				
Nitrofurantoin	***MACRODANTIN***	50mg 100mg	Macro-crystal Cap.	Procter & Gamble	213.00/100 427.00/100
	URANTOIN	100mg	Tab.	Rafa	41.84/500
	MACRO-FURAN	100mg	Cap.	BPC	35.00/24
Nalidixic Acid	***NEGGRAM***	250mg/5ml 250mg 500mg 1000mg	Susp. Tab. Tab. Tab.	Sterling-Winthrop	256.00/160ml 95.00/56 140.00/56 301.00/100
	URIGRAM	500mg	Tab.	Trima	76.20/60
	U-GRAM	250mg 500mg 250mg/5ml	Tab. Tab. Susp.	JePharm	45.00/50 90.00/50 43.00/100ml

Ciprofloxacin	***CIPROCARE***	250mg 500mg	Tab.	Pharmacare	27.00/10 50.00/15
	CIPROGIS	125mg 250mg 500mg 750mg	Tab.	Agis	24.00/6 69.00/10 175.00/10 252.65/10
	FLOXIN	250mg 500mg	Tab.	JePharm	68.00/20 68.00/10
	ANTI-TUBERCULOSIS				
Isonia-zide	***ISONIAZID***	50mg	Tab.	Rekah	73.70/50
Rifam-picin	***RIMACTAN***	150mg 300mg 100mg/5ml	Cap. Cap. Syrup	Sandoz	250.70/80 250.70/40 74.00/50ml
Pyrazin-amide	***Not available in local pharmacies.***				-
Etham-butol	***MYAMBUTOL***	100mg 400mg	Tab.	Lederle	62.90/100 123.70/100
	ANTI-PARASITICS				
Metronidazole	***FLAGYL***	250mg 500mg 125mg/5ml	Oral Tab. Vag. Tab. Susp.	Specia	14.00/20 18.00/10 26.00/120ml
	METROGYL	250mg 500mg	Oral Tab. Vag. Tab.	Teva	6.30/20 6.00/10
	METROZOLE	250mg 500mg 125mg/5ml 1000mg	Tab. Tab. Susp. Vag. Supp.	BPC	6.00/20 15.00/ 14.00/100ml 14.00/6
	ENTOGYL	250mg 125mg/5ml	Tab. Susp.	JePharm	7.50/20 15.00/120ml
Mebend-azole	***VERMOX***	100mg 100mg/5ml	Tab. Susp.	Abic	11.00/10 14.00/30ml
	VERMAZOL	100mg 100mg/5ml	Tab. Susp.	JePharm	10.00/6 12.00/30ml
Niclos-amide	***YOMESAN***	500mg	Tab.	Bayer	20.00/4
Albend-azole	***ESKAZOLE***	400mg	Tab.	GSK	591.00/60

	ANTI-FUNGALS				
Nystatin	***NYSTATIN***	100,000 U 500,000 U 100,000 U/ml	Vag. Tab. Drags Mixture	Taro	14.50/10 42.00/28 35.00/30ml
	CANDISTAN	100,000 U 100,000 U/ml	Vag. Tab. Oral Drops	BPC	8.50/15 9.00/12ml
Miconazole Nitrate	***DAKTARIN ORAL GEL***	2%	Gel	Abic	41.00/40g
	GYNO-DAKTARIN	1200mg	Ovule (vaginal inserts)	Abic	35.50/3
	DAKTAZOL ORAL GEL	2%	Gel	JePharm	12.00/40g
	FUNGAZOLE	2%	Cream	Pharmacare	10.00/15g
	GYNO-DAKTAZOL	2%	Vaginal Cream	JePharm	30.00/40g
	GYNO-DAKTAZOL OVULES	400mg	Ovules	JePharm	21.00/3
Griseo-fulvin	***GRIFULIN FORTE***	125mg	Tab.	Teva	24.00/60
	SPORO-FULVIN	125mg 125mg/5ml	Tab. Susp.	JCL	17.50/20 17.50/100ml
	ANTI-VIRALS				
Acyclovir	***SUPRAVIRAN***	800mg 200mg/5ml	Tab. Susp.	Pharmacare	110.00/35 55.00/125ml
	ZOVIRAX	200mg 400mg 200mg/5ml	Tab. Tab. Susp.	GSK	48.00/25 138.00/70 307.00/125ml
	VIRAX	200mg	Tab.	BPC	Not in private pharmacies

ENDOCRINE DISORDER DRUGS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
	ANTIDIABETICS				
	Insulin				
Regular Insulin	***NOVOLIN R***	Regular Insulin	IV or IM	Novo Nordisk	120.00/10ml
	HUMULIN R	Regular Insulin	IV or IM	Lilly	102.00/10ml
NPH	***NOVOLIN N***	NPH	IM	Novo Nordisk	120.00/10ml
	HUMULIN N	NPH	IM	Lilly	120.00/10ml
	Oral agents				
Glibenclamide/ Glyburide	***DAONIL***	5mg	Tab.	HMR	62.00/100
	DECLAMIDE	5mg	Tab.	JCL	7.00/20
	GLUCOCARE	5mg	Tab.	Pharmacare	8.00/30
	GLUCONIL	5mg	Tab.	JePharm	7.00/30
	GLIBETIC	5mg	Tab.	Teva	10.00/30
Met-formin-	***GLUCOPHAGE***	850mg	Tab.	BMS	15.00/30
	GLUCOMET	850mg	Tab.	BPC	10.00/30
	THYROID DISORDERS				
Thyro-xine	***ELTROXIN***	50mcg 100mcg	Tab.	GSK	16.00/100 19.00/100
PTU	***PROPYL-THIOCIL***	50mg	Tab.	Teva	12.00/30
	CORTICOSTEROIDS Refer to Prednisone in the Respiratory Chapter price list.				

CONTRACEPTIVE PREPARATIONS

Generic Name	BRAND NAME	STRENGTH/ DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
Combined Contraceptive Agents				
Ethinyloestradiol & Gestodene	***GYNERA***	Ethinyloestradiol 0.03mg Gestodene 0.075mg	Schering	27.00 (21 Tab. sachet)
	MINULET	Ethinyloestradiol 0.03mg Gestodene 0.075mg	Wyeth	24.90 (21 Tab. sachet)
Norethisterone & thinyloestradiol	***MINOVLAR*** *(mono-phasic):*	Norethisterone 1mg Ethinyloestradiol 0.05mg	Schering	(21 Tab. sachet)
	OVYSMEN *(mono-phasic):*	Norethisterone 0.5mg Ethinyloestradiol 0.035mg	Ortho	30.00 (21 Tab. sachet)
Norethisterone & Ethinyloestradiol	***TRINOVUM*** *(Triphasic)*	7 Tab.: Norethisterone 0.5mg Ethinyloestradiol 35mcg 7 Tab.: Norethisterone 0.75mg Ethinyloestradiol 35mcg 7 Tab.: Norethisterone 1mg Ethinyloestradiol 35mcg	Ortho	29.00 (21 Tab. sachet)
Levonorgestrel & Ethinyloestradiol	***MICROGYNON*** *(mono-phasic)*	Levonorgestrel 0.15mg Ethinyloestradiol 0.03mg	Schering	13.50 (21 Tab. sachet)
	NORDETTE *(mono-phasic)*	Levonorgestrel 0.15mg Ethinyloestradiol 0.03ml	Wyeth	13.00 (28 Tab. sachet)
Levonorgestrel & Ethinyloestradiol	***LOGYNON*** *(tri-phasic)*	6 Tab.: Levonorgestrel 0.05mg Ethinyloestradiol 0.03mg 5 Tab.: Levonorgestrel 0.075mg Ethinyloestradiol 0.04mg 10 Tab.: Levonorgestrel 0.125mg Ethinyloestradiol 0.03mg	Schering	17.00 (21 Tab. sachet)

	TRINORDIOL *(tri-phasic)*	6 Tab.: Levonorgestrel 0.05mg Ethinyloestradiol 0.03mg 5 Tab.: Levonorgestrel 0.075mg Ethinyloestradiol 0.04mg 10 Tab.: Levonorgestrel 0.125mg Ethinyloestradiol 0.03mg	Wyeth	19.00 (21 tab. sachet)
	Progestin Only Products			
Progestin	***FEMULEN***	Ethynodiol diacetate 0.5mg (28 Tab.)	Searle	19.00 (28 tab. sachet)
	DEPO-PROVERA	Medroxy-progesterone Acetate 150 mg/ml (Vial, IM)	Upjohn	49.00/ 1 ml (one dose vial)

ANTIEPILEPTICS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
Carbamazepine	***CARBI***	200mg	Tab.	AlphaPharm	33.50/50
	TEGRETOL	200mg 100mg/5ml 200mg CR 400mg CR	Tab. Syrup Tab. Tab.	Novartis	87.00/50 44.00/250ml 70.00/50 70.00/30
	TEGREPINE	200mg	Tab.	JePharm	47.00/50
	TERIL	200mg 400mg	Tab.	Taro	65.00/50 54.00/30
Clonaze -pam	***KLONOPIN/ RIVOTRIL***	2.5mg/ml	Drops	Roche	25.50/10ml
	CLONEX	0.5mg 2mg	Tab.	Teva	10.00/30 19.00/30
ESX.	***ZARONTIN***	250mg	Cap. Syrup	Parke-Davis	53.00/50 73.00/300ml
Phenobarb.	***PHENOBARB***	100mg 15mg	Tab. Tab.	Eastern Chem.	15.00/40 8.00/40
Pheny-toin	***EPANUTIN***	50mg 100mg 30mg/5ml	Cap. Cap. Susp.	Parke-Davis	130.00/500 34.00/100 19.85/100ml
Valproic acid	***DEPALEPT***	200mg 500mg 200mg/ml 200mg/5ml	Tab. Tab. Solution Syrup	CTI	55.90/40 129.00/40 41.00/50ml 21.00/110ml
	VALPORAL	200mg 200mg/5ml	Cap. Syrup	Teva	41.10/40 14.10/100ml

ANTIPARKINSONISM

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
Anticholinergics					
Benzo-Tropine	***COGENTIN***	2mg	Tab.	MSD	/20 Not available in the private market.
Trihexy-Phenidyl	***ARTANE***	2mg 5mg	Tab.	Lederle	34.00/100 38.00/100
	PARTANE	2mg 5mg	Tab.	Taro	7.50/50 11.00/50
Dopaminergic Drugs					
Amant-adine	***PARITREL***	100mg	Tab.	Trima	47.00/20
	SYMMETREL	100mg	Cap.	Novartis	44.00/20
Bromo-criptine	***LACTOPAR***	2.5mg	Tab.	BCP	65.00/30
	PARILAC	2.5mg 10mg	Tab.	Teva	102.00/30 214.00/20
	PARLODEL	2.5mg	Tab.	Novartis	107.00/30
Carbidopa/ Levodopa	***SINEMET-110***	10mg/ 100mg	Tab.	Dupont	Not available in the market
	SINEMET-275	25mg/ 250mg	Tab.	Pharm.	Not available in the market
	SINEMET CR	50mg/ 200mg	Tab.	Pharm.	111.30/30
	DOPICAR	25mg/ 250mg	Tab.	Assia/Riesel	76.00/30

PSYCHOACTIVE DRUGS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
	Antidepressants				
Amitriptyline	***AMYVIL***	25mg	Tab.	JePharm	Not in private market.
	ELATROL	25mg	Tab.	Assia/Riesel	12.50/50
	ELATROLET	10mg	Tab.	Assia/Riesel	9.00/50
	TRYPTAL	25mg	Drags	Unipharm	9.00/50
	TRYPTA-LETTE	10mg	Drags	Unipharm	4.00/50
Imipr-amine	***PRIMONIL***	25mg	Tab.	Teva	9.00/50
	TOFRANIL	25mg	Tab.	Novartis	37.00/50
Fluoxetine	***AFFECTINE***	20mg	Cap.	Taro	66.10/28
	FLUOXICARE	20mg	Cap.	Pharmacare	26.00/14
	FLUTINE	20mg	Caps	Teva	67.50/30
	PRIZMA	20mg 40mg	Tab.	Unipharm	67.00/30 126.50/20
	PROZAC	20mg	Cap.	Lilly	101.00/14 216.10/28
	Hypnotics And Anxiolytics				
Diazepam	***ASSIVAL***	2mg 10mg	Tab.	Teva	4.00/30 10.00/30
	DIAZ	2mg 5mg 10mg	Tab.	Taro	3.80/30 6.70/30 10.30/30
	DISOPAM	2mg 5mg 10mg	Tab.	Dexxon	2.80/30 4.80/30 6.00/30
	HARMONAL	2mg 5mg	Tab.	JCL	3.00/20 3.50/20
	SEREPAM	2mg 5mg 10mg	Tab.	BPC	3.50/20 4.50/20 5.00/20
Lora-zepam	***LORIVAN***	1mg	Tab.	Dexxon	14.00/50
	LOROCARE	1mg 2.5mg	Tab.	Pharmacare	8.00/40 8.50/20
	Neuroleptics				
CPZ	***TAROCTYL***	25mg 100mg	Tab.	Taro	17.00/50 20.00/50
Halo-peridol	***HALIDOL/HALDOL***	5mg 2mg/ml	Tab. Drops	Abic	35.25/60 12.87/15ml
	PERIDOL	5mg	Tab.	Eastern Chem.	9.00/20
	PERIDOR	1mg	Tab.	Unipharm	14.40/60

OPTHALMIC PREPARATIONS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
ANTI-INFECTIVES					
Antibiotics					
Chloramphenicol	***CHLOROCETIN***	5% 0.5%	Eye Drops. Eye Oint.	Eastern Chem.	10.00/7ml 7.00/3.6g
	CHLOROPTIC	0.5%	Eye Drops	Allergan	17.50/10ml
	SYNTHO-MYCINE	5%	Eye Oint.	Abic	6.00/4g
	LOMIXIN	5mg/ml	Eye Drops	Jordan	9.00/10ml
	RAMACETINE	5%	Eye Oint. Eye Drops	BCP	8.00/3.5g 5.50/10ml
Tetracyclines	***JORDACYCLINE***	0.5% Oxy.	Eye Oint.	JCL	7.5.00/4g
	OXYCIN	0.5% Oxy.	Eye Oint.	BCP	5.00/3.5g
	RECYCLINE	1% Tetrac.	Eye Oint.	Rekah	14.00/3.5g
	TEVACYCLINE	1% Tetrac.	Eye Oint.	Teva	9.00/3.5g
Genta-mycin	***GARAMYCIN OPHTHALMIC***	0.3%	Solution	Schering Plough	9.00/5ml
	GENTICIN	0.3%	Eye Drops	JePharm	10.00/5ml
Antivirals					
Idox-uridine	***VIRUSAN***	1mg 5mg	Eye Drops Eye Oint.	Teva	7.00/7ml 17.00/5g
Anti-Inflammatory Preparations					
Corticosteroid	***OPTISOLONE***	0.5% Pred-nisolone	Eye Drops	JePharm	9.00/5ml
	PREDNICORT	0.12% 1% Prednisolone acetate	Drops Forte Drops	Eastern Chem.	13.00/7ml 19.00/7ml
	STERODEX	0.1% Dexa-methasone	Eye Drops	Fischer	11.00/5ml
	ULTRACORTENOL	0.5% Predni-solone trimethyl-acetate	Eye Oint. Eye Drops	Novartis	23.00/5ml
Cromo-glycate	***OPTICROM***	2%	Eye Drops	Fisons	71.00/13.5ml

	Beta-Blockers				
Timolol Maleate	***TILOPTIC***	0.25% 0.5%	Eye Drops	Assia/Riesel	14.00/5ml 14.00/5ml
	SINOPTIC	0.25% 0.5%	Eye Drops	Eastern Chem.	10.00/5ml 12.00/5ml
	TIMOLIN	0.25% 0.5%	Eye Drops	JePharm	14.00/5ml 18.00/5ml
	Mydriatics and Cycloplegics				
Atropine Sulfate	***ATROSPAN***	1%	Eye Drops	Fischer	10.00/10ml
	ATROPED	1%	Eye Drops	Eastern Chemical	10.00/10ml

OTIC PREPARATIONS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
	Ear Wax Removers				
Cerumol	***CERUMOL***	Paradichloro-benzene 2g Benzocaine 2.7g Chlorbutol 5g Ol-terebinth 10cc/100cc	Drops	Tamar	24.00/11ml
Most anti-infective and anti-inflammatory otic products are available in combination products:					
Combination Products	***BETNESOL***	0.1% Beta-methasone	Drops	GSK	8.00/5ml
	DEX-OTIC	*Each 1ml contains*: Dexamethasone 1mg Neomycin 5mg Polymyxin 10,000 IU	Drops	Teva	11.00/5ml
	HYCOMYCIN	Hydrocortisone 1.5% Neomycin 0.5%	Drops Ointment	Teva	9.00/5ml 9.00/3.5g
	NOVOCORT	Dexamethasone 0.1% Neomycin 0.5% Polymyxin B 0.119%	Drops	JCL	10.00/10ml
	OTOCORT	Dexamethasone 1mg Neomycin 5mg Polymyxin B 10,000 IU/ml	Drops	BCP	10.00/5ml
	OTOSPORIN	Polymyxin-B 10,000 IU Neomycin 5mg Hydrocortisone 10mg/ml	Drops	GSK	51.00/5ml
	POLYMICIN	Polymyxin B 2500 IU Chloramphenicol 0.2% w/v	Drops	JePharm	10.00/5ml

DERMATOLOGICALS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
	General				
Vaseline	***JOHNSON'S JELLY***	100% pure Petroleum	Jelly	Johnson & Johnson	12.00/250g
	VASELINE	100% pure Petroleum	Jelly	Elida Faaberge	15.00/212g
	VESALINE (scented)	100% pure Petroleum	Gel	Medix	6.00/50g
	WHITE PETROLEUM	White petroleum	Jelly	Lader	12.00/200g
Zinc Oxide/Calamine	***ADINOL*** *(includes mineral oil, + vaseline.)*	40% ZnO	Ointment	Teva	13.00/100
	CALADERM	12.5% Calamine 8% ZnO	Cream Lotion	JePharm	10.00/30g 10.00/100ml
	CALAMINE	15% Cal. 5% ZnO	Lotion	Sam-On	9.00/100ml
	CALATRIM	15% Cal. 5% ZnO	Lotion	Trima	12.00/100ml
	DYPROTEX	40% ZnO	Medicated Pads	Mediline	17.00/30g
Lignocaine	***ESRACAIN***	5% Lignoc.	Ointment	Rafa	11.00/20g
	ESRACAIN JELLY	2% Lignoc.	Jelly	Rafa	10.00/30g
	XYLENE	2% Lignoc.	Gel	BPC	8.00/40g
	Antifungals				
Miconazole Nitrate	***DAKTARIN***	2%	Cream Lotion	Abic	22.00/15g 22.00/20ml
	DAKTAZOL	2%	Cream Oral gel	JePharm	10.00/15gm 17.00/40gm
	FUNGAZOLE	2%	Cream	Pharmacare	9.50/15gm
	FUNGITRIN	2%	Cream Oral gel	BPC	10.00/15gm 14.00/30gm
Clotrimazole	***AGISTEN***	1%	Cream Lotion	Agis	17.00/20g 20.00/15ml
	MYCOHER-MAL	1%	Cream Solution	Neopharm	20.00/20g 22.80/20ml
	CANESTEN/ AGISTIN	1%	Cream Solution	Agis/Bayer	17.00/20g 20.00/20ml
	CANAZOLE	1%	Cream	JePharm	13.00/20mg
	CANDIZONE	1%	Cream	BCP	15.00/15gm

Keto-conazole	***NIZORAL***	2%	Cream	Abic	40.00/15gm
	NIZORAL	2%	Shampoo	Abic	48.00/100ml
Tolnaftate	***ATHLETES FOOT***	1%	Powder	Scholl	25.70/80g
	PITREX	1%	Ointment Solution	Teva	17.00/15g 17.00/10ml
	TINADERM	1%	Solution	Schering	Not in the market.
	Antibacterials				
Oxytetracycline/ Tetracycline	***RECYCLINE***	3% Oxy.	Ointment	Rekah	14.00/14g
	TETRACARE	3% Oxy.	Ointment	Pharmacare	6.00/20g
	TETRAPHARM	3% Oxy.	Ointment	JePharm	7.50/20g
	OXYCIN	3% Tetracyc.	Ointment	BCP	5.00/18g
	JORDA-CYCLINE	3% Tetracyc.	Ointment	JCL	7.50/16g
Gentamycin	***GARAMYCIN***	0.1% Genta.	Cream Ointment	Schering	13.00/15g 13.00/15g
	GENTATRIM	0.1% Genta.	Cream Ointment	Trima	15.00/15g 15.00/15g
	GARAMINE	0.1% Genta.	Cream	JCL	12.00/16g
Mupir-ocin	***BACTROBAN***	2%	Ointment	GSK	48.00/15g
	Antivirals				
Acyclovir	***SUPRAVIRAN***	5%	Cream	Pharmacare	Not in market yet.
	ZOVIRAX	5%	Cream	GSK	34.00/2g 146.00/10g
	Antiseptics/Disinfectants				
Ethyl Alcohol	***ETHYL ALCOHOL***	Different containers, depending on hospital or pharmacy.			
Povidone-Iodine	***BETADINE***	10% (1% iodine)	Ointment Solution	Rafa	44.00/1L
	POLYDINE	10%	Solution Tincture	Fischer	10.00/20ml
	IODOCARE	10%	Solution-Mouthwash	Pharmacare	9.00/100ml
	IOSEPT	10%	Solution	BPC	11.00/100ml

Cetrimide & Chlorhexidine	***CARE*** *first aid solution*	0.5% Cetrim. 0.05% Chlorh.	Solution	Pharmacare	3.00/100ml
	CARE 15% *first aid solution*	15% Cetrim. 1.5% Chlorh.	Solution	Pharmacare	Not sold in private pharmacies.
	CETRIN	15% Cetrim. 1.5% Chlorh.	Concentrated solution	Vitamid	52.00/1L
	SAVIOR *first aid solution*	0.5% Cetrim. 0.05% Chlorh.	Solution	Travenol	7.00/100ml
	TISEPT	0.15% Cetrim. 0.015% Chlorh.	Solution	Seton	100ml Not sold in pharmacies.
	UNISCRUB	4% Chlorh.	Solution	Seton	45.00/500ml
	Antiparasitics				
Benzyl Benzoate	***BENZOCIDE***	12.5% 25%	Lotion	Trima	30.00/100ml
	SCABICIDE	25%	Emulsion	BCP	12.00/100ml
	SCABIEX	25%	Emulsion	Rekah	
Crotamiton	***CRUTEX***	10% Crotam.	Cream Lotion	BCP	14.50/20gm 12.50/50ml
	DUO-SCABIL	10% Crotam. 8% Sulfur	Cream	Agis	26.00/20g
	EURAX	10% Crotam.	Cream Lotion	Novartis	15.00/20g 25.00/50ml
	SCABICIN	10% Crotam.	Lotion	Fischer	24.00/100ml
Lind-ane	***BICIDE***	1% Lindane	Cream	Fischer	25.00/50ml
	PARAZINE	1% Lindane	Cream	al-Razi	24.00/200g
Mal-thion	***NOURYL***	0.5%	Lotion	Chefaro	Not available in WB market.
	PRIODERM	1%	Cream-Shampoo	Napp/Rafa	17.00/40g
	Keratolytic Agents				
Salicylic Acid	***OXY CLEAN*** *medicated soap*	3.5 % Sal. acid	Soap	GSK	17.00/Bar
	SALATAC	12% Sal. acid	Gel	Dermal Labs	58.00/8g
	ZINO PADS	40% Sal. acid	Pads	Scholl	8.00/5 pads
	SALISOL-2 (contains ethanol 70%)	2% Sal. acid	Solution	Rekah	10.00/100ml
Sulfur	Not available as single agent products.				

	Miscellaneous				
Corticosteroids	***BETACARE***	0.1% Beta-methasone Valerate	Cream	Pharmacare	10.00/15gm
	BETACORT-V	0.1% Beta-methasone Valerate	Cream	JCL	7.00/16gm
	BETACORTEN	0.1% Beta-methasone 17-valerate	Cream Ointment	Trima	10.00/15g 10.00/15g
	BETAMESONE	0.1% Beta-methasone Valerate	Cream Ointment	JePharm	7.00/15g 7.00/15g
	BETNOVATE	0.1% Beta-methasone 17-valerate	Cream Ointment	GSK	10.00/15g 10.00/15g
	DERMOVATE	0.05% Clobetazole propionate	Cream Ointment	GSK	24.00/25g 28.00/25g
	PSORIDERM	0.05% Clobetazole propionate	Ointment	BPC	17.00/25g
	VALECORT	0.1% Beta-methasone Valerate	Cream Ointment	BPC	12.00/15g 8.50/15g
Retinoic Acid	***LOCACID***	0.5% 0.1%	Cream Lotion	Fabre/Mediline	40.00/30g 40.00/15ml
	RETAVIT	0.05% 0.025% 0.05% 0.025%	Cream Gel	CTI	36.00/20g 20.00/20g 36.00/20g 20.00/20g
	RETIN-A	0.05% 0.025%	Cream	JanssenCilag	49.00/30g 40.00/30g
	AIROL	0.05%	Cream Lotion	Roche	35.00/20g 52.00/50ml
Benzoyl Peroxide	***OXY***	5% 10%	Vanishing - cream	GSK	39.00/28g 39.00/28g
	ACNEMASK	5%	Lotion	Neutrogena	22.00/

Sunscreens

There are various products available in pharmacies that a person can choose from, which range in price (20-90NIS) and SPF (6-45) that cannot all be listed. But some examples include:

Various Ingredients	***CAPITOL SOLEIL SUN BLOCK***	SPF 15 SPF 25 SPF 45	Face Cream	Vichy	79.00/50ml 79.00/50ml 84.00/50ml
	HYDROSOL	SPF 6 SPF15 SPF 25	Lotion	Henkel/Raed	21.00/125ml 25.00/125ml 29.00/125ml
	ULTRASOL	SPF 15 SPF 25 SPF 34 SPF 45	Cream	Dr. Fisher	25.00/50g 30.00/50g 35.00/50g 40.00/50g

VITAMINS AND MINERALS

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
Fat Soluble Vitamins available as single products					
Retinol	***AVIPUR***	Vitamin A 50,000U	Drags	Taro	17.00/30
Alpha-tocopherol & thinyloestradiol	***EPHYNAL***	Vitamin E 100mg	Chewable-Drags	Roche	27.00/30
	EVITOL	Vitamin E 100mg 200mg	Tab.	Teva	12.00/30 19.00/30
	SANATOGEN	Vitamin E 100mg	Tab.	Fisons	12.00/
	VITAMIN E/ *(with wheat germ oil)*	200IU/ 200mg 400IU/ 20mg 600IU/ 66mg	Cap.	Burton Feingold	42.00/45 caps 59.00/40 62.00/60
Water Soluble Vitamins available as single products					
Pyridoxine	***ANACRODYNE***	Vitamin B6 30,100mg	Tab.	Rekah	13.00/
	B. SIX 300	Vitamin B6 300mg	Tab.	Sam-On	33.00/30
Ascorbic Acid	***C 500***	Vitamin C 500mg	Tab.	Rekah	22.00/100
	REDOXON	Vitamin C 1000mg	Efferves. Tab.	Roche	16.00/10
	VI-C 500	Vitamin C 500mg	Chewable Tab.	Sam-On	10.00/10
	VITASCARBOL	Vitamin C 500mg	Lozenges	Specia	7.00/12
Folic Acid	***FOLIC ACID***	Folic Acid 5mg	Tab.	Sam-On	15.00/30
Vit. B3	***NICOLAR***	Niacin/ Nicotinic Acid 500mg	Tab.	Armour	263.00/100
Minerals NOTE: The strengths below are expressed in their elemental equivalence. (i.e. 600mg of elemental calcium is equivalent to 1500mg of calcium carbonate)					
Calcium	***CALTRATE 600***	Ca Carbonate 600mg	Enteric Coated Tab.	Lederle	57.00/60
	TUMS	Ca Carbonate 500mg	Chewable Tab.	GSK	17.00/36 29.00/75

Iron	***FERRO 15***	Ferrous Gluconate 15mg/5ml	Syrup	Sam-On	16.00/120ml
	FERRO 23	Ferrous Gluconate 23mg/5ml	Syrup	Sam-On	18.00/120ml
	FERRO-GRAD	Ferrous Sulfate 105mg	Tab.	Abbott	17.00/30
	SLOW-FE	Ferrous Sulfate 50mg	Slow Release Tab.	Novartis	10.00/28
Fluoride	***FLUDEN***	Na Floride 0.5mg	Tab.	Rekah	8.00/100
	FLUVIUM-20	Na Floride 20mg	Tab.	Rekah	26.00/60
	TEETH TOUGH	Na Floride 0.25mg/2 drops	Oral drops	Vitamed	/50ml
	ZYMAFLUOR	Na Floride 0.25 1 mg	Tab.	Novartis	18.00/100
Potassium	***SLOW-K***	Potassium Cl 600mg (equiv. to 315 mg K^+)	Slow Release Tab.	Novartis	17.00/100

Vitamins and Minerals Available in COMBINATION PRODUCTS				
Generic Name	**BRAND NAME**	**DOSAGE FORM/ STRENGTH**	**MANUFACT-URER**	**SELLING PRICE (NIS)/ # OF DOSAGE FORM**
	CALCIUM SANDOZ + VIT C	**(Efferves. Tab.)** Vit. C 1000mg Ca Gluconate 578mg, Ca Lactate 422mg, Cal Carbonate 327mg	Novartis	18.00/10
	CAl-C-VITA	**(Effervesc. Tab.)** Vit. C 1000mg Ca 250mg Vit. D 300 IU Vit. B_6 15mg Citric Acid 1350mg	Roche	20.00/10
	CALTRATE 600+ VIT. D.	**(Enteric Coated Tab.)** Ca Carbonate 1500 eq. to 600mg elemental Ca. + Vit. D 125 IU	Lederle	57.00/60
	CENTRUM-V	**(Tab.)** Vit. A 5000 IU, Vit. E 30 IU Vit. C 90mg, Vit. B_1 2.25mg Vit. B_2 2.6mg, Vit. B_6 3mg Vit. B_{12} 9mcg, Vit. D 400 IU Folic Acid 400mcg Niacin 20mg, Biotin 45mcg Vit. B_5 10mg, Ca 16mg Phosphorus 125mg Iodine 27mg, Mg 100mg Copper 3mg, Mn 7.5mg K 7.5mg, Zn 22.5mg	Lederle	55.00/30
	CENTRUM JUNIOR ADVANCED + IRON	**(Chewable Tab.)** Vit. A 5000 IU, Vit. D 400 IU Vit. E 30 IU, Vit. C 60mg Vit. B_6 2mg, Vit. B_{12} 6mcg Vit. K 10mcg, Biotin 45mcg Folic Acid 400mcg Thiamine 1.5mg, Vit. B_5 10mg Vit. B_2 1.7mg, Niacin 20mg Iron 18mg, Mg 40mg Iodine 150mcg, Copper 2mg Phosphorus 50mg, Ca 108mg Zn 15mg, Chromium 20mcg Mn 1mg	Lederle	49.00/30

	CENTRUM PLUS	**(Tab.)** Vit. A 4000 IU, Vit. E 30 IU Betacarotene 1000IU Vit. C 60mg, Vit. B_1 1.5mg Vit. B_2 1.7mg, Vit. B_6 2mg Vit. B_{12} 6mcg, Vit. D 400 IU Vit. K 25mcg, Niacin 20mg Folic Acid 400mcg Biotin 30mcg, Vit. B_5 10mg P 150mg, Ca 194mg, Iodine 150mcg, Iron 18mg Mg 100mg, Mn 2.5mg Cu 2mg, Zinc 15mg Cr 25mcg, Se 60mcg Molybedenum 60mcg Nickel 5mcg	Lederle	55.00/30
	KIDDI	**(SYRUP)** Vit. A 2000 IU Vit. D_2 400 IU Vit. B_1 10mg, Vit. B_2 6mg, Vit. B_{12} 10mcg, Vit. B_6 3mg Ca 39 Phosphorous 61 mg Lycine pharmaton 200mg Nicotinamide sugar excip 10ml	Pharmaton	40.00/100ml
	MATERNA ENHANCE FORMULA	**(Tab.)** Vit. A 5000 IU, Vit. B_1 3mg Vit. B_2 3.4mg, Vit. B_5 10mg Vit. B_{12} 12mcg, Vit. B_6 10mg Vit. D 400 IU, Vit. E 30 IU Niacin 20mg, Biotin 30mcg Iron 60mg, Ca 250mg Iodine 150mcg, Mg 25mg Copper 2mg, Zn 25mg Chromium 25mg, Mn 5mg Molybdenum25mcg	Lederle	140.00/100 48.00/30
	ORACAL-D	**(Cap.)** Ca Carbonate 1500 eqv. to 600mg elemental Ca. + Vit. D 125 IU	BPC	35.00 /50
	POLYVIT	**(Drags)** Vit. A 5000 IU, Vit. B_1 5mg Vit. B_2 3mg, Vit. B_6 1mg Vit. B_{12} 20mcg, Vit. C 50mg Vit. D 400 IU, Vit. B_5 3mg Folic Acid 2mg, Niacin 25mg Iron 3.3mg, Ca 60mg P 40mg, Mn 167mcg Mg 6.67mg	Taro	66.00/30
	SLOW-FOLIC	(Tab.) Ferrous sulphate 160mg (eq. to 50 mg Fe), Folic acid 400 mcg	Novartis	15.00 /28

	STRESSTAB.	**(Tab.)** Vit. E 30 IU, Vit. C 600mg Vit. B_1 15mg, Vit. B_2 15mg Vit. B_6 25mg, Vit. B_{12} 12mcg Niacin 100mg, Vit. B_5 20mg Folic Acid 400mcg	Lederle	40.00/30
	STRESSTAB. 600 WITH IRON	**(Tab.)** Vit. E 30 IU, Vit. C 600mg Vit. B_1 15mg, Vit. B_2 15mg Vit. B_6 25mg, Vit. B_{12} 12mcg Niacin 100mg, Vit. B_5 20mg Folic Acid 400mcg Iron 27mg	Lederle	36.00/30
	SUPRADYN N	**(Drags, Efferves. Tab.)** Vit. A 3333 IU, Vit. B_1 20mg Vit. B_2 5mg, Vit. B_6 10mg Vit. B_{12} 5mcg, Vit. C 150mg Vit. D 500 IU, Vit. E 10mg Vit. B_5 11.6mg, Niacin 50mg Folic Acid 1mg, Biotin 0.25 Ca, Iron, Mg, Mn, Phosphorus, Copper Molybdenum, Zinc	Roche	35.00/30
	VI-DAYLIN PLUS IRON	**(Syrup)** Vit. A 2500 IU, Vit. D 400 IU Vit. E 15 IU, Vit. C 600mg Vit. B_1 1.05mg, Vit. B_2 1.2mg Vit. B_{12} 4.5mcg, Vit. B_6 1.05mg Niacin 13.5 mg, Iron 10mg	Abbott	33.00/240
	MINOVIT	**(Tab.)** Vit. A 800 IU, Vit. D 400 IU Vit. E 0.75MG, Vit. C 25mg Folic Acid 0.1mg, Vit. B_1 5mg Vit. B_2 1mg, Vit. B_5 6mg Vit. B_{12} 1mcg, Vit. B_6 2mg Ferrous Ammon. Citrate 3mg Ca 40mg, Niacin 6mg Mg 20mg, Mn 4mg	JePharm	14.00./30
	ABECIDEN	**(Tab.)** Vit. A 5000 IU, Vit. B_1 2.5mg Vit. B_2 2.5mg, Vit. B_6 2mg Vit. B_{12} 10mcg, Vit. C 50mg Vit. D 400 IU, Vit. E 30 IU Niacin 30mg, Vit. B_5 3mg Folic Acid 0.8mg Ca 125mg, Iron 18mg Mg 10mg, Iodine 0.15mg	BPC	18.00/30
	VICAL	**(Efferves. Tab.)** Vit. C 1000mg, Ca 250mg Vit. D 300 IU, Vit. B_6 15mg	BPC	14.00/10

There are several other products that contain various vitamins and minerals in other concentrations, or in combination with herbal or amino acids (i.e. ginseng, lysine, pantothenate) that will not be listed.

VACCINES

Generic Name	BRAND NAME	STRENGTH	DOSAGE FORM	MANUFACT-URER	SELLING PRICE (NIS)/ # OF DOSAGE FORM
BCG	***BCG***	As recommended by WHO			
OPV	***POLIO SABIN***	As recommended by WHO	Oral use only	GSK	19.59/1 dose amp.
IPV	***IMOVAX POLIO***	0.5 ml contains inactivated poliovirus type 1,2 &3 for one immunization dose.	SC or IM	Pasteur Merieux	
Tetanus	***TETANOL***	0.5 ml contains tetanus toxoid at least 40 IU.	Suspension given IM or deep SC	Chiron Gehring	
	TETANUS TOXOID PTAP	0.5 ml tetanus toxoid as recom-mended by WHO	Suspension for IM	Rafa	4.00/1 dose ampoule
DPT	***D.T.COQ***	Purified diphtheria toxoid at least 30 IU Purified tetanus toxoid at least 60 IU Bordetella pertussis at least 4 IU	Suspension for injection given IM or deep SC	Rhone Poulenc group	
	DiTePer ANATOXAL BERNA	Purified adsorbed diphtheria-tetanus-Pertussis at least 20,000 million-Toxoids	Suspension for injection given IM or deep SC	Swiss Serum and Vaccine Institute Berne	
Measles	***RIMEVAX***	Not less than 1.000 TCID50 of the Schwarz strain	Lyophilized powder to be reconstituted for SC only	GSK	48.50/1 dose vial
MMR	***MMR VACCINE***	Live attenuated strains of Edmonston-Zagreb measles, mumps and Wistar RA 27/3 rubella virus.	Freeze-Dried vial for dilution given by deep SC	Serum Institute of India LTD	
	TRIMOVAX MERIEUX	Live hyper-attenuated measles (Schwarz strain), mumps (Urabe 9 strain), rubella (RA27/3M strain)	Powder for dilution given SC or IM.	Pasteur Merieux	

Hepatitis B	***ENERGIX-B***	Pediatric: 10 ug in 0.5ml rDNA hepatitis Adult: 20*u*g/1ml	Solution for IM use	GSK	77.00/1 dose vial for child. 102.00/1 dose vial for adult.
	EUVAX B Inj.	Purified HBs Antigen 10 *u*g in 0.5 ml	Susp. for IM use only	LG Chemical Ltd.	
	HEPAVAX-GENE RECOMBINANT	10 *u*g of HbsAG in 0.5 ml	IM injection only	Korea Green Cross Corp	
Influenza vaccine	***Every season there is a different preparation depending on influenza strains.***	-	Solution for IM use		Price range from 25 - 35 NIS./1 dose vial.
Hib Vaccine	***HibTitter***	Haemophilus-b saccharide 10ug in 0.5ml (Diphtheria CRM 197 protein conjugate)	Solution for IM only	Lederle Lab	122.00/1 dose vial

Appendix B - Definitions

Word	Definition
Absorption	The passage of the drug from its site of administration into the blood.
Acquired Resistance	Bacteria can become resistant by incorporating a "resistance factor" into their genes to render the antibiotic ineffective.
Antibiotics	Agents derived from natural substances.
Antitoxin	A solution of antibodies derived from the serum of animals immunized with specific antigens (e.g. diphtheria antitoxin and botulinum antitoxin) used to achieve passive immunity or for treatment.
Autoinfection	Infection by an organism existing within the body or transferred from one part of the body to another part.
Bactericidal	Agents that kill the microorganism.
Bacteriostatic	Agents that inhibit the growth of the microorganisms by producing reversible changes. This delay in the growth will give the immune system the chance to get rid of the microorganism.
Bioavailability	The fraction of the drug that reaches its action sites after administration by any route. It is the rate and extent of absorption of a drug from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in the urine.
Bioequivalence	When the same 2 dosage forms for the same active ingredient in the same dose give the same bioavailability criteria, i.e. the same maximum concentration (C_{max}) at the same time (T_{max}), that is their rates and extent of absorption do not show significant differences.
Blood Dyscrasia	A pathologic condition manifested by fever, sore mouth or throat, unexplained fatigue and easy bruising or bleeding.
Broad Spectrum	The range of activity extends to many micro-organisms. (e.g. Tetracyclines depress G+ve, G-ve, *Rickettsiae* and *Chlamydiae*.)
Chemical Equivalence	When the same 2 dosage forms for the same active ingredient contain the same amount of the active ingredient, obtained after chemical analysis.
Coenzyme	It is a dissociable, low-molecular weight, non-proteinaceous organic compound (often nucleotide) participating in enzymatic reactions as acceptor or donor of chemical groups or electrons.
Compliance	Faithful adherence by the patient to the prescriber's instructions.
Cross Resistance	The passage of the acquired resistance to another bacterium.
Cross-Sensitivity	When a person is severely allergic to a certain drug, he/she might as well be sensitive to another drug which is similar in chemical structure or in pharmacological effect. e.g. Aspirin and other NSAIDs.
Cumulative Effect	Increase in drug effect that results when intake of repeated doses exceeds the rate of drug elimination form the body.
Distribution	The delivery of the drug to the tissues.

Disulfiram Type Reaction	An antabuse type reaction, that presents with symptoms such as facial flushing, pounding, headache, sweating, slurred speech, abdominal cramps, nausea, vomiting, tachycardia, fever, drop in blood pressure, dyspnea, and sense of chest constriction; symptoms may last up to 24 hours.
Drug	Any substance presented for treating, curing or preventing disease in human beings or in animals. A drug may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions.
Elimination	The process by which the drug's concentration decreases in the body by metabolism and excretion.
Enzyme Induction	Stimulation of microsomal enzymes by a drug resulting in metabolism acceleration leading to decreased activity.
Excipient	Any component of a finished dosage form other than the indicated therapeutic active ingredient(s).
Excretion	The process whereby drugs are transferred from the internal to the external environment. The principal organs involved in this process are the kidneys, lungs, biliary system and intestines.
Half-life ($t_{1/2}$)	Time required for concentration of a drug in the body to decrease by 50%. Half-life also represents time necessary to reach steady state or to decline from steady state after a change in dosing regimens.
Immune Globulin (IG)	A sterile solution containing antibodies from human blood. It is obtained by cold ethanol fractionation of large pools of blood plasma and contains 15-18% protein.
Metabolism	The process by which the drugs are modified in the body into a more or less water-soluble-substance, or more or less toxic substances.
Milliequivalent Unit (meq)	It is related to the total number of ionic charges in solution and also takes into account the valiance of the ions. Thus, it measures the amount of chemical activity of an electrolyte.
Me-too drug	It is a compound that is structurally very similar to already known drugs, with only minor pharmacological differences.
Narrow Spectrum	Agents that kill the microorganism. The range of activity for this antibiotic is small. It affects 1-2 micro-organisms only. (For example, Penicillin-G affects G+ve organisms and *Neisseriae*.)
Pharmacodynamics	The process of interaction of drugs with the cells. It includes: the binding of drugs to cells, their uptake, and intracellular metabolism, dose response relationships as well as therapeutic effects. (The effect of the drug on the body).
Pharmacokinetics	The process of handling of a drug within the body, which includes its absorption, distribution, metabolism, and excretion. (The effect of the body on the drug; or the drug fate in the body).
Photosensitivity	Drug induced skin changes resulting in unusual susceptibility to effects of sunlight or ultraviolet light.

Procurement	Selecting suppliers, placing and monitoring orders, checking delivery quantities and quality, and paying suppliers.
Prodrug	Any compound that undergoes biotransformation before exhibiting its pharmacological effects. Prodrugs can thus be viewed as drugs containing specialized non-toxic protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule.
Pulmonary Edema	Excessive fluid in the lung tissue manifesting one or more of the following: shortness of breath, cyanosis, persistent productive cough (frothy sputum may be blood tinged), expiratory rales (?), restlessness, increased heart rate, sense of chest pressure and/or anxiety.
Superinfection / Suprainfection	A new infection by an organism different from the initial infection being treated by antimicrobial therapy, presented by one or more of the following: black, hairy tongue, glossitis, stomatitis, anal itching, loose foul-smelling stools, vaginal itching or discharge, sudden fever, cough.
Therapeutic Equivalence	When the same 2 dosage forms for the same active ingredient provide the same therapeutic effect and safety.
Therapeutic Window/ Therapeutic Index (TI)	Range of drug concentration level, within which a particular drug has its safest and optimal therapeutic effects, that is, the limits between therapeutic and toxic response to a drug.
Tolerance	Decreased responsiveness to pharmacodynamic action of a drug that occurs during repeated administration of constant drug doses. Larger or more frequent doses or both are required to achieve the same effects observed with initial dosing.
Toxoid	A modified bacterial toxin that has been rendered nontoxic but retains the ability to stimulate the formation of antitoxin.
Urinary Secretion	The process by which drugs are secreted from the plasma into the kidney tubules (ex. Pen. G) in order to be excreted by the urine.
Vaccine	A suspension of live (usually attenuated) or inactivated microorganism (bacteria, viruses, or rickettsiae) or fraction of them, administered to induce immunity and thereby prevent infectious disease.

Appendix C
Summary of drugs used for allergic reactions or anaphylactic shock

Allergic reactions, anaphylactic shock and conditions such as angioedema are medical emergencies that need immediate action to avoid cardiovascular collapse and/or death. Prompt treatments of possible laryngioedema, bronchspasm and/or hypotension are required.

1. Vital signs

Maintain an open airway; give oxygen by mask, restore blood pressure.

2. A sympathomimetic as first line treatment

Epinephrine (adrenaline) 1:1000 given IM

Adult	500 microgram (0.5 ml)
Child 6 mon.-6 yrs.	120 microgram (0.12 ml)
Child 6-12 yrs.	250 microgram (0.25 ml)
Infant < 6 mon.	50 microgram (0.05 ml)

The dose may be repeated several times if necessary at 5 minute intervals, according to the blood pressure, pulse and respiratory function.

When patient is severely ill (i.e. shock) and there is doubt about adequacy of the circulation and absorption from the IM route, **IV administration** can be given slowly in a dose of 500 microgram (5 ml of the **dilute 1:10,000 epinephrine**) at a rate of 100 microgram per minute, until a response has been obtained. Half doses of adrenaline (epinephrine) may be safer for patients on amitriptyline, imipramine, or beta-blocker.

If cardiac arrest occurs, 1:10,000 epinephrine in a dose of 10 ml by IV is preferred through a central line. Atropine 3 mg IV as single dose maybe administered or other cardiac drugs as case requires.

3. Antihistamines

Administer promethazine or chlorphinarime by slow IV over 1 min.
Promethazine: Adult 25-200 mg/d, Child: 1 mg/kg/d, deep IM or slow IV injection.

4. Corticosteroids

Steroids do not have an immediate effect on the symptoms but are useful in reducing or eliminating further deterioration. Hydrocortisone by slow IV may be administered as follows:

Adult	100-300 mg
Child up to 1 year	25 mg
Child 1-5 yrs.	50 mg
Child > 5 yrs.	100 mg

5. Intravenous fluids

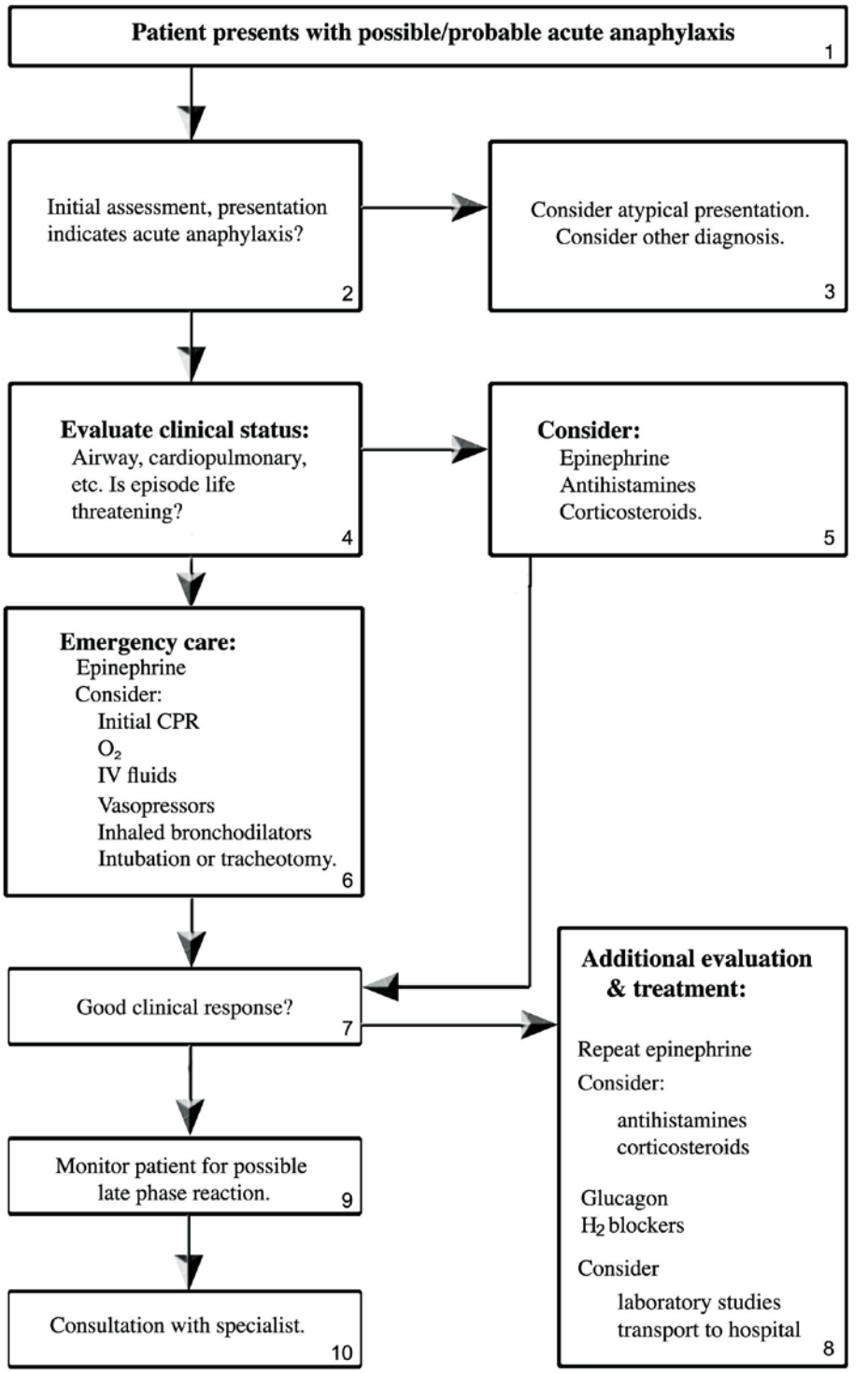
Start infusion with sodium chloride: 0.5-1 liter during the first hour. Repeat if necessary until circulation, tissue perfusion and blood pressure improve.

6. Asthma like symptoms

Bronchospasm unresponsive to epinephrine: Salbutamol nebulized, 1 mL salbutamol respirator solution + 1 mL 0.9% sodium chloride solution. Repeated 2–4 hourly if necessary OR continue with salbutamol, oral, 0.15 mg/kg 6 hourly for 24 hours.
Can administer aminophylline 5 mg/kg IV over 20 mins. if salbutamol is not available.

** Refer to individual drug monographs for further details about individual drugs.*

Algorithem of Treatment of Acute Anaphylaxis



Nicklas, et al. J Allergy Clin Immunol. June 1998(s470).

Appendix D
Local Manufactures

Birzeit Palestine Pharmaceutical Company (BPC) P.O Box 20, Birzeit, Palestine Tel: (970)-2-295-6581, Fax: (970)-2-295-3253 E-mail: bpc@uppm.org
Gama Chemical Company (GCC) P.O. Box 782, Beitunia, Palestine Tel: (970)-2-290-0911, Fax: (970)-2-290-0064 E-mail: gcc@uppm.org
Jerusalem Pharmaceutical Company (JEPHARM) P.O. Box 3570, el-Bireh, Palestine Tel: (970)-2-240-6550, Fax: (970)-2-240-3246 E-mail: jpharm@palnet.com, jepharm@uppm.org

Jordan Chemical Laboratory P.O. Box 58, Beit Jala, Palestine Tel: (970)-2-274-2855, 277-6880, 277-6881 Fax: (970)-2-274-1072 E-mail: info@jclaboratory.com, jcl@uppm.org
MEGAPHARM Industrial Zone, Beit Hanoun, Gaza Strip Tel: (970)-8-245-5011, 245-5012, Fax: (970)-8-245-5051 E-mail: megapharm@palnet.com, megapharm@uppm.org
Pharmacare Ltd Company (Pharmacare) P.O. Box 677, Ramallah, Palestine Tel: (970)-2-290-0980/1, Fax: (970)-2-290-5189 E-mail: pharmacare@pharmacare-ltd.com, pharmacare@uppm.org

Registered Local Drug Stores

Act Medical Co., Jerusalem Tel: 026799048, Fax: 026782818
al-Azouni Trading D.S., Nablus Tel: 092372296/2377231, Fax: 092371312
al-Barghouti Co. D.S., Ramallah Tel: 022985957
al-Basheer D.S., Bethlehem Tel: 022776666, Fax: 022742402
al-Du'wali D.S., Ramallah Tel: 022955797, 022955026
al-Hayya D.S., Jenin Telfax: 062503074
al-Hayya D.S., Ramallah Tel: 022989444, Fax: 022989444
al-Nour Medical Co. D.S., Jerusalem Tel: 022349788, Fax: 022349775
al-Ram D.S., Jerusalem Tel: 022349839, Fax: 022349735

al-Rasheed D.S., Nablus Tel: 092388101, Fax: 2381894
al-Razi D.S., Ramallah Tel: 022956395, Fax: 022956396
al-Salameh D.S., Jerusalem Tel: not available.
al-Shak'a D.S., Nablus Tel: 092382660, Fax: 092381420
al-Thulathia D.S. Co., Nablus Tel: 092385304, Fax: 092385304
al-Walid Medical Trading Co., Ramallah Tel: 022956416, Fax: 022956413
al-Watani D.S., Bethlehem Telfax: 022747033
al-Wihda D.S., Nablus Tel: 0962382534, Fax: 2385820
Beit Hanina D.S., Jerusalem Tel: 025857918, Fax: 025856257

Bethlehem Medical D.S., Bethlehem Tel: 022742906, Fax: 022777414
Dana D.S., Jerusalem Tel: 022348616
DespoMed Co., Jerusalem Tel: 025834075/6, Fax: 025834077
F.A. Hanna D.S., Ramallah Tel: 026284985, Fax: 026284987
Hikmat for Medicines D.S., Hebron Tel: 022234177
Ibn al-Haytham D.S , Hebron Tel: 022228550, Fax: 022226767
Ibn Sina D.S., Nablus Tel: 092378159, Fax: 092372264
Intermed Co., Ramallah Tel: 026283822, Fax: 026272661
InterPal Co. for Medical Imports, Gaza Tel: 082822728, Fax: 082822718
Khalil al-Rahman D.S., Hebron Tel: 022219366
Lyn Co. for Medical Equipment, Beitunia Tel: 022902193, Fax: 022902204
Masrouji Trading Co., al-Bireh Tel: 022404060, Fax: 022403958
MediPharm Co. for Medical Needs, Bethlehem Tel: 022775245, Fax: 022775244
MediSerf D.S., Tulkarem Telfax: 09 2676433
MSS, Beitunia Tel: 022959372/3/4, Fax: 022959375
Nablus Co. for Med. Equipment, Nablus Tel: 092389965, Fax: 092389966

Naseeb al-Jadeed D.S., Bethlehem Tel: 022774044, Fax: 022774045
Nazal D.S., Ramallah Telfax: 022955990
Nobil Co. for Medical Equipment, Ramallah Tel: 022900251, Fax: 022900890
NutriPharm D.S., Hebron Telfax: 022226440
Omnipal Co. for Trade & Marketing, al-Bireh Tel: 022958018, Fax: 022958019
Palestinian-British Co. for Trading & Contracting, Gaza Tel: 082837708/ 082822726, Fax: 082823967
Pharmacare D.S., Jerusalem Tel: 025813515
Razan D.S., Ramallah Telfax: 022985698
Riyam D.S., Jerusalem Tel: 025810288, Fax: 025819047
Sami Anabtawi D.S., Nablus Tel: 092374006, Fax: 092370237
Siamco for Medicines and Trade, Ramallah Tel: 022963246, Fax: 0229559949
Sufian Med. Equipment Company, Jerusalem Tel: 022796863, Fax: 026263521
Sukhtyan Brothers Co., Nablus Tel: 092377718 , Fax: 092387234
Sun Trading Co, Nablus Tel: 092397181, Fax: 092397184
Tulkarem D.S., Tulkarem Tel: 092382821

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