

Treatment of Respiratory Tract Infections

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Objectives of the lecture

At the end of lecture, the students should be able to understand the following:

- ▶ The **types** of respiratory tract infections (RTI)
- ▶ The **antibiotics** that are commonly used to treat RTIs & their **side effects**
- ▶ Understand the **mechanism** of action & **pharmacokinetics** of individual drugs.

Classification of RTIs

- ▶ Upper respiratory tract infections (URTI)
- ▶ Lower respiratory tract infections (LRTI)

Upper respiratory tract

Nasal cavity

Pharynx

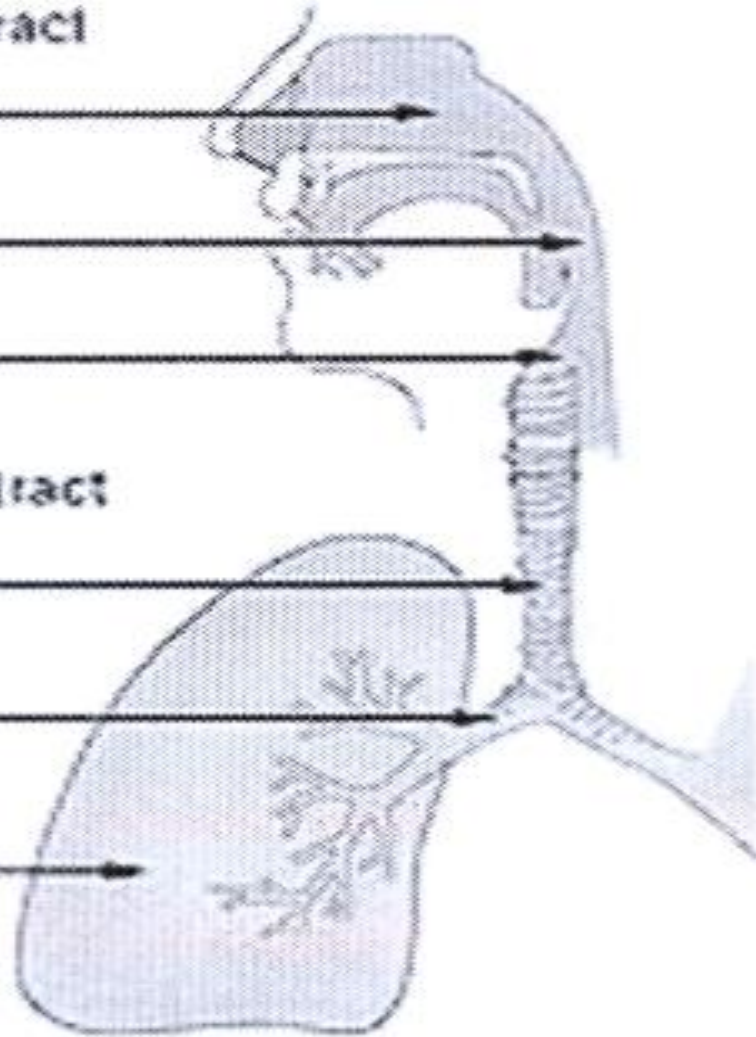
Larynx

Lower respiratory tract

Trachea

Primary bronchi

Lungs



Causes of URTIs

- ▶ **Viruses**; Most URTIs are of viral etiology
(Should NOT be treated with antibiotics)

Treatment: rest & plenty of fluids, OTC cold & pain relievers.

- ▶ **Bacteria** (mainly Group A streptococcus, H. influenza)

Treatment: Antibiotics. The type depends on:
Type of bacteria
Sensitivity test.

LRTIs (costly & more difficult to treat)

▶ **Bronchitis** (inflammation of major bronchi & trachea)

Acute, or Chronic, or Acute exacerbation of chronic bronchitis

Causes: viruses or bacteria (*H. influenza*, *Streptococcus pneumonia* & *Moraxella catarrhalis*).

▶ **Pneumonia** (Serious infection of bronchioles & alveoli)

Community –Acquired (CAP)

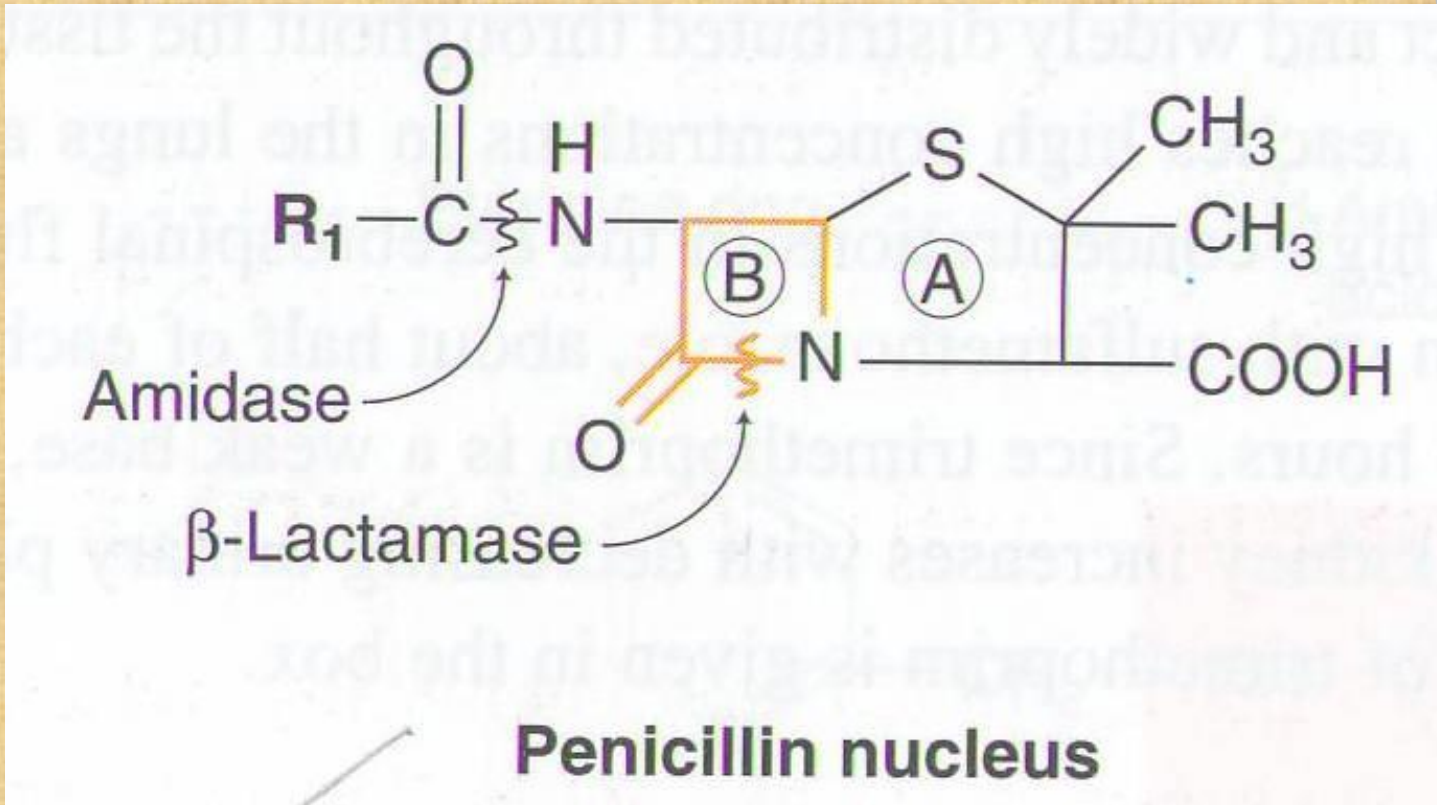
Hospital-acquired

Causes: Bacteria *S. pneumonia*** (66%), *H. influenza* (20%), *M. catarrhalis* (20%).

Antibiotics commonly used in the treatment of RTIs

- ❑ **Beta-lactam antibiotics (Penicillins / Cephalosporins)**
- ❑ **Macrolides**
- ❑ **Fluoroquinolones**
- ❑ **Aminoglycosides**
- ❑ **Tetracyclines.**

Penicillins



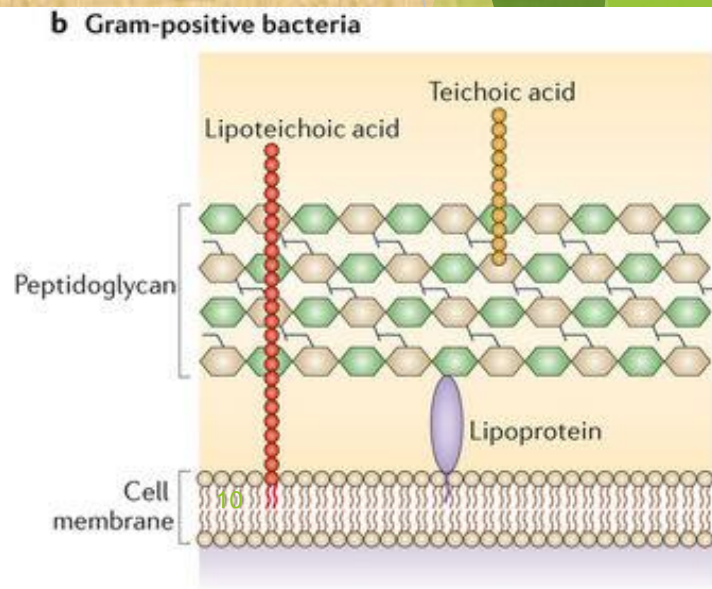
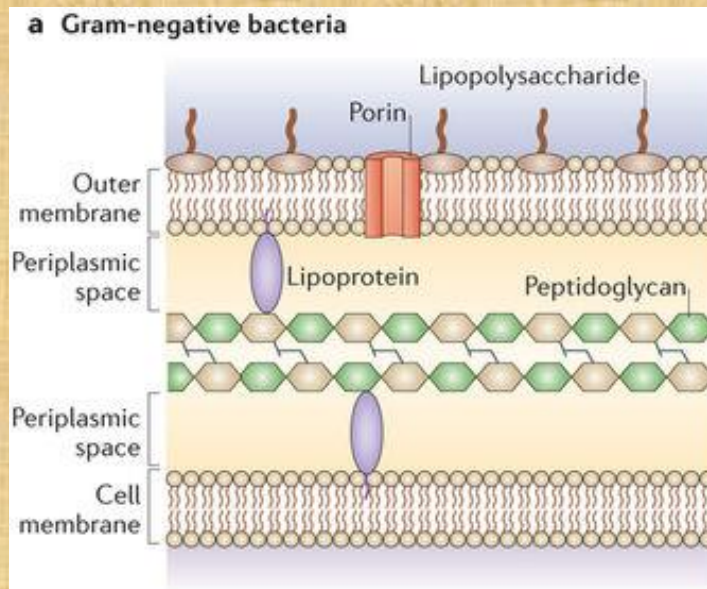
Broad-spectrum penicillins

- ▶ **Amoxicillin- Clavulanic acid**
- ▶ **Ampicillin- Sulbactam**
- ▶ **Piperacillin- tazobactam**

Act on both gram+ve & gram-ve microorganisms.

Mechanism of action of Penicillins

- ▶ Inhibit bacterial cell wall synthesis through inhibition of peptidoglycan layer of the cell wall.
- ▶ Bactericidal.



Pharmacokinetics of Penicillins

- ❖ Given orally or parenterally
- ❖ Relatively lipid insoluble
- ❖ Not metabolized in human
- ❖ Excreted mostly unchanged in urine
- ❖ Probenecid slows their elimination & prolong their half live
- ❖ Half-life 30-60 min (increased in renal failure).

Hypersensitivity
reactions

Convulsions
(after high
i.v. dose or in
renal failure)

*Adverse
effects*

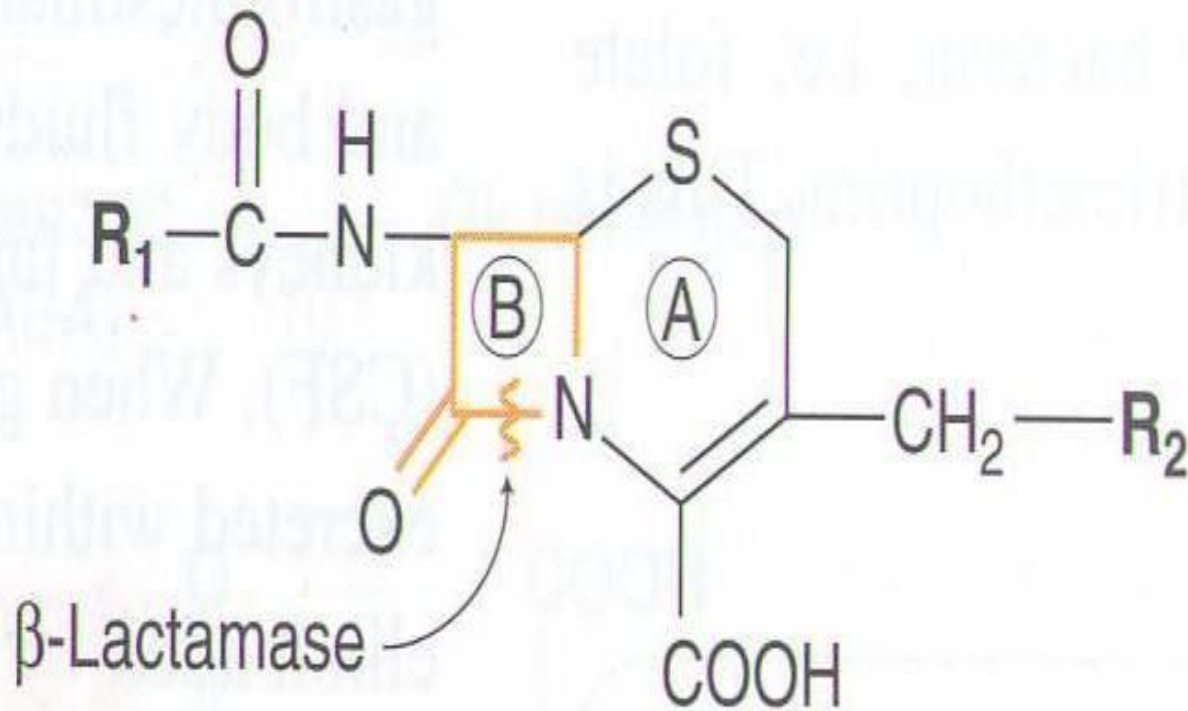
Nephritis

Diarrhea
Superinfections

Therapeutic uses of Penicillins

- ▶ URTIs
- ▶ LRTIs.

Cephalosporins



Cephalosporin nucleus

Mechanism of action of Cephalosporins

- ▶ **Inhibit bacterial cell wall synthesis**
- ▶ **Bactericidal**
(Similar to Penicillins)

Classified into 3 gps:

1st Generation Cephalosporins

▶ e.g. Cephalexin

- Given po
- Effective against gram positive bacteria
- Effective in URTIs.

2nd Generation Cephalosporins

E.g. Cefuroxime, cefaclor

- ▶ Given po
- ▶ Effective mainly against Gram-negative bacteria
- ▶ Well absorbed orally
- ▶ Active against β -lactamase –producing bacteria

Uses:

- ▶ Upper & lower RTIs.

3rd Generation Cephalosporins

Ceftriaxone / Cefotaxime / Cefixime

- ▶ **Given by intravenous route**
- ▶ **More effective against gram-negative bacilli**
- ▶ **Effective in treatment of pneumonia.**

Pharmacokinetics of Cephalosporins

- ▶ Cephalosporins are given parenterally & po
 - ▶ Relatively lipid insoluble (like penicillins)
 - ▶ Hence, do not penetrate cells or the CNS, except for third generations
 - ▶ Mostly excreted unchanged by the kidney (glomerular & tubular secretion)
 - ▶ Probenecid slows their elimination & prolong their half lives
- Half-life: 30-90 min; except ceftriaxone 4-7 hr.**

Adverse effects of cephalosporins

1

- Hypersensitivity reactions

2

- Thrombophlebitis

3

- Superinfections

4

- Diarrhea

Macrolides

```
graph TD; A[Macrolides] --> B[Erythromycin]; B --> C[Azithromycin]; B --> D[Clarithromycin]
```

Erythromycin

Azithromycin

Clarithromycin

Mechanism of action

Inhibit bacterial **protein** synthesis by binding to 50-S subunit of the bacterial ribosomal RNA

Bacteriostatic

Bactericidal at high concentrations.

Clarithromycin

- ▶ **More effective on G+ve bacteria**
- ▶ **Stable at gastric acidity**
- ▶ **Inhibits cytochrome P450 system**
- ▶ **Metabolized in liver to active metabolite**
- ▶ **Biliary route is the major route of elimination**
- ▶ **Only 10-15% excreted unchanged in the urine**
- ▶ **Half-life 6-8 hours.**

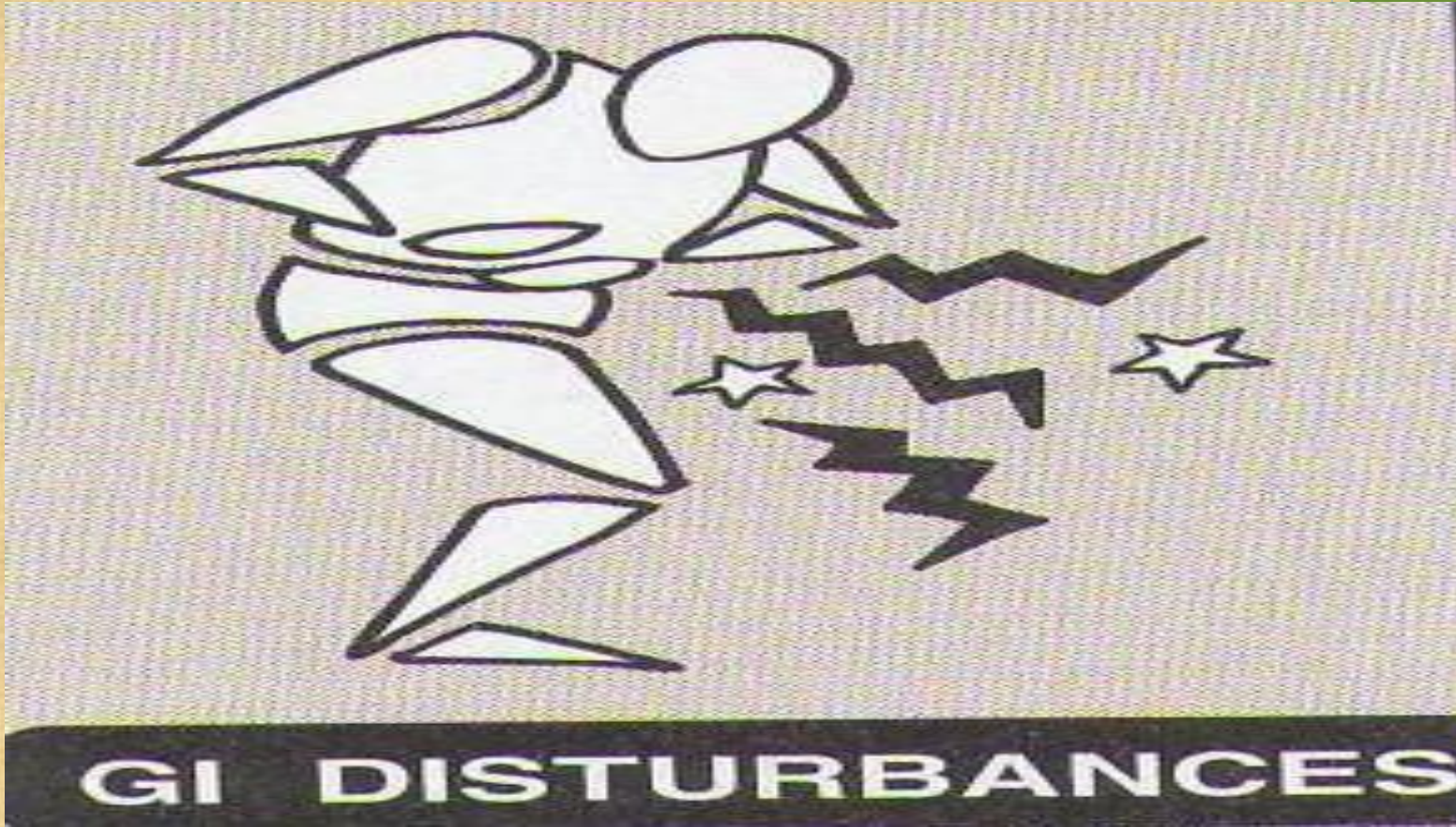
Azithromycin

- ▶ **More effective on G-ve bacteria**
- ▶ **Stable at gastric acidity**
- ▶ **Undergo some hepatic metabolism (inactive metabolite)**
- ▶ **Biliary route is the major route of elimination**
- ▶ **Only 10-15% excreted unchanged in the urine**
- ▶ **Half-life (3 days)**
- ▶ **Once daily dosing**
- ▶ **No effect on cytochrome P- 450.**

Clinical uses of Macrolides

- ▶ **Chlamydial pneumonia**
- ▶ **Legionella pneumonia.**

Adverse effects



✓

✓ **Hypersensitivity Reactions.**

Fluoroquinolones

```
graph TD; A[Fluoroquinolones] --- B[Ciprofloxacin]; A --- C[Moxifloxacin]; A --- D[Gatifloxacin];
```

Ciprofloxacin

Moxifloxacin

Gatifloxacin

Mechanism of action

Block bacterial DNA synthesis by inhibiting **DNA Gyrase enzyme** (an enzyme involved in DNA supercoiling).

Antibacterial spectrum

- ▶ **Ciprofloxacin mainly effective against G–ve bacteria**
- ▶ **Moxifloxacin & Gatifloxacin G –ve & G+ve**

(highly active against Pseudomonas species)

Pharmacokinetics

- **Given po or parenterally**
- **Concentrates in many tissues (kidney, prostate, lung & bones/ joints)**
- **Excreted mainly through the kidney**
- **Their relatively long Half-life allow once daily (moxifloxacin & Gatifloxacin) & twice-daily (ciprofloxacin) dosing.**

Clinical Uses

1

Acute exacerbation of chronic obstructive pulmonary disease

2

Community acquired pneumonia

3

Legionella pneumonia

Adverse effects

- ❖ **Nausea, vomiting, diarrhea**
- ❖ **CNS effects (confusion, insomnia, headache, anxiety)**
- ❖ **Damage of growing cartilage (arthropathy)**
- ❖ **Phototoxicity (avoid excessive sunlight).**

Contraindications

- ▶ **Not recommended for patients younger than 18 years**
- ▶ **Pregnancy**
- ▶ **Breast feeding women.**

Aminoglycosides

```
graph TD; A[Aminoglycosides] --- B[Streptomycin]; A --- C[Neomycin]; A --- D[Gentamicin]
```

Streptomycin

Neomycin

Gentamicin

Aminoglycosides

Mechanism of action

- ▶ Inhibit bacterial protein synthesis by binding to 30-S subunit of the bacterial ribosomal protein
- ▶ Bactericidal
- ▶ Only active against gm negative **aerobic organisms.**

Pharmacokinetics

- Poorly absorbed po (highly charged), given parenterally (IM, IV)
- $T_{1/2}$ is 2-3 h & increased to 24-48 h in renal impairment
- Cross placenta
- Excreted unchanged in urine

Gentamicin

Adverse effects :

- Ototoxicity
- Nephrotoxicity
- In very high doses, neuromuscular blockade that results in respiratory paralysis.

Therapeutic uses of Gentamicin

- Severe infections caused by gram negative organisms.

Tetracyclines

e.g. chlortetracycline, doxycycline
Minocycline

Mechanism of action & antimicrobial activity

- ▶ Broad-spectrum bacteriostatic antibiotics
- ▶ Inhibit protein synthesis by binding reversibly to 30-S subunit of the bacterial ribosome
- ▶ Active against many gram-positive & gram-negative bacteria (anaerobes, rickettsiae, chlamydiae & mycoplasmas).

Doxycycline

It is a long acting tetracycline

Pharmacokinetics

- ▶ Usually given orally
- ▶ Absorption is 90-100%
- ▶ Absorbed in the upper s. intestine & best in absence of food
- ▶ Food & di & tri-valent cations (Ca, Mg, Fe, AL) impair absorption
- ▶ Protein binding 40-80 %
- ▶ Distributed well, including CSF
- ▶ Cross placenta & excreted in milk
- ▶ Largely metabolized in the liver

Doxycycline (Cont.)

Side effects

1. nausea, vomiting ,diarrhea & epigastric pain (give with food)
2. Thrombophlebitis – i.v
3. Hepatic toxicity (prolonged therapy with high dose)
4. Brown discoloration of teeth – children
5. Deformity or growth inhibition of bones – children
6. Phototoxicity
7. Vertigo
8. Superinfections.

Contraindications of doxycycline

- ▶ **Pregnancy**
- ▶ **Breast feeding**
- ▶ **Children (below 10 yrs)**

Uses of Doxycycline

- ▶ **Treatment of URTIs caused by *S. pyogenes*, *S. pneumonia* & *H. influenza*.**

THANK YOU

