Treatment of Respiratory Tract Infections

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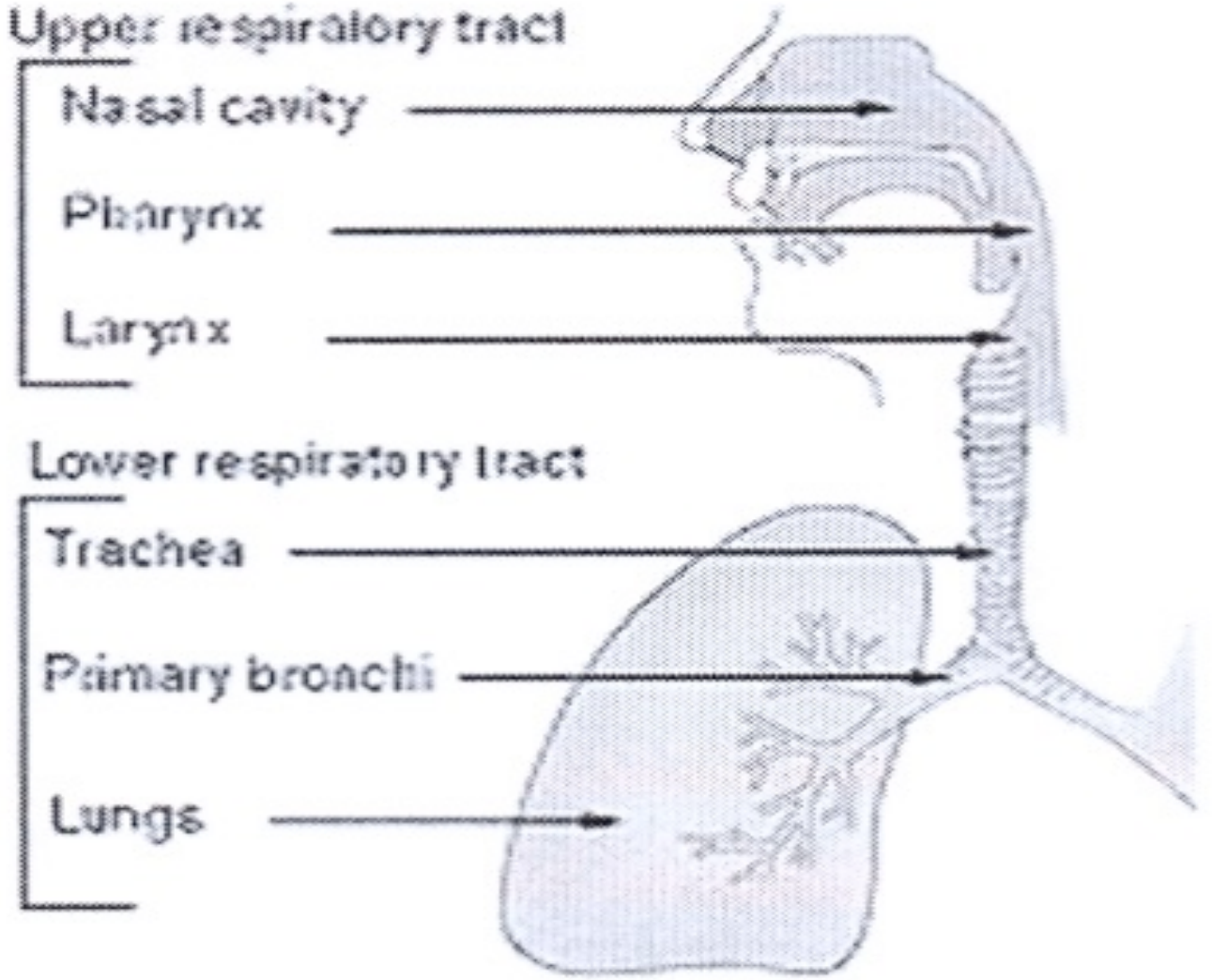
Objectives of the lecture

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)

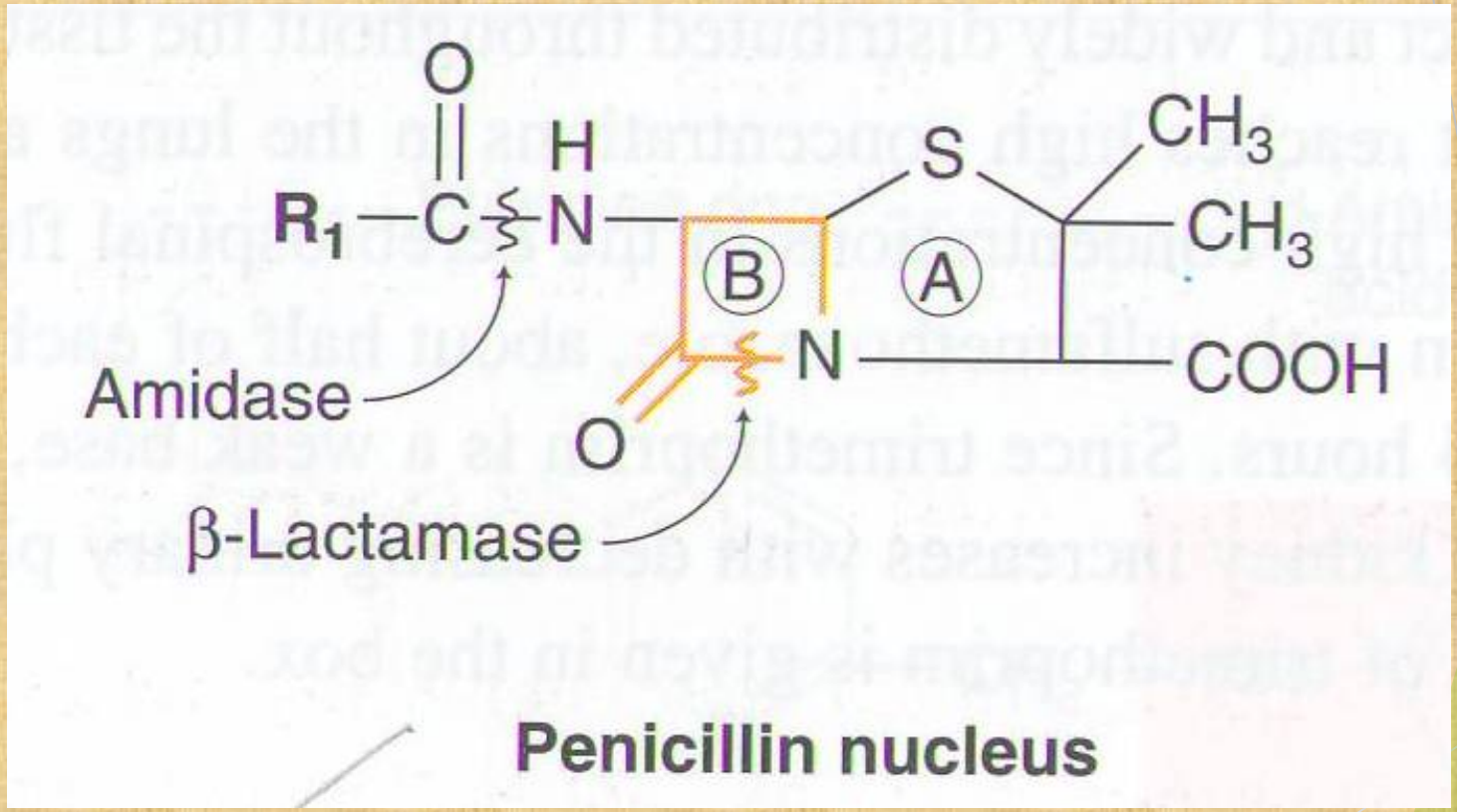
Hospital-acquired

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



Penicillin nucleus

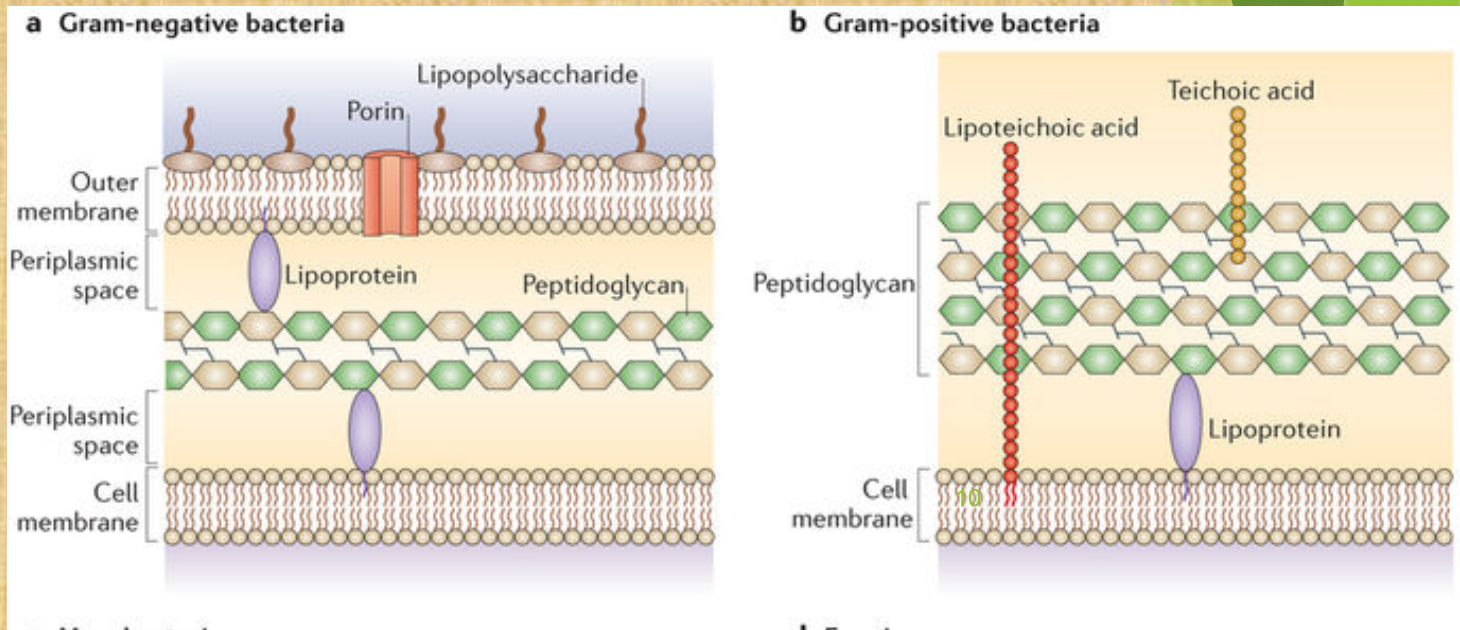
Broad-spectrum penicillins

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

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

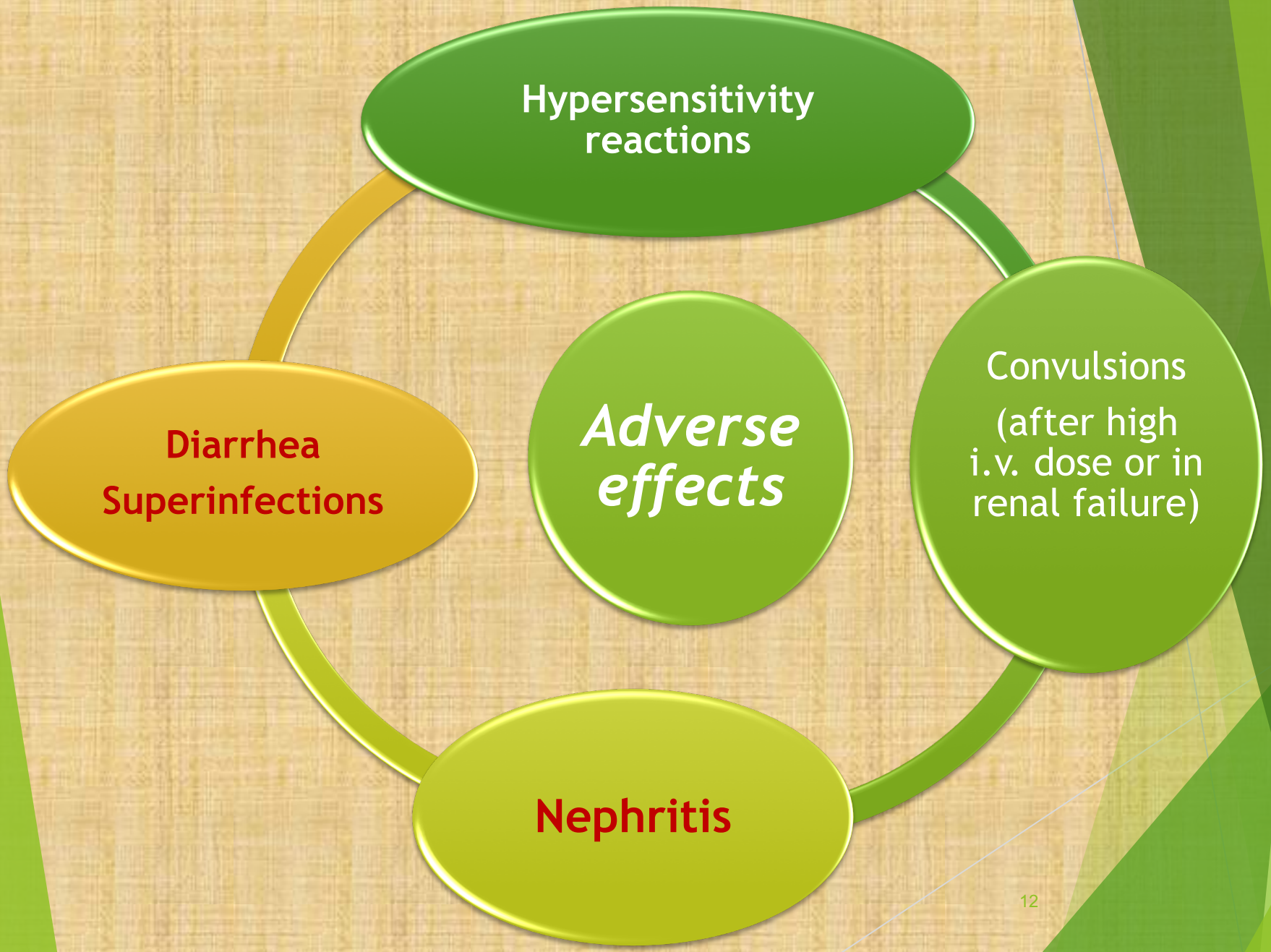
Mechanism of action of Penicillins

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



Pharmacokinetics of Penicillins

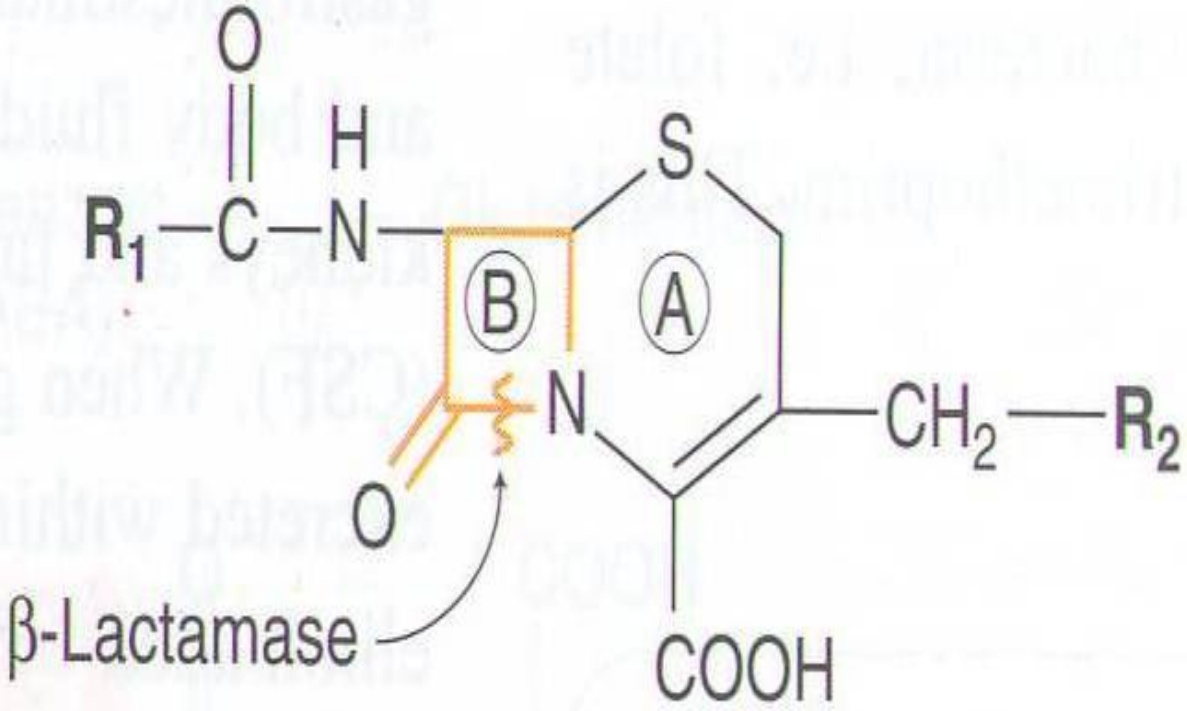
- Given orally or parenterally
- Relatively lipid insoluble
- Not metabolized in human
- Excreted mostly unchanged in urine
- Probenecid slows their elimination & prolong their half live
- Half-life 30-60 min (increased in renal failure).


Hypersensitivity reactions
Convulsions (after high i.v. dose or in renal failure)
Nephritis
Diarrhea Superinfections
Adverse effects

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.

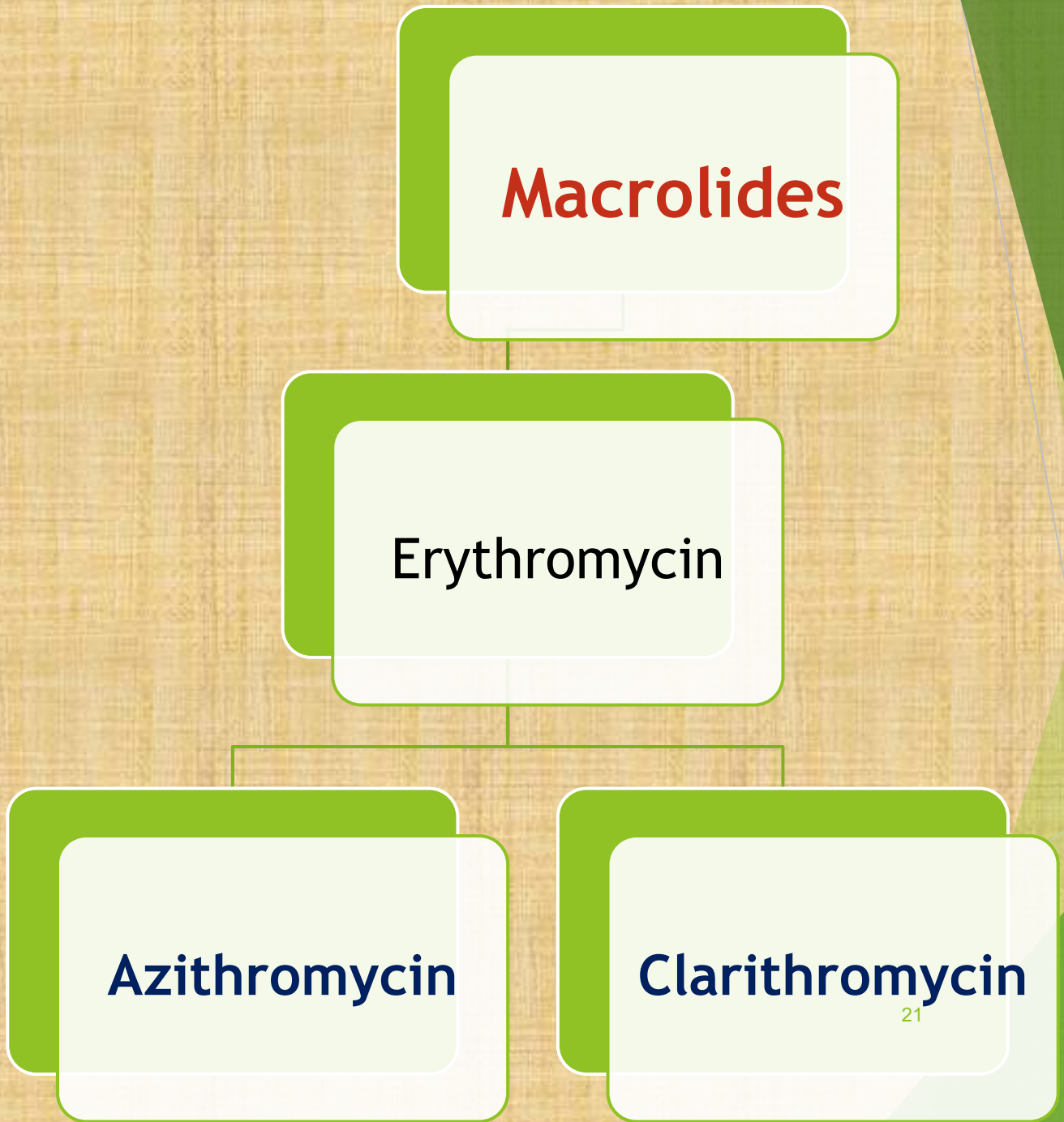
Pharmacokinetics of Cephalosporins

- 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. Thrombophilibitis
3. Superinfections
4. Diarrhea


Macrolides
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.

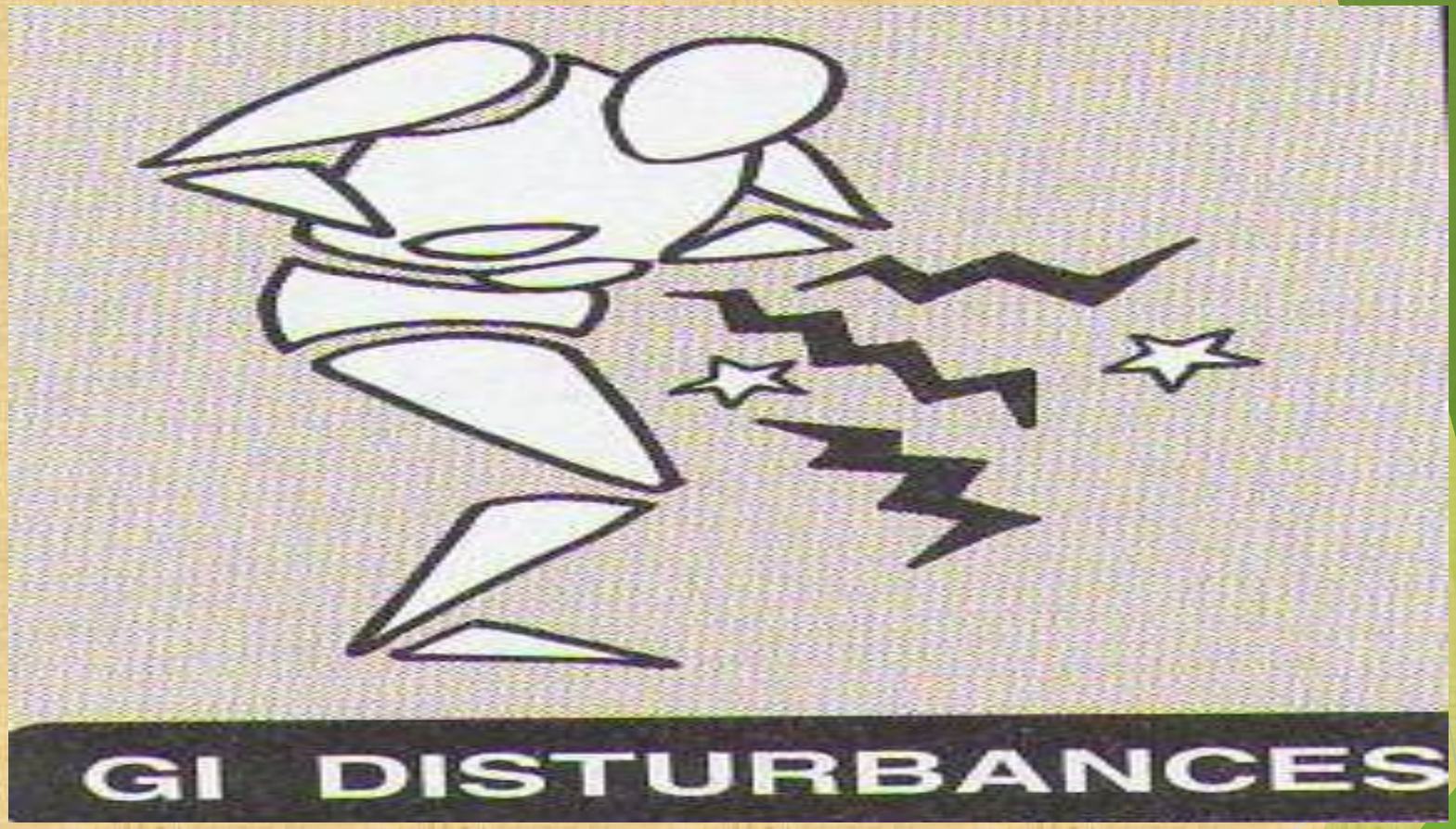
Azithromycin

- 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.

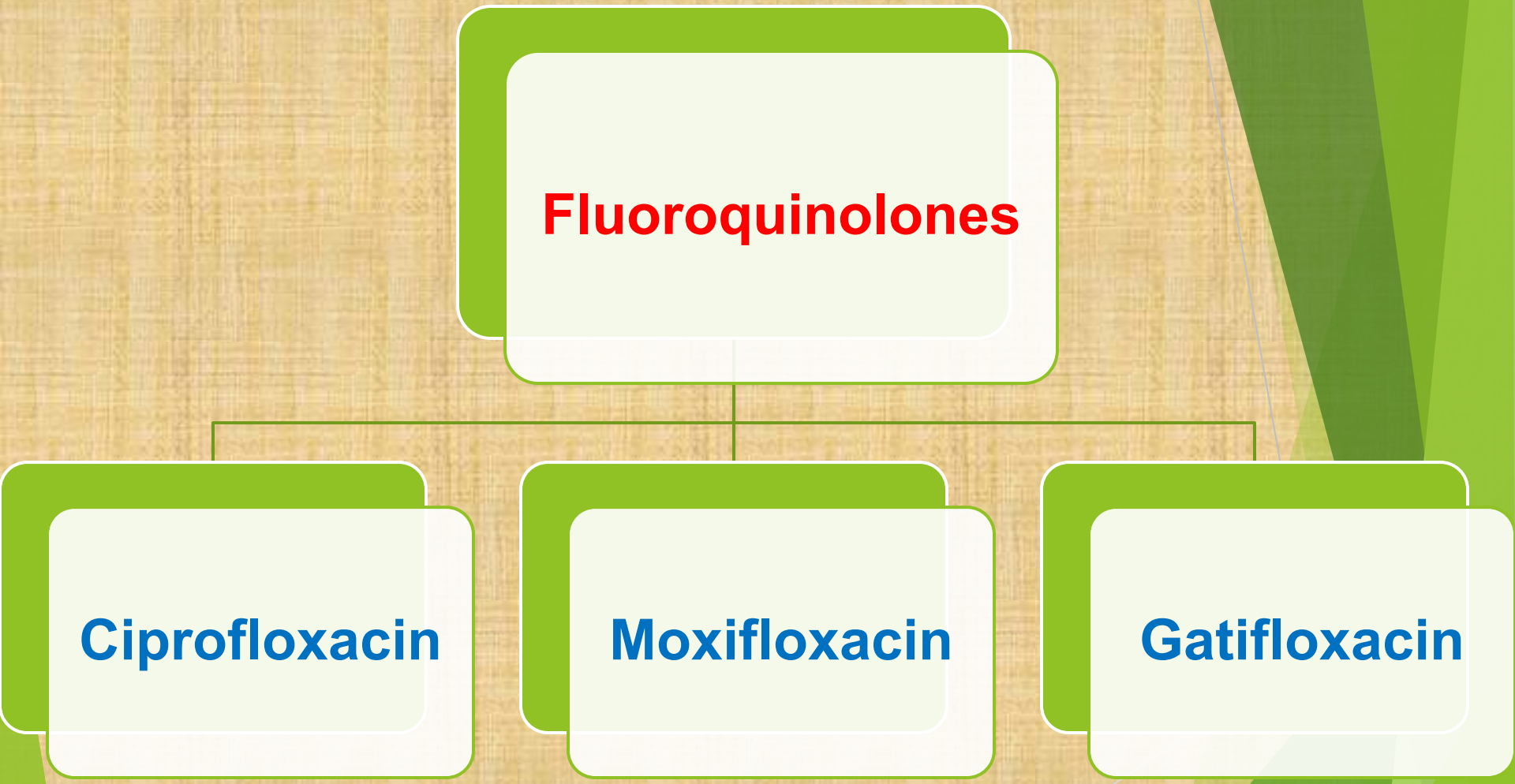
Clinical uses of Macrolides

- Chlamydial pneumonia
- Legionella pneumonia.

Adverse effects



- ✓
- ✓ **Hypersensitivity Reactions.**


Fluoroquinolones
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

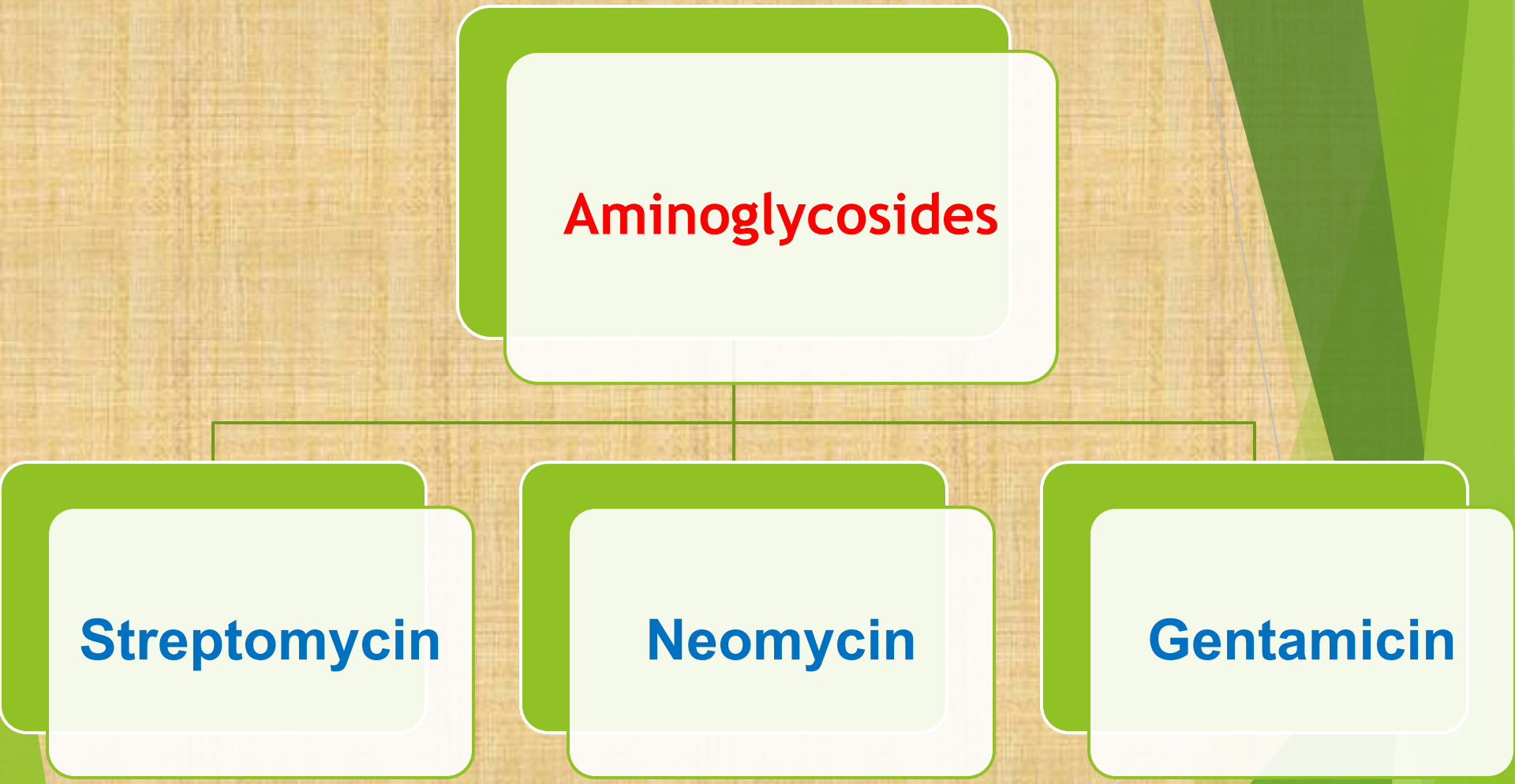
1. Acute exacerbation of chronic obstructive pulmonary disease
2. Community acquired pneumonia
3. Legionella pneumonia

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
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