Pharmacology Team 437

غيـــداء آل مصـمـع
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MED437
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Respiratory Block

9 Treatment of Respiratory Tract Infections

Objectives :

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

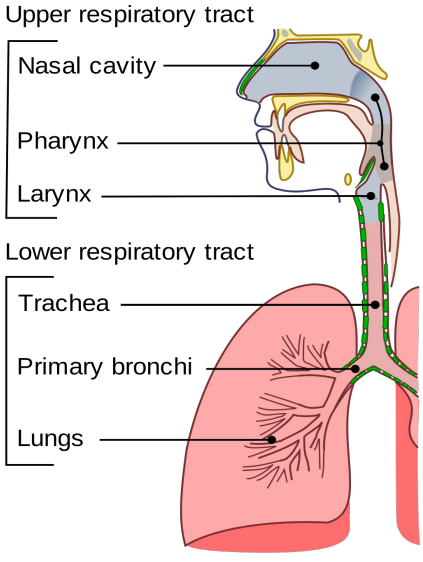
1. The types of respiratory tract infections (RTI)
2. The antibiotics that are commonly used to treat RTIs & their side effects
3. Understand the mechanism of action & pharmacokinetics of individual drugs.

Color index:
Red: important
Grey: Notes or extra information

Respiratory Tract Infections

Respiratory Tract Infections Classification

Upper Respiratory Tract Infections



Viruses; Most URTIs are of viral etiology.

Treatment:
(Should NOT be treated with antibiotics)
Rest & plenty of fluids, OTC cold & pain relievers.

OTC : over the counter, without description like Panadol.

Bacteria (mainly Group A streptococcus, H. influenza).

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

Lower Respiratory Tract Infections
(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*).

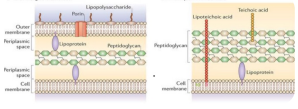
Pneumonia (Serious infection of bronchioles & alveoli)
- Community –Acquired (CAP).
- Hospital-acquired.

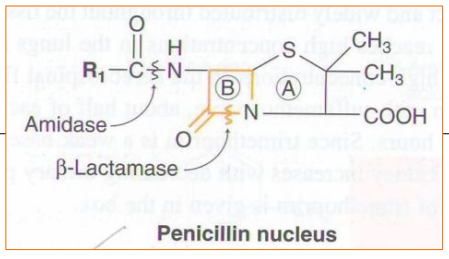
Causes: Bacteria
S.pneumoniae (66%), H. influenza (20%), M. catarrhalis (20%).

Antibiotics commonly used in in the treatment of RTIs:

1- Beta-lactam antibiotics (Penicillins/ Cephalosporins)
2- Macrolides
3- Fluoroquinolones
4- Aminoglycosides
5- Doxycycline

Penicillins

Broad-spectrum penicillins	- Amoxicillin- Clavulanic acid * - Ampicillin- Sulbactam* - Piperacillin-tazobactam * Act on both gram +ve and gram -ve microorganisms
Mechanism of action	- Inhibit bacterial cell wall synthesis → through inhibition of peptidoglycan layer on the cell wall - Bactericidal 
Pharmacokinetics	❖ Given po or parenterally ❖ Not metabolized in human ❖ Relatively lipid insoluble ❖ Excreted mostly unchanged in urine ❖ Probenecid slows their elimination & prolong their half live ❖ Half-life 30-60 min (increased in renal failure)
Adverse effects	● Hypersensitivity reactions ● Diarrhea ● Superinfections ● Nephritis ● Convulsions (after high i.v. dose or in renal failure)
Therapeutic uses	● URTIs ● LRTIs

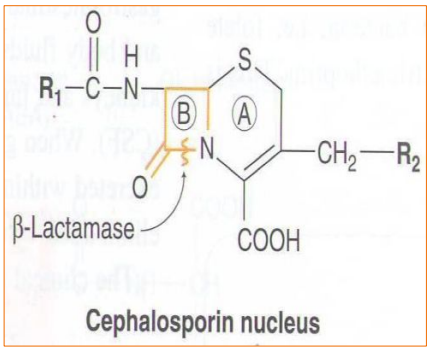


- Bacteria produces beta-lactamase which is an enzyme that cleaves beta-lactam and stops the penicillin from working, so we add beta-lactamase inhibitor to the penicillin. For example: amoxicillin (penicillin) clavulanic acid (beta-lactamase inhibitor)
- Extra: amoxicillin-clavulanic acid commercial name is Augmentin

Cephalosporins

Features (MOA):

- Inhibit bacterial cell wall synthesis
- Bactericidal (**similar to Penicillins**)
- Classified into 3 generations:



Cephalosporin nucleus

Generation	1st	2nd	3rd
Drugs	Cephalexin	Cefuroxime, Cefaclor	Ceftriaxone, Cefotaxime, Cefixime
Route of administration	Orally	Orally Well absorbed	I.V
Spectrum	Gram-**positive** bacteria	Gram-**negative** bacteria (Active against β-lactamase –producing bacteria)	Gram-**negative** bacilli
Uses	Effective in URTIs	Upper & lower RTIs	Effective in treatment of pneumonia

Pharmacokinetics of Cephalosporins

- Cephalosporins are given parenterally & po. "po= orally"
- Relatively lipid insoluble **(like penicillins).**
- Don't penetrate cells or the CNS, except for third generations. 3rd generation is more lipid soluble
- Mostly excreted unchanged by the kidney **(glomerular & tubular secretion).**
- Probenecid slows their elimination & prolong their half lives

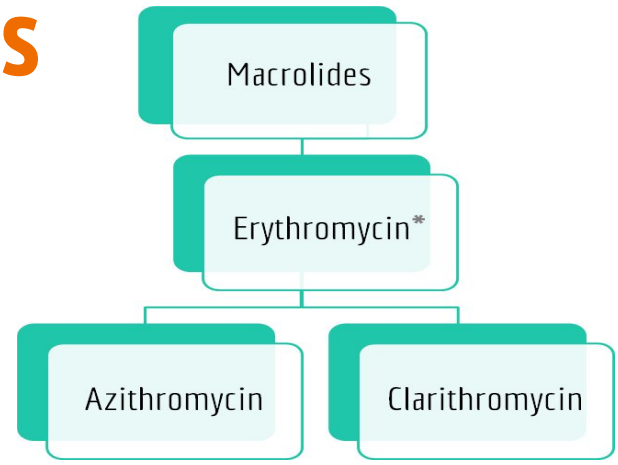
Half-life: 30-90 min; except ceftriaxone 4-7 hr.

Adverse effects of Cephalosporins *

- Hypersensitivity reactions.
- Thrombophilibitis. Inflammation of the wall of vein
- Superinfections. Because of killing of normal flora
- Diarrhea.

***Dr. Aliah said:** Local irritation can produce pain after IM injection & thrombophlebitis after IV injection.

Macrolides



Mechanism of action

- Inhibit bacterial protein synthesis by binding to 50S subunit of the bacterial ribosomal RNA.
- Bacteriostatic.**
- Bactericidal at high concentration.***

*Dr. Aliah said: Erythromycin is the prototype , Clarithromycin & azithromycin are semisynthetic derivatives of erythromycin.
** **Bacteriostatic:** hold bacteria from growing.
*** **Bactericidal:** kill bacteria.

Drugs	Clarithromycin	Azithromycin
Antibacterial spectrum	• More effective on G**+ve** bacteria	• More effective on G**-ve** bacteria
Pharmacokinetics	• 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	• Stable at gastric acidity • No effect on cytochrome P-450. • Undergo some hepatic metabolism (inactive metabolite) • Biliary route is the major route of elimination • Only 10-15% excreted unchanged in the urine
Half-life	• Half-life 6-8 hours	• Half-life (3 days)
Dose	-	• Once daily dosing
Clinical Uses	1. Chlamydial pneumonia 2. Legionella pneumonia	
Adverse effects	• GI Disturbances • Hypersensitivity Reactions *Dr. Aliah's notes: Anorexia, nausea, vomiting, & diarrhea are common. GI intolerance, which is due to a direct stimulation of gut motility, is the most common reason for discontinuing erythromycin & substituting another antibiotic.	

Dr. Aliah's notes:

- Erythromycin base is destroyed by stomach acid and must be administered with enteric coating. Clarithromycin is derived from erythromycin by addition of a methyl group and has improved acid stability and oral absorption compared with erythromycin.
- Erythromycin & clarithromycin inhibit CytP 3A4
- Erythromycin is active against susceptible strains of gram-positive organisms, especially pneumococci, streptococci, staphylococci, & corynebacteria.
- Mycoplasma pneumoniae, L pneumophila, Chlamydia trachomatis, Chlamydia psittaci, Chlamydia pneumoniae, H pylori, Listeria monocytogenes, & certain mycobacteria (Mycobacterium kansasii, Mycobacterium scrofulaceum) are also susceptible.
- Clarithromycin & erythromycin are similar with respect to antibacterial activity except that clarithromycin is > active against Mycobacterium avium complex.
  The advantages of clarithromycin compared with erythromycin are lower incidence of GI intolerance & less frequent dosing.

Fluoroquinolones

Drugs	Ciprofloxacin	Moxifloxacin	Gatifloxacin
Antibacterial spectrum	G**–ve** bacteria highly active against Pseudomonas species	G –ve & G+ve highly active against Pseudomonas species	
Pharmacokinetics	• Given po or parenterally • Concentrates in many tissues (kidney, prostate, lung & bones/ joints) it means it can treat infections in these organs. • Excreted mainly through the kidney • long Half-life		
Dose	twice-daily	once daily	
Mechanism of action	Block bacterial DNA synthesis by inhibiting **DNA Gyrase enzyme** (an enzyme involved in DNA supercoiling).		
Clinical Uses	1. Acute exacerbation of chronic obstructive pulmonary disease. 2. Community acquired pneumonia. 3. Legionella pneumonia.		
Adverse effects	❖ Nausea, vomiting and diarrhea ❖ CNS effects (confusion, insomnia, headache and anxiety) ❖ Damage of growing cartilage (arthropathy) ❖ Phototoxicity (avoid excessive sunlight) cause skin irritation		
Contraindications	• Not recommended for patients younger than 18 years • Pregnancy • Breastfeeding women		

Remember

- Penicillin,Moxifloxacin and Gatifloxacin are Effective against gram-ve and gram+ve.
- Cephalexin,Clarithromycin effective against gram+ve only.
- Cefuroxime,Cefaclor,Ceftriaxone, Cefotaxime, Cefixime,Azithromycin and Ciprofloxacin Effective against gram-ve oniy.
- Penicillin and Cephalosporins are Inhibit bacterial **cell wall** synthesis (Bactericidal).
- Macrolides (Azithromycin,Clarithromycin) :Inhibit **protein** synthesis by binding to 50S subunit of the bacterial ribosomes (Bacteriostatic) and At high doses: Bactericidal.
- Fluoroquinolones (Ciprofloxacin, Moxifloxacin ,Gatifloxacin): inhibits **DNA** gyrase enzyme, which is an enzyme involved in DNA supercoiling.

MCQs

1-Which of the following cephalosporins is used against gram positive bacteria ?

A. Cephalexin
B. Clarithromycin.
C. Penicillin.
D. Moxifloxacin.

2-Penicillins are used to treat

A. URTIs
B. LRTIs
C. Both a and c
D. None of above

3-Legionella pneumonia can be treated with

A. Clarithromycin.
B. Ciprofloxacin
C. Moxifloxacin
D. All of above

4-which antibiotic is contraindicated for pregnant women?

A. Gatifloxacin
B. Ampicillin
C. Cefaclor
D. Amoxicillin

5-which of these is a side effect of Fluoroquinolones?

A. CNS effects (confusion, insomnia, headache & anxiety)
B. Arthropathy
C. Phototoxicity
D. All of above

6-which of these antibiotics is safely used in renal failure?

A. Gatifloxacin
B. Ampicillin
C. Azithromycin
D. Amoxicillin

SAQs

- **What is the drug is used in both LRTIs and URTIs ?**
- **What are 3 adverse effect that is expected to see in this patient after giving him the drug ?**

Answers:
1. A
2. C
3. D
4. A
5. D
6. C

Answers:
1. Penicillin.
2. Hypersensitivity reactions, diarrhea and superinfections.

Good Luck & Thank you !

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