PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Treatment of respiratory tract infections

Objectives:

- 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.

Important

In male and female slides

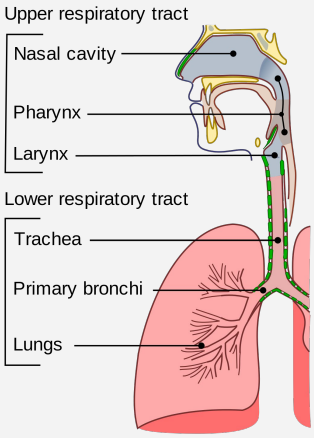
Only in male slides

Only in female slides

Extra information

Editing file

Respiratory Tract Infections Classification



❖ **Upper Respiratory Tract Infections**
, caused by:

Viruses

Most URTIs are of viral etiology.

Treatment: Rest and plenty of fluids, over the counter (OTC) cold & pain relievers.

-Should **NOT** be treated with antibiotics

Bacteria

Mainly group A streptococcus and H. Influenza.

Treatment: Antibiotics

Type depends on:

1) Type of bacteria
2) Sensitivity test

❖ **Lower Respiratory Tract Infections**
(Costly & more difficult to treat):

Bronchitis

(Inflammation of major bronchi & trachea)

It could be:

Acute, 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 (Nosocomial).

Causes: Bacteria -S. pneumoniae (66%)
-H. Influenza (20%)
-M. catarrhalis (20%)

Antibiotics commonly used in the treatment of RTIs:

- Beta-lactam antibiotics (Penicillins/Cephalosporins)
- Macrolides
- Aminoglycosides
- Tetracycline or in boy's slides (Doxycycline it's derived from tetracycline)
- Fluoroquinolones

#438

This page is for your understanding only, but we **HIGHLY RECOMMEND** that you read it

Antibiotics Classification

Beta-Lactams	Aminoglycoside	Macrolides	Tetracycline	Cephalosporins	Quinolones	Sulfonamide
Penicillins Cephalosporins Carbapenems Monobactams	**suffix**: mycin	**suffix**: Thromycin	**suffix**: Cycline	**Prefix**: Ceph Or Cef	**suffix**: Floxacin	**Prefix**: Sulfa

Antibiotics

Mechanism of Action:

Bactericidal (kills the bacteria) by either:
1- Destroying the cell wall
2- Destroying the Nucleic Acid (DNA or RNA)

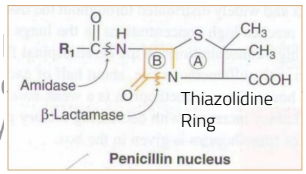
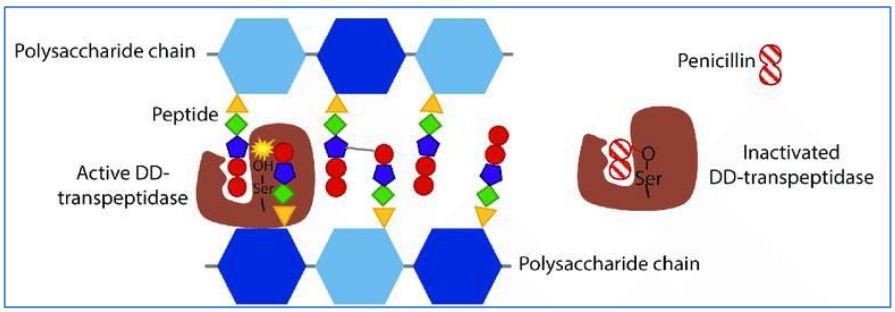
Bacteriostatic (stops the growth) by:
1- Affecting the protein synthesis

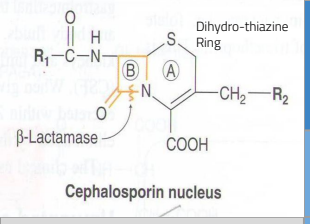
EXCEPTION: Aminoglycoside affects the protein synthesis but is considered **Bactericidal**

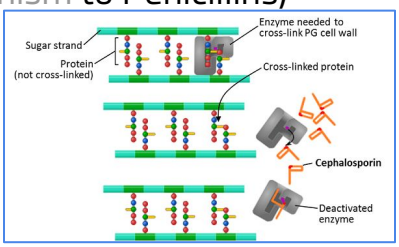
Cell Wall Synthesis	Nucleic Acid Synthesis	Protein Synthesis
- Beta Lactams Note: Beta Lactams are sometimes combined with beta lactamase inhibitors such as: clavulanic acid, sulbactam, tazobactam, this is because some strains of bacteria have evolved into species that can cleave beta lactam ring through an enzyme called beta lactamase.	**DNA:** Quinolones **RNA:** Rifampin, Rifabutin **Folate synthesis:** Sulfonamide, TMP-SMX	**30S:** - Aminoglycoside -Tetracycline **50S:** - Macrolides (Erythromycin) - Clindamycin - Chloramphenicol - Linezolid

buy AT 30 CCEL (sell) at 50:

AT: Aminoglycoside, Tetracycline **CCEL**: Clindamycin, Chloramphenicol, Erythromycin, Linezolid

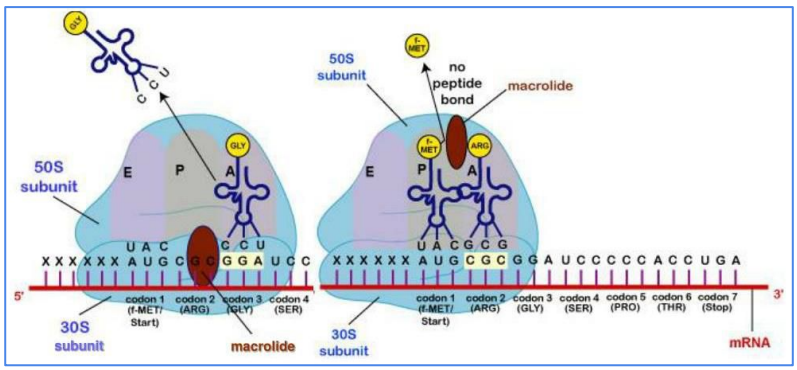
Broad-spectrum penicillins	❖ Amoxicillin-Clavulanic acid (Augmentin). ❖ Ampicillin-Sulbactam. ❖ Piperacillin-Tazobactam. - Act on both gram +ve & gram -ve microorganisms Note: Beta Lactams are sometimes combined with beta lactamase inh clavulanic acid, sulbactam, tazobactam, this is because some strains evolved into species that can cleave beta lactam ring through an enzy lactamase. 
MAO **You have to know whether the antibiotic is bacteriostatic or bactericidal**	- Bactericidal. - Inhibit bacterial cell wall synthesis through inhibition of peptidoglycan layer on the cell wall (it inhibits transpeptidase enzyme -> failure of cross-links -> unstable cell wall -> bacteria burst). 
Pharmacokinetics (PK)	- Given orally or parenterally. - Not metabolized in human. - Relatively lipid insoluble. - Excreted mostly unchanged in urine (most of its excretion is through the kidney). - Half-life: 30-60 min (increased in renal failure). - Probenecid (uricosuric) **slows** their elimination and prolongs their half life by competing over tubular secretion with penicillin.
ADRs	-Hypersensitivity reactions (rash,urticaria,fever). - Diarrhea. - Superinfections (a second infection superimposed on an earlier one especially by a different microbial agent resistant to the treatment being used against the first infection). - Nephritis. (Inflammation of the kidney) - Convulsions (after high I.V dose or in renal failure).
therapeutic uses	- URTIs: acute otitis media especially those produced by Group A gram positive beta hemolytic streptococci (GAP). - LRTIs.



	Cephalosporins - Classified into 3 generations:		
	First generation	**Second generation**	**Third generation**
e.g.	**Cephalexin**	**Cefuroxime** **Cefuroxime axetil** (prodrug of cefuroxime, in other words tablets contain cefuroxime as cefuroxime axetil) **Cefaclor**	**Ceftriaxone** **Cefixime** **Cefotaxime** 
Route of administration	Orally	well absorbed Orally	-Mainly IV -oral preparation (cefixime)
Spectrum	Gram +ve Bacteria (mild infection)	-Mainly Gram -ve Bacteria -active against β-lactamase-producing bacteria.	More effective against Gram -ve bacilli
Uses	URTIs	-URTIs: sinusitis, Otitis media. -LRTIs	In treatment of pneumonia produced by β-lactamase bacteria
MOA	- Bactericidal. - Inhibit bacterial cell wall synthesis (similar mechanism to Penicillins) -more stable than penicillins to β-lactamase. 		
PK	-Given parenterally & orally. -Relatively lipid insoluble (like penicillins). -do not penetrate cells or the CNS except for 3rd generation. -Mostly excreted unchanged by the kidney (glomerular & tubular secretion). -Probenecid slows their elimination & prolongs their half lives. -Penetration into CSF -Half-life: 30-90 min , long half-life-> ceftriaxone (4-7 hr).		
ADRs	-Hypersensitivity reactions. -Thrombophlebitis (inflammation and clot due to trauma of vein by IV administration). -Superinfections. -Diarrhea.		

Q:which of the following is a first generation cephalosporin.

Macrolides
Prototype: Erythromycin

	Clarithromycin	Azithromycin
Spectrum (in comparison to erythromycin)	More effective on G+ve bacteria	More effective on G-ve bacteria
Half-life	Half -life: 6-8 hours	Half -life: 3 days , Once daily dosing
metabolism	Metabolized in liver to active metabolite	Undergo some hepatic metabolism (inactive metabolite)
Cyt p450	Inhibits cytochrome P450 system (like erythromycin)	No effect on cytochrome P450 (no drug interactions)
MAO	-Bacteriostatic. -Bactericidal at high concentrations. -Inhibit bacterial protein synthesis by binding to 50S ribosomal subunit of the bacterial ribosome.  	
PK	-Major route of elimination: biliary route. -Stable at gastric acidity (in comparison to the prototype, erythromycin, which is not stable at gastric acidity). -clarithromycin & azithromycin-> only 10-15% excreted unchanged in urine. -clarithromycin-> Excreted in urine 20-40 % unchanged or metabolite & 60 % in bile.	
Clinical Uses	-Chlamydial pneumonia -Legionella pneumonia	
ADRs	-GI disturbances (nause, vomiting, abdominal cramps, and diarrhea) -Hypersensitivity reactions	

Fluoroquinolones

	Ciprofloxacin (prototype)	Moxifloxacin	Gatifloxacin
dose	Twice daily	Once daily	
spectrum	Mainly against Gram -ve bacteria	-G-ve & G+ve bacteria -Highly active against pseudomonas species.	
MOA	-block bacterial DNA synthesis by Inhibiting DNA gyrase enzyme (an enzyme involved in DNA supercoiling)(inhibit bacteria transcription and replication)		
PK	-Given oral or parenteral -Concentrates in many tissues (kidney, prostate, lung, and bones/joints) -Excreted mainly through kidney (must examine kidney function for patients taking these antibiotics chronically) -Relatively long half-life		
uses	-Acute exacerbation of COPD. -Community acquired pneumonia. -Legionella pneumonia.		
ADRs	-Nausea , vomiting , diarrhea. -CNS effects (confusion, insomnia, headache, anxiety). -Damage of growing cartilage (arthropathy). -Phototoxicity (so, advise patient to avoid excessive sunlight to prevent skin pigmentation).		
Contraindications (C.I)	-Not recommended for patients under 18 years (not given to children since it causes arthropathy). -Pregnancy. -Breast feeding women.		

Tetracyclines
Chlortetracycline, Doxycycline, Minocycline

Doxycycline (a long acting tetracycline)

MAO	-bacteriostatic antibiotics. -Broad-spectrum-> Active against many Gram +ve and Gram -ve bacteria (anaerobes, rickettsiae, chlamydiae, and mycoplasmas). -Inhibit protein synthesis by binding reversibly to 30S ribosomal subunit of the bacterial ribosome.
PK	-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 (dairy/cationic food impairs drug function by reducing absorption) -Protein binding 40-80 %. -Distributed well, including CSF. -Cross placenta and excreted in milk. -Largely metabolized in the liver.
Uses	Treatment of URTIs caused by S.pyogenes, S.pneumonia & H. influenza.
ADRs	-Nausea, vomiting ,diarrhea & epigastric pain (give with food but not dairy productions). -Thrombophlebitis – i.v -Hepatic toxicity (prolonged therapy with high dose). -Brown discolouration of teeth – children (bind to calcium in teeth). -Deformity or growth inhibition of bones – children. -Phototoxicity. -Vertigo. -Superinfections.
C.I	-Children (below 10 yrs). -Pregnancy. -Breast feeding.

Aminoglycosides
Streptomycin, Neomycin, Gentamicin

MOA	-Bactericidal antibiotics -only active against Gram -ve aerobic organisms. -Inhibits bacterial protein synthesis by binding to 30S subunit of the bacterial ribosome.
PK	-Poorly absorbed orally (highly charged). -Given parenterally IM , IV (used in emergency via injection) -Half-life=2-3 hours and increased to 24-48 in renal impairment- -Cross placenta (so, contraindicated in pregnancy) -Excreted unchanged in urine
Uses	Severe infections caused by Gram -ve organisms.
ADRs (at chronic use or overdose or renal impairment)	-Ototoxicity (hearing loss, dizziness). -Nephrotoxicity. -**In very high doses**:neuromuscular blockade that results in respiratory paralysis.

MCQ

1-Pneumonia mainly caused by			
A- S.pneumonia	B- H.influenza	C- M.catarrhalis	D- None of them

2-Amoxicillin-Clavulanic acid acts on			
A- Gram +ve bacteria	B- Gram -ve bacteria	C- Gram -ve bacilli	D- A&B

3-Which of the following antibiotics does NOT bind to the 30s subunit			
A-Streptomycin	B-Azithromycin	C-Doxycycline	D-Gentamicin

4-Which of the following is the best for chlamydial pneumonia?			
A-Neomycin	B-Streptomycin	C-Moxifloxacin	D-Azithromycin

5-A 20-year-old woman presents to the emergency room with headache, stiff neck, and fever for 2 days and diagnosed with meningitis. Which is the best agent for the treatment of meningitis in this patient?			
A- Cephalexin	B- Cefazolin	C- Cefotaxime	D- Cefuroxime

6-Which of the following drugs should not be consumed with dairy?			
A-Doxycycline	B-Streptomycin	C-Gentamicin	D-Moxifloxacin

Q5:Cefotaxime is The only drug on this list with adequate CSF penetration to treat meningitis.

Answers

1	2	3	4	5	6
A	D	B	D	C	A

SAQ

Q1) Mention TWO bacteria that could cause bronchitis.

Q2) Describe the mechanism of action of penicillins.

Q3) Mention TWO drugs that are active against β-lactamase-producing bacteria.

Q4) What drug is effective against G–ve bacteria only and suitable for treating acute exacerbation of chronic obstructive pulmonary disease? Mention its MOA.

Q5) Which antibiotic family is considered as Bacteriostatic and Bactericidal at high doses? Give 2 examples.

Q6) Describe the MOA of the drugs mentioned above.

Answers

A1) H. Influenza, Streptococcus pneumonia

A2) Inhibit bacterial cell wall synthesis through inhibition of peptidoglycan layer on the cell wall.

A3) Cefuroxime, Cefaclor

A4) Ciprofloxacin; Inhibit DNA gyrase enzyme (an enzyme involved in DNA supercoiling)(

A5) Macrolides. Clarithromycin, azithromycin.

A6) Inhibit protein synthesis by binding by 50s subunit of the bacterial ribosomes.

GOOD LUCK!

Team Leaders

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