PHARMACOLOGY

Lecture: treatment of respiratory tract infections

OBJECTIVES:

- The types of respiratory tract infections
- The antibiotics that are commonly used to treat respiratory tract infections and their side effects.
- Understand the mechanism of action, pharmacokinetics of individual drugs.

Please note that this lecture is a brief summary of most important antibiotics used for treatment of RTI's, and thus some details are left unmentioned.

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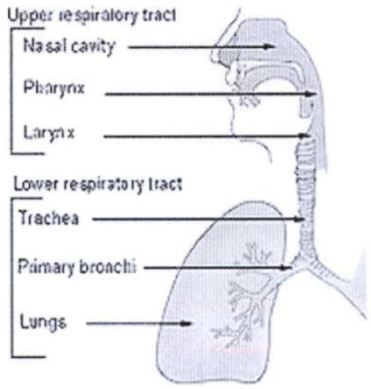
- Important.
- Extra notes.

Classification & antibiotics for respiratory tract infections

Respiratory tract infections

Upper respiratory tract infections (URTI's)



- **Caused by Viruses**
  - Should NOT be treated with antibiotics
  - **Treatment:** rest and plenty of fluids, OTC cold, pain relievers.

  OTC: over-the-counter cold medicines
- **Caused by Bacteria**
  - URTI's bacteria are mainly group A Streptococcus & H. Influenzae
  - **Treatment:** Antibiotics; depending on: 1-Type of bacteria 2-Sensitivity test

Lower respiratory tract infections (LRTI's)

- **Bronchitis**
  - Bronchitis is an **inflammation of major bronchi& trachea**
  - It could be Acute, Chronic, or acute exacerbation of chronic bronchitis
  - **Causes:** virus, or bacteria: (H.Influenzae, S.pneumonia, M.catarralis)
- **Pneumonia**
  - Pneumonia is a **serious infection of bronchioles & alveoli.** It can be:

    1- Community acquired (CAP)
    2- Hospital acquired (HAP)
  - S.pneumonia (66%), H.influenza (20%), M.catarrhalis (20%)

NOTES:

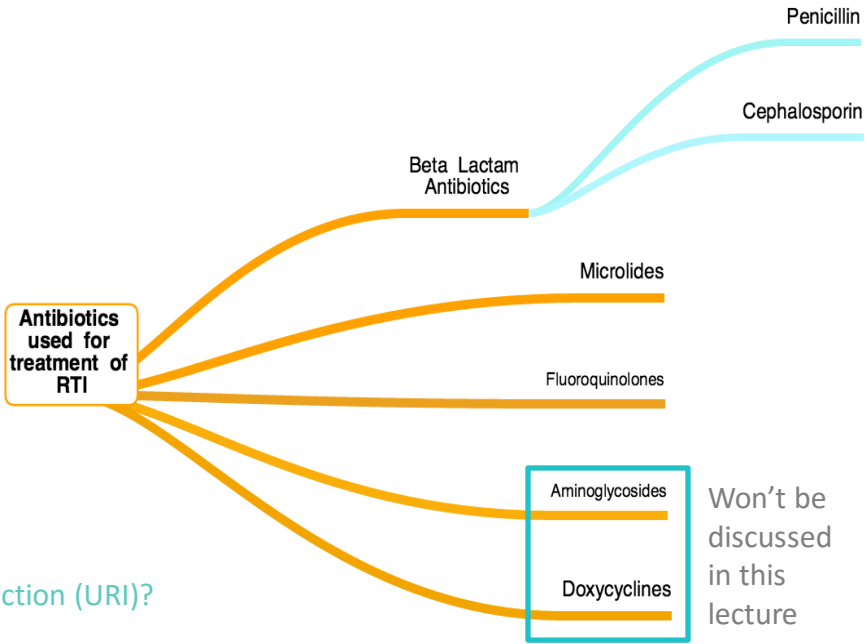
*Upper respiratory tract infections are most common due to exposure to external environment.

* Lower respiratory tract infections are costly & more difficult to treat.

*The air we breath will go to trachea then bronchi and finally to the alveoli then the circulation. The lower respiratory infections are the most dangerous because it will be in place that hard for antibiotics to reach and could lead to death.

* Most common routes of administration of antibiotics:

- Oral for URTI's
- IV Injection for LRTI's (possible hospital admission)



What is an upper respiratory infection (URI)?

1. Penicillins (β-lactam)

Broad- spectrum Penicillins
(Act on both gram +ve & gram-ve microorganisms)

- Amoxicillin - Clavulanic acid
- Ampicillin - Sulbactam
- Piperacillin - Tazobactam

* Formulation with **β-lactamase inhibitors** protects **Penicillins** from enzymatic hydrolysis (by the β-lactamase produced by bacteria) and extends their antimicrobial spectra.

Mechanism

1. Inhibits bacterial cell wall synthesis **through inhibition of peptidoglycan layer of the cell wall.** Penicillin inhibits transpeptidase enzyme which is a bacterial enzyme that cross-links peptidoglycan chains to form rigid cell walls.
2. Bactericidal (kills bacteria)

Pharmacokinetics

1. **Given orally or parenterally**
2. **Not metabolized in human, thus excreted mostly unchanged in urine.**
3. **Relatively lipid insoluble.** Doesn't cross placental barrier nor BBB, but yet used in meningitis because inflamed meninges are more permeable to the penicillins. (inflammation = ↑ permeability)
4. **Half-life=30-60 min (increased in renal failure).**

Adverse effects

1. **Hypersensitivity reactions.** Most serious ADR! Penicillins could cause Anaphylactic shock, so it is important to do skin test before prescribing the drug
2. **Convulsions (**due to increased concentration in plasma**, either after high IV dose or in renal failure)**
3. **Nephritis**
4. **Diarrhea**
5. **Superinfections** (superinfection is a second infection superimposed on an earlier one, mostly due to healthy normal flora eradication by antibiotics)

Therapeutic uses

1. Upper respiratory tract infections
2. **used in treatment of Acute otitis media especially those produced by Group A streptococci, which is gram positive (beta-hemolytic).**
3. Lower respiratory tract infections

2. Cephalosporins (β-lactam)

Mechanism of action:

Inhibit bacterial cell wall synthesis as penicillin but more resistant to β-lactamase, **cephalosporins are also bactericidal.**

From the first generation to the third generation of cephalosporins, there is:
—A decrease in gram-positive coverage
—An increase in gram-negative coverage
—An increase in CNS penetration
—An increase in resistance to β-lactamase

Cephalosporins

First generation

- Cephalexin
- Rout of administration: orally
- Effective against gram-positive bacteria.
- Effective in Upper respiratory tract infection

Second generation

- Cefuroxime axetil, Cefaclor
- Well absorbed orally
- Effective mainly against Gram-negative bacteria. can affect some gram positive as well.
- Active against β-lactamase-producing bacteria.
- Uses:
  - Upper and lower respiratory tract infections
  - Sinusitis, otitis media

Third generation

- Ceftriaxone, Cefotaxime, Cefixime
- Given by intravenous route because they can't be absorbed orally, except for cefixime
- More effective against gram-negative bacilli
- Effective in treatment of pneumonia produced by β-lactamase bacteria
- Good penetration into CSF (Cerebrospinal fluid)

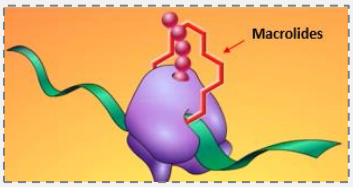
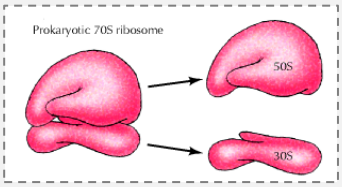
Adverse effects

1. **Hypersensitivity reactions** (↓than penicillin's)
2. **Thrombophilibitis** (injury & necrosis of vein's wall after IV administration)
3. **Superinfections and Diarrhea** can be with most antibiotics.

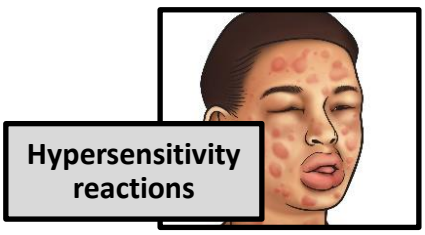
Pharmacokinetics

1. **Excreted Mostly unchanged in urine,** except for ceftriaxone "biliary excretion"
2. **Ceftriaxone has the longest half life (4-7 hours) .**

3. Macrolides

	Erythromycin's analogous:	
	Clarithromycin	**Azithromycin**
Mechanism of action	Macrolides are antibiotics used for both upper & lower respiratory tract infections **Mechanism of action:** inhibition of protein synthesis by binding to **50 S subunit** of the bacterial ribosomes. **They are bacteriostatic,** But when used at **higher** concentration → **bactericidal**  Bacterial ribosomes are called 70s Each ribosome is composed of Small subunit → 30s Large subunit → 50s 	
Spectrum	**More effective on Gram positive bacteria**	**More effective on Gram negative bacteria** (most respiratory tract infections are caused by gram negative)
Stability	**Stable at gastric acidity** → can be taken orally	
Drug interaction	**Inhibits cytochrome P- 450** → increase duration & toxicity of co-administered drugs	**No effect on cytochrome P- 450 enzyme** → no drug-drug interaction
Pharmacokinetics – **Metabolism**	**Metabolized to active metabolite**	**Undergo some hepatic metabolism to inactive metabolite**
Pharmacokinetics – **Excretion**	• **20-40% in urine whether unchanged or as metabolite** • **60% in bile** (mostly as metabolite)	**Biliary route is the major route of elimination, Only 10-15% excreted unchanged in the urine**
Pharmacokinetics – **Half- life**	**6-8 hours**	**3 days** (very long)
Dose		**Once daily dosing**
Clinical use	▪ **Chlamydial pneumonia** ▪ **Legionella pneumonia** (only seen in elders & smokers)	

Adverse effects:



YouTube Macrolides: Mechanisms of Action and Resistance

4. Fluoroquinolones

Mechanism of action: **inhibits DNA gyrase enzyme, which is an enzyme involved in DNA supercoiling.**

fluoroquinolones

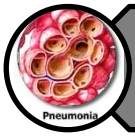
- **Ciprofloxacin** (Given twice-daily)
  - Mainly effective against gram -ve
  - Has high activity against pseudomonas species
- **Moxifloxacin** (given once-daily)
- **Gatifloxacin** (given once-daily)
  - Effective against gram-ve and gram +ve

Pharmacokinetics:

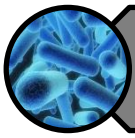
- **Given orally or parentally.**
- **Concentrates in many tissues (kidney, prostate, lung, bones and joints),** thus more likely effective in these tissues infections
- **Excreted mainly trough the kidney.** So we should rule it out in patients with kidney frailer
- **Has long half life.**

Clinical uses


Acute exacerbation of chronic obstructive pulmonary disease.



Community acquired pneumonia


Legionella pneumonia

Adverse effects:

1. Nausea, vomiting and diarrhea.
2. CNS effects (confusion, insomnia, headache and anxiety)
3. Damage of growing cartilage (arthropathy)
4. Phototoxicity (use sunscreen & avoid excessive sun light)

contraindications:


Not recommended for patients under 18 years.


pregnancy


Breast feeding women

Antibiotics for RTI's drugs summary

Drug	Pharmacokinetics	ADRS	Uses
Cell wall synthesis inhibitors (through inhibition of peptidoglycan layer of the cell wall.)			
Beta lactam antibiotics Penicillins (Bactericidal)			
Amoxicillin Taken with: **Clavulanic acid** **Ampicillin** **Sulbactam** **Piperacillin** **Tazobactam**	• Given orally or parenterally • Not metabolized in human. • Relatively lipid insoluble. • Excreted mostly unchanged in urine. • Half-life 30-60 min (increased in renal failure).	• Hypersensitivity Diarrhea. • Superinfections. • Convulsions (after high IV dose or in renal failure) • Nephritis.	**URTI's, Acute otitis media** (especially produced by Group A gram + β-haemolytic streptococci). **LRTI's.**
Beta lactam antibiotics Cephalosporins (Bactericidal)			
1st Generation Cephalosporins — **Cephalexin**	• Given **orally**. • Manly against **gram + bacteria.**	• Hypersensitivity reactions. • Thrombophlebitis. • Superinfections. • Diarrhea.	**URTI's**
2nd Generation Cephalosporins — **Cefuroxime axetil**, **Cefaclor**	• Well absorbed **orally**. • mainly against **Gram - bacteria.** • **Active against β-lactamase – producing bacteria.**		• **URTI's** • **LRTI's** • Sinusitis • otitis media
3rd Generation Cephalosporins — **Ceftriaxone**, **Cefotaxime** (IV); **Cefixime** (Orally)	• Manly against **Gram - bacilli.** • Penetration into CSF • Excreted mostly in **urine** • Long Half-life(4-7h) (**Ceftriaxone**)		Effective treatment in **pneumonia** produced by β-lactamase bacteria
Protein synthesis inhibitors (by binding to **50S** subunit of the bacterial ribosomes)			
Macrolides Cephalosporins (Bacteriostatic) (Bactericidal at high concentration)			
Erythromycin		**Hypersensitivity Reactions**	**Chlamydial pneumonia** **Legionella pneumonia**
Azithromycin	• mainly against **Gram - bacteria** / • **Inactive** metabolite • T½ = 3 d, Once daily dosing. / • Stable at gastric acidity. • **No effect** on cytochrome P450 system. • **Biliary route** is the major route of elimination. • Only 10-15% excreted unchanged in the urine.		
Clarithromycin	• Manly against **gram + bacteria.** • Stable at gastric acidity. / • **Active** metabolite. • **Inhibits** cytochrome P450 system. • Excreted in urine 20-40% & 60% in bile. Half-life 6-8h.		
DNA synthesis inhibitors (Inhibit DNA Gyrase enzyme (an enzyme involved in DNA supercoiling))			
Fluoroquinolones			
Ciprofloxacin **Moxifloxacin** **Gatifloxacin**	Given **orally** or **parenterally**. / Excreted mainly in **kidney,** Concentrates in many tissue (kidney, prostate, lung, bones) Relatively ↓ T½ allows once daily (**moxifloxacin** & **Gatifloxacin**) & twice-daily (**Ciprofloxacin**). **Antibacterial spectrum:** **Ciprofloxacin** mainly effective **Gram - bacteria,** **Moxifloxacin** & **Gatifloxacin** G – & G + & given once daily (highly active against Pseudomonas species) **Contraindications:** < 18 years, Pregnancy, Breast feeding.	Nausea , vomiting , diarrhea. • **CNS effects** confusion, insomnia, headache, anxiety). • Arthropathy. • **Phototoxicity** (avoid excessive sunlight)	• Acute exacerbation of COPD. • Community acquired pneumonia. • Legionella pneumonia.

Respiratory Tract Infections

Classification of respiratory tract infections:

Upper respiratory tract infections (URTI)

- Viruses Treatment: rest and plenty of fluids, OTC cold, pain relievers.
- Bacteria (mainly **Group A streptococcus** or **H. influenza**)

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

Lower respiratory tract infections (LRTI)

- Bronchitis Acute, Chronic, & Acute exacerbation of chronic bronchitis.

  Causes: viruses or bacteria(**H. influenza**, **S. pneumonia**& **M. catarralis**).
- Pneumonia Community-acquired(CAP) or Hospital-acquired.

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

Antibiotics

Can be **bactericidal** or **bacteriostatic**

ACCORDING TO MECHANISM OF ACTION

INHIBITION OF CELL WALL SYNTHESIS (by inhibiting peptidoglycan layer)

(**Beta lactam** antibiotics)

- **Penicillins**
  1. Natural penicillins.
  2. Antistaphylococcal penicillins.
  3. Antipseudomonal penicillins.
     - **Piperacillin / Paired with Tazobactam**
  4. Broad- spectrum penicillins.

     (Acts on both gram +ve & -ve microbes)
     - **Amoxicillin / Clavulanic acid**
     - **Ampicillin / Sulbactam**

These drugs are inactivated by Penicillinase (bacteria inhibiting Penicillin). Thus they are commonly paired with β-lactamase inhibitors.

β-lactamase
Is purposed by bacteria, an enzyme that binds to certain Penicillin. It counteract the effects of an antibiotic.

- **Cephalosporin**
  - 1st Generation Cephalosporins.
    - **Cephalexin**
  - 2nd Generation Cephalosporins
    - **Cefuroxime axetil / Cefaclor**
  - 3rd Generation Cephalosporins
    - **Ceftriaxone / Cefotaxime / Cefixime**

Classification based on general features of antimicrobial activity.

INHIBITION OF PROTEIN SYNTHESIS (by binding to 50S subunit of bacterial ribosomes)

- **Erythromycin / Azithromycin / Clarithromycin**
- **Chloramphenicol / Tetracyclines / Aminoglycosides**

INHIBITION OF DNA SYNTHESIS (Inhibit DNA Gyrase enzyme (an enzyme involved in DNA supercoiling))

- **Quinolones**

INHIBITION OF FOLATE METABOLISM

- **Sulphonamides, / Trimethoprim**

INHIBITION OF RNA synthesis (by binding to RNA polymerase)

- **Rifampicin**

ACCORDING TO spectrum

Broad spectrum

- **Ampicillin**
- **amoxicillin.**

Narrow spectrum

- Penicillin G.
- Aminoglycosides

QUIZ

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

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Thanks for sarah alhussain for all her great work for the drug summaries

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology.med435@gmail.com

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