بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

PHARMACOLOGY

FINAL | Lecture 7

Drugs for Bacterial Pneumonia 2

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﴿ وَلَقَدْ نَعْلَمُ أَنَّكَ يَضِيقُ صَدْرُكَ بِمَا يَقُولُونَ ﴿٩٧﴾ فَسَبِّحْ بِحَمْدِ رَبِّكَ وَكُن مِّنَ السَّاجِدِينَ ﴾

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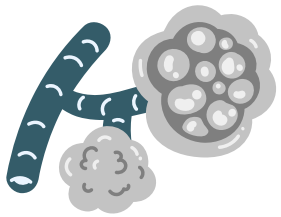

Fluoroquinolones

- They block bacterial **DNA synthesis** by inhibiting bacterial **topoisomerase II** (**DNA gyrase**) and **topoisomerase IV**.
- Levofloxacin, Ciprofloxacin, Moxifloxacin :
  - It has excellent **gram-negative** activity (Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus and Campylobacter) and **moderate to good** activity against **gram-positive** bacteria.
  - **Levofloxacin** has superior activity against ***Streptococcus pneumoniae***.
  - **Ciprofloxacin** (Prototypical) is the **most active** against ***Pseudomonas aeruginosa***.

Fluoroquinolones

- **Moxifloxacin** has good activity against **anaerobic bacteria**.
- **Fluoroquinolones** are also active against agents of **atypical pneumonia** (*Mycoplasma* and *Chlamydia*) and against **intracellular pathogens** such as *Legionella* and *Mycobacteria*.
- Used for **upper** and **lower** respiratory tract infections (levofloxacin, gatifloxacin, gemifloxacin, and moxifloxacin because of gram positive and atypical bacteria activity).
- Good for many other infections

Fluoroquinolones' Adverse Reactions:

1. Nausea, vomiting and diarrhea.
2. Headache, dizziness, insomnia, skin rash or abnormal liver function tests
3. **Photosensitivity** have been reported with **lomefloxacin** and **perfloxacin**.
4. **QTc prolongation** can occur with **gatifloxacin**, **levofloxacin**, **gemifloxacin** and **moxifloxacin** → arrhythmogenic.
   - QT prolongation is arrhythmogenic and may cause polymorphic ventricular tachycardia progressing to ventricular fibrillation and death; it **can occur with fluoroquinolones**, but is **more common with the four mentioned agents**.

Fluoroquinolones: Hepatic Enzyme Elevation and Photosensitivity Reactions

- Elevation of liver enzyme levels after using fluoroquinolones does not necessarily indicate hepatotoxicity; however, values **≥3 times the upper limit of the reference range suggest possible hepatotoxicity**—e.g., if the ALT upper reference limit is 40 U/L, levels **≥120 U/L warrant monitoring**.
- Photosensitivity may occur with fluoroquinolones and is a **non-allergic phototoxic or photoallergic reaction due to histamine release triggered by UV light**. **Non-IgE-mediated histamine release** may occur with physical or chemical stimuli (e.g., cold exposure, opioids, neuromuscular junction blockers, and muscle relaxants used in general anesthesia); therefore, **caution and monitoring are advised**, but **combination is not contraindicated**.

"Due to histamine" is not accurate.

Fluoroquinolones' Adverse Reactions:

5. **Hyperglycemia** has been associated with **gatifloxacin** even in patients receiving **oral hypoglycemic agents**.
   - Gatifloxacin damages pancreatic β-cells, causing **initial release of stored insulin and hypoglycemia; subsequent impairment of insulin production leads to hyperglycemia**.
6. Damage of **growing cartilage** and development of **arthropathy**. Should **not** be used in patients **under 18 years of age**. Arthropathy is reversible (?!)
   - The doctor believes that arthropathy **may not be completely reversible and may be irreversible in some cases**.
7. **Tendonitis** and **tendon rupture** (especially achilles tendon which links foot and leg) have been reported in adults.
8. **Contraindicated** in **pregnancy**.
   - **They are avoided because** they damage cartilage in the fetus and impair **skeletal system development**.

Polymyxins

- **Rarely** used; they are the most nephrotoxic drugs ever used.
- They are a group of basic peptides active against **gram-negative** bacteria and include polymyxin B and polymyxin E (colistin).
- Polymyxins act as **cationic** detergents. They attach to and disrupt bacterial **cell membranes**.
- **Gram-positive** organisms, Proteus sp, and Neisseria sp are **resistant**.
- Because of their **nephrotoxic** effects after systemic use, they are largely **restricted** to **topical** use (**inhalation** only) in **resistant** pneumonia (e.g., *Pseudomonas aeruginosa*) when organisms are resistant to conventional antibiotics.

Polymyxins

- Emergence of strains of **Acinetobacter baumannii**, **Pseudomonas aeruginosa**, and **Klebsiella pneumonia** that are **resistant to all other agents** led to their renewed use as **parenteral agents** for **salvage therapy** of infections caused by these organisms.
- Polymyxin **nebulization** is used to deliver high concentrations of the antibiotic **directly** to the lungs to treat **severe** respiratory tract infections.
- Parenteral does not mean injection only; it refers to any route other than the oral route.

Polymyxins' Adverse Effects:

1. Nephrotoxicity
2. Severe hypocalcemia, hypomagnesemia, and hypokalemia follow renal injury
3. Neurotoxicity
4. Allergic reactions
5. Clostridium difficile associated diarrhea (it is rare because it occurs after **oral** administration and can also occur with **IV use**, but **not** with **topical** use)
6. Rhabdomyolysis

Rhabdomyolysis

- Creatine kinase elevation may occur with minor muscle injury (e.g., trauma or intramuscular injection) and does not necessarily indicate rhabdomyolysis; however, **marked creatine kinase elevation suggests rhabdomyolysis**, leading to **potassium release causing hyperkalemia and cardiac arrhythmias**, and **myoglobin release with renal deposition**, resulting in **tubular obstruction, direct tubular toxicity, and acute renal failure**.

Macrolide Antibiotics

- Erythromycin, Clarithromycin, Azithromycin:
  - **Bacteriostatic** inhibitors of protein synthesis.
- **Therapeutic Uses:**

1. Is the drug of choice for **corynebacterial infections** (diphtheria, sepsis, erythrasma).
2. **Chlamydia** infections (respiratory, neonatal, ocular, genital).
3. Community acquired pneumonia (Mycoplasma, Legionella and pneumococcus).

Macrolide Antibiotics' Therapeutic Uses:

4. Alternative to penicillin in patients with streptococcal or pneumococcal and susceptible staphylococcal infections who are allergic to penicillins.
   - When *Staphylococcus* is described as susceptible to penicillin, this means that the strain **does not produce penicillinase**; however, in clinical practice, **such strains are uncommon** and resistance is usually assumed, since most *Staphylococcus* species produce penicillinase. Therefore, **staphylococcal infections are treated empirically with anti-staphylococcal antibiotics rather than penicillin**.
5. Emergence of resistance make them less attractive first line agents for pharyngitis, skin and soft tissue infections and typical pneumonia.
   - Macrolides are drugs of choice for atypical pneumonia
6. Legionnaire's disease.

Macrolide Antibiotics' Adverse Effects:

1. Acute cholestatic hepatitis (erythromycin estolate): intrahepatic obstruction to bile flow. Fever, jaundice and impaired hepatic functions. Probably is a hypersensitivity reaction.
2. Other allergic reactions include fever, eosinophilia and rashes.
3. Epigastric distress, anorexia, nausea, vomiting and diarrhea.

- Epigastric distress (dyspepsia) is the **major adverse effect of macrolides** and may **lead to drug discontinuation**.

Macrolide Antibiotics' Adverse Effects:

4. Increased gastrointestinal motility due to stimulation of motilin receptors → colic and diarrhea (erythromycin and not the others).
   - Metoclopramide is a prokinetic agent used for nausea and vomiting by enhancing forward GI motility, but it is **avoided in children because it causes extrapyramidal side effects** (abnormal muscle tone). **Erythromycin** can be used instead as a **prokinetic**; however, **tolerance** develops and its effect **decreases** with continuous use.
5. Drug interactions: erythromycin **inhibits** CYP3A4 and other cytochrome P450 enzymes, and thus **increase** concentrations of many drugs including theophylline, methyprednisolone, cyclosporine, oral anticoagulants and CCBs. It increases the **bioavailability** of **digoxin**. This is **not** seen with **azithromycin**.

Tetracyclines

- Doxycycline, Minocycline, Tigecycline
  - **Tigecycline** is the **newest** generation of tetracyclines and is **more effective** but **more toxic** than other tetracyclines.
- They inhibit microbial protein synthesis
- Active against many gram positive and gram negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasma, L forms, and amebae.
- Used only as alternatives to macrolides if there is resistance or contraindication, for the treatment of **atypical** pneumonia caused by chlamydiae and mycoplasma.
- Tetracyclines are broad-spectrum antibiotics but are **not commonly used as first-line therapy for typical bacterial infections**; they are **mainly used for atypical organisms**, and they cause **pseudomembranous colitis at a much lower incidence** compared to clindamycin, fluoroquinolones, and cephalosporins.

Tetracyclines Adverse effects:

1. Hypersensitivity reactions including drug fever and skin rash.
2. GIT: nausea, vomiting, diarrhea and Pseudomembranous colitis by **Clostridioides**.
3. Superinfections: Pseudomonas, Proteus, Staphylococcus aureus, Coliforms, Clostridia and Candida.
4. Bone & teeth:
   - Fetal teeth: fluorescence, discoloration, and enamel dysplasia.
   - Fetal bone: deformity or growth inhibition.
   - Similar changes occur in children below 8 years of age (Contraindicated).
5. Very dangerous during **pregnancy**

Tetracyclines Adverse effects:

6. Liver toxicity: hepatic necrosis and impairment of hepatic function.
7. Kidney toxicity: renal tubular acidosis and other renal injury.
8. Local tissue toxicity: **Thrombophlebitis** after **IV** administration, **Local pain** after **IM** administration.
9. Photosensitivity.
10. Vestibular reactions: dizziness, vertigo, nausea, vomiting.

- **Tigecycline** is the tetracycline most likely to cause these adverse reactions.

Vancomycin

- It **inhibits** **cell wall synthesis**.
- Therapeutic Uses:
  1. Pseudomembranous colitis caused by Clostridium difficile. (orally). Metronidazole is preferred.
  2. Methicillin-resistant Staphylococcus aureus (MRSA) infections (sepsis and endocarditis). (IV). **Most common** therapeutic use (**main indication** for **vancomycin**)
  3. Staphylococcal and streptococcal infections in patients allergic to penicillin (endocarditis). (IV).
- Methicillin-sensitive Staphylococcus aureus (MSSA) infections are treated with **anti-staphylococcal antibiotics** rather than vancomycin.

Vancomycin's Therapeutic Uses:

4. **Vancomycin** in combination with **gentamicin** is an alternative for treatment of **enterococcal endocarditis** in patients with **penicillin allergy**.
5. **Vancomycin** in combination with **cefotaxime**, **ceftriaxone**, or **rifampin** for **meningitis** caused by highly **penicillin-resistant** strains of **pneumococci**.

- Therapeutic concentrations: peak 20-40 mg/L, trough 5-10 mg/L.
- Rifampin is an **anti-tubercular, broad-spectrum antibiotic** and may be used **in specific cases**, usually **in combination therapy**, for *Staphylococcus* and *Streptococcus* infections.
- Vancomycin and aminoglycosides are similar in principle regarding **therapeutic drug monitoring**; two serum concentrations are measured: the **peak level after administration** and the **trough level immediately before the next dose**.

Vancomycin Adverse Effects:

1. Hypersensitivity reactions, including drug fever.
2. Ototoxicity and nephrotoxicity are **rare** with vancomycin; however, **concomitant** use with other ototoxic or nephrotoxic drugs may result in **synergistic** toxicity.
3. Neutropenia.
4. Phlebitis at site of injection (irritating to tissues/vein), in case of IV administration.
5. "Red man" or "red neck" syndrome. Infusion related **flushing** caused by release of **histamine**. Can be reduced by **prolonging infusion** (reducing the rate) or increasing the dosing interval.
   - **Slow infusion** of vancomycin followed by **slow injection** is used to prevent **Red Man Syndrome**.

Linezolid

- Linezolid is used as a substitute for vancomycin in cases of **contraindication or resistance**, for example **vancomycin-resistant *Staphylococcus aureus***.
- It **inhibits** initiation of protein synthesis
- Active against **gram-positive** organisms: Staphylococci, streptococci, enterococci, gram positive anaerobic cocci, gram-positive rods (Corynbacteria, Listeria monocytogenes).
- It is primarily **bacteriostatic**, except for **streptococci** where it is **bactericidal**.
- Bacteriostatic antibiotics work when the immune system is functioning normally; however, in **immunocompromised patients, bactericidal agents are generally preferred**, and **bacteriostatic drugs** may be less effective, preferably avoided.

Linezolid's Therapeutic Uses:

- Infections caused by **vancomycin-resistant Staphylococcus aureus** and **Enterococcus faecium**, **nosocomial pneumonia**, **community-acquired pneumonia** and **skin infection**.
- It should be **reserved** for infections caused by **multi-drug resistant gram-positive bacteria**.

Linezolid's Adverse Effects:

1. Gastrointestinal upset.
2. Headache.
3. Allergy – rash.
4. Thrombocytopenia, neutropenia.
5. Weak MAO inhibition.

- By inhibiting MAO, linezolid **increases catecholamine levels**, which may result in **hypertension, tachycardia, and arrhythmias**, and **leads to significant interactions with MAO-related drugs**.

PHARMACOLOGY QUIZ LECTURE 7

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