Antibiotics for Treatment of Pneumonias

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Main Causative Microorganisms:

1. ***Streptococcus pneumonia*** **(community acquired)**
2. ***Mycoplasma pneumonia*** **+ other atypical bacteria (community acquired)**
3. **Gram-negative aerobic bacilli, *S. aureus*, and multidrug-resistant (MDR) pathogens. *Pseudomonas aeruginosa, Acinetobacter, E. coli*, *Klebsiella* spp, *Enterobacter* spp, *Proteus* sp, *Citrobacter, Bacillus,* and *Serratia* (Hospital acquired)**
4. **Anaerobic bacteria following aspiration of gastric or oropharyngeal contents.**
5. **Others.**

Penicillins

β-Lactam Antibiotics:

- **They are inhibitors of cell wall synthesis**

Ampicillin/salbactam and Amoxicillin/clavulanate:

- **They are active against gram positive cocci, anaerobes, enterococci, *Listeria monocytogenes* and β-lactamase-negative strains of gram negative cocci and bacilli such as *Haemophilus influenzae, E. coli, proteus mirabilis* and *Salmonella sp*. *Acinetobacter* is treated with ampicillin/salbactam.**

Penicillins

Therapeutic uses:

1. **Upper respiratory tract infection caused by *Streptococcus pyogens, Streptococcus pneumoniae, H. influenzae* (sinusitis, otitis media, acute exacerbation of chronic bronchitis and epiglottitis.**
2. **Urinary tract infection due to *E. coli*.**
3. **Meningitis due to:**

   a. *H. influenzae, Sterptococcus pneumoniae, Neisseria meningitis*.

   b. Listeria monocytogenes in immunocompromized patients (excellent activity).

Penicillins

Piperacillin/tazobactam

- **Used for *Pseudomonas aeruginosa* pneumonia alone or in combination with others (see next) according to infection severity.**
- **May be used in *Enterobacter* and indole positive *Proteus*, acquired usually in hospitals by immunocompromized hosts, {in combination with aminoglycosides or fluoroquinolones.**
- **Active against methicillin-sensitive *Staphylococcus aureus*.**

Penicillins

Oxacillin, Nafcillin:

- **Favored for methicillin-sensitive Staphylococcal infrections**

Penicillins

Adverse Effects:

1. **Hypersensitivity reactions (0.7-10% of patients): Range from maculopapular rash, urticaria, fever, bronchospasm, vasculitis, serum sickness, angioneurotic edema, exfoliative dermatitis and anaphylaxis (0.05%).**
2. **Toxic nonallergic skin rash in patients with infectious mononucleosus given ampicillin (100% of patients).**
3. **Superinfection: pseudomembranous colitis due to *Clostridium difficile* and diarrhea, vaginal candidiasis with extended-spectrum penicillins.**

Penicillins

4. **Heart failure with antipseudomonal penicillins due to Na^+ overload → hypokalemia. Piperacillin contains 2 mEq Na^+ / gram.**
2. **Bone marrow depression, granulocytopenia and hepatitis – oxacillin, nafcillin.**
3. **Oral lesions, fever, interstitial nephritis, eosinophilia, hemolytic anemia and vasculitis.**

Cephalosporines

Second-generation cephalosporins (Cefuroxime):

Therapeutic uses:

1. **Sinusitis, otitis and lower respiratory tract infections caused by *Haemophilus influenzae* and *Moraxella catarrhalis.***
2. ***Community acquired pneumonia* caused by β-lactamase producing *Haemophilus influenzae, & Klebsiella and penicillin-resistant pneumococc***

Cephalosporines

Third-generation cephalosporoins (Ceftazidime):

- **For *Pseudomonas aeruginosa* infection in combination with aminoglycosides.**

Fourth-generation cephalosporins (cefipime):

- **Has good activity against *Psuedomonas, Enterobacteriaceae, Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant), *Haemophilus influenzae*.**

Cephalosporines

Adverse Effects:

1. **Hypersensitivity reactions are the most common. Similar to those with penicillins. There is ~ 5-10% cross-sensitivity with penicillins.**
2. **Bone marrow depression, granulocytopenia.**
3. **Nephrotoxicity, including interstitial nephritis and even tubular necrosis especially with preexisting renal disease or in the presence of other nephrotoxic agents.**

Cephalosporines

4. **Local irritation can produce severe pain after IM injection and thrombophlebitis after IV injection.**
5. **Serious bleeding: hypoprothrombinemia, thrombocytopenia and platelet dysfunction.**

Carbapenams

Imipenem, Meropenem:

1. **Drugs of choice for Enterobacter infections.**
2. **Susceptible organisms (including *P. aeruginosa*) resistant to other drugs.**
3. **Empiric treatment of febrile neutropenic patients in combination with aminoglycosides.**
4. **Intra-abdominal and gynecological infections.**
5. **Active against many highly penicillin-resistant strains of pneumococci.**
6. **Mixed aerobic and anaerobic infections caused by nosocomial organisms.**

Carbapenams

7. **Urinary tract infections, lower respiratory infections, skin and soft tissue infections, bone and joint infections.**

Meropenem:

- **More activity against gram negative aerobes and less activity against gram positive organisms.**

Carbapenams

Adverse Reactions:

1. **Nausea, vomiting and diarrhea – most common.**
2. **Seizures with high doses or in patients with CNS lesions or renal insufficiency (less with meropenem and ertapenem).**
3. **Hypersensitivity reactions, with some cross-sensitivity with other β-lactams.**
4. **Local reactions at infusion sites.**

Monobactams

Aztreonam:

- **Active against the Enterobactriaceae (*Serratia*) and *Pseudomonas aeruginosa* in addition to *H. influenzae* and gonococci.**
- **Gram positive bacteria and anaerobes are resistant to aztreonam.**

Monobactams

Adverse Effects:

1. Occasional skin rash.
2. Elevation of serum aminotransferases (? hepatitis).
3. Local reactions at site of injection.
4. GIT upset
5. Thrombocytopenia
6. Neutropenia

Aminoglycosides

- They are bactericidal inhibitors of protein synthesis.
- Include: Gentamicin, Amikacin, Tobramycin and others.

1. Mostly used against gram negative enteric bacterial infections (pseudomonas, proteus, enterobacter, acinetobacter, klebsiella, serratia).
2. They are almost always used in combination with a β-lactam antibiotic because of synergism and to extend coverage to include gram positive bacteria such as enterococci, streptococci

Aminoglycosides

Adverse Reactions:

1. **Ototoxicity and nephrotoxicity are more likely to be encountered when therapy is continued for more than 5 days, at higher doses, in the elderly, in renal failure and with concurrent use of other ototoxic and nephrotoxic agents such as loop diuretics, vancomycin or amphotericin.**

- **Ototoxicity can manifest either as auditory damage resulting in tinnitus and high frequency hearing loss initially, or vestibular damage manifested by vertigo or loss of balance.**

Aminoglycosides

2. **Neuromuscular junction block at high doses → respiratory paralysis. Calcium gluconate and neostigmine are antidotes.**
3. **Hypersensitivity reactions rare.**
4. **Pain at the injection site.**
5. **Contraindicated during pregnancy.**

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 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.**

Fluoroquinolones

5. **Hyperglycemia has been associated with gatifloxacin even in patients receiving oral hypoglycemic agents.**
6. **Damage of growing cartilage and development of arthropathy. Should not be used in patients under 18 years of age. Arthropathy is reversible (?!).**
7. **Tendonitis and tendon rupture have been reported in adults.**
8. **Contraindicated in pregnancy.**

Polymyxins

- 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 d isrupt bacterial cell membranes.
- Gram positive organisms, Proteus sp, and Neisseria sp are resistant.
- Because of their nephtotoxic effects after systemic use, they are largely restricted to topical use.

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.**

Polymyxins

Adverse Effects:

1. **Nephrotoxicity**
2. **Severe hypocalcemia, hypomagnesemia, and hypokalemia follow renal injury**
3. **Neurotoxicity**
4. **Allergic reactions**
5. ***Clostridium difficile* associated diarrhea**
6. **Rhabdomyolysis**

Macrolide Antibiotics

Erythromycin, Clarithromycin, Azithromycin:

- **Bactriostatic 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

4. **Alternative to penicillin in patients with streptococcal or pneumococcal and susceptible staphylococcal infections who are allergic to penicillins.**
5. **Emergence of resistance make them less attractive first line agents for pharyngitis, skin and soft tissue infections and 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.**

Macrolide Antibiotics

4. **Increased gastrointestinal motility due to stimulation of motilin receptors → colic and diarrhea (erythromycin).**
5. **Drug interactions: erythromycin inhibits CYP3A4 and other cytochrome P450 enzymes, and thus increase concentrations of many drugs including theophylline, methyprednisolone, cyclosporine and oral anticoagulants. It increases the bioavailability of digoxin. This is not seen with azithromycin.**

Tetracyclines

Doxycycline, Minocycline, Tigecycline

- **They inhibit microbial protein synthesis**
- **Active against many gram positive and gram negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasma, L forms, and amebae.**
- **Used alternatives to macrolide for treatment of pneumonia caused chlamydiae and mycoplasma.**

Tetracyclines

Adverse effects:

1. **Hypersensitivity reactions including drug fever and skin rash.**
2. **GIT: nausea, vomiting and diarrhea.**
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.**

Tetracyclines

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

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).**
3. **Staphylococcal and streptococcal infections in patients allergic to penicillin (endocarditis). (IV).**

Vancomycin

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.**

Vancomycin

Adverse Effects:

1. **Hypersensitivity reactions, including drug fever.**
2. **Ototoxicity.**
3. **Nephrotoxicity.**
4. **Neutropenia.**
5. **Phlebitis at site of injection (irritating to tissues.**
6. **“Red man” or “red neck” syndrome. Infusion related flushing caused by release of histamine. Can be reduced by prolonging infusion or increasing the dosing interval.**

Linezolid

- **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.**

Linezolid

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

Adverse Effects:

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