Antimicrobials for Respiratory Tract Infections

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Antimicrobials commonly used for non-specific respiratory tract infections

- Betalactams
- Macrolides
- Tetracyclines
- Trimethoprim-sulfamethoxazole
- Respiratory quinolones
Betalactams (1)

The betalactam antibiotics used in RTIs:

- **Penicillins**: Amoxicillin, ampicillin, coamoxiclav (amoxicillin + clavulanate), piperacillin-tazobactam
- **Cephalosporins**:
  - First generation: cefadroxil, cephradine, etc.
  - Second generation: cefuroxime
  - Third generation: cefotaxime, ceftriaxone, etc.
  - Fourth generation: cefepime
- **Others**:
  - Carbapenem: meropenem
  - Betalactamase inhibitors: clavulanic acid, tazobactam
Betalactams (2)

General characteristics of the betalactams:

- Inhibit bacterial cell wall synthesis by binding to the Penicillin binding proteins (PBPs)
- Bactericidal, except for the betalactamase inhibitors (eg. tazobactam, clavulanic acid)
- Tolerability:
  - In general they are remarkably safe
  - Common SE: hypersensitivity, local irritation, skin rash unrelated to hypersensitivity reaction
Betalactams (3)

- Uncommon SE: seizure, interstitial nephritis, hypoprothrombinemia (associated with cephalosporins containing methylthiotetrazole group, eg. cefoperazone, cefamandole)

Note: For other essential information, read *Farmakologi dan Terapi, 5th ed*, pp. 664-693.
Macrolides (1)

- Derivatives:
  - erythromycin, clarithromycin, azithromycin, roxithromycin, spiramycin, telithromycin, clindamycin

- Erythromycin (prototype):
  - Active mainly against gram-positive cocci and atypical microorganisms (mycoplasma, chlamydia), corynebacterium, legionella, some atypical mycobacteria
Macrolides (2)

- Pharmacokinetics:
  - Destroyed by stomach acid → enteric coated formulation
  - Absorption is reduced by food
  - Mainly excreted through the bile
  - Indications: upper and lower respiratory tract infections due to gram-positive cocci (including streptococcal pharyngitis) and atypical pathogens, diphtheria
Macrolides (3)

- Side effects: gastrointestinal intolerance, liver toxicity, prolongation of QTc interval
- Interactions: inhibition of cytochrome P450 enzymes → increase of the concentration of theophylline, oral anticoagulants, cyclosporine, methylprednisolone
- Oral dose: 4 x 250-500 mg/day
- Notes: macrolides are relatively safe for children and pregnant women.
Macrolides (4)

- Clarithromycin:
  - Has relatively high tissue concentration
  - More active against *M. avium* complex
  - Less gastrointestinal side effects
  - Oral dose: 2 x 250-500 mg/day

- Azithromycin:
  - Highly active against chlamydia
  - Tissue concentration is much higher than serum concentration
  - Slowly released from the tissue
  - Oral dose: day 1: 500 mg/day, the next 3 days: 250 mg/day
Macrolides (5)

- Roxithromycin:
  - Less likely to cause gastric irritation than erythromycin
  - Absorption is minimally affected by food
  - Long T1/2 $\rightarrow$ twice daily administration
  - Especially active against *Chlamydia trachomatis*
Macrolides (6)

- Spiramycin:
  - Active primarily against gram positive cocci
  - Indications: respiratory tract infections caused by sensitive pathogens
  - Oral dose: 3 x 500 mg/day

- Telithromycin:
  - Indications: CAP, acute exacerbation of chronic bronchitis, sinusitis, streptococcal pharyngitis.
Macrolides (7)

- Clindamycin:
  - Active against anaerobes
  - Indication: aspiration pneumonia and pneumonia caused by *Pneumocystis jiroveci* (in combination with primaquine)
  - Oral dose: 1-3 x 150 mg/day
Tetracyclines (1)

- Derivatives: tetracycline, oxytetracycline, doxycycline, minocycline
- Their absorption is impaired if given with food (except doxycycline and minocycline) or other drugs containing bivalent or trivalent cations
- Doxycycline is occasionally used in the treatment of exacerbation of chronic bronchitis, community acquired pneumoniae, and non-tuberculous mycobacterial infections
Tetracyclines (2)

- Today, their clinical use have been largely supplanted by other agents due to the development of resistance
- SE: gastrointestinal irritation, teeth discoloration in children, hepatotoxicity, nephrotoxicity (due to expired product), vestibulotoxicity, hypersensitivity reactions
- CI: children and pregnant women
Cotrimoxazole (1)

- This is a fixed dose combination of trimethoprim + sulfamethoxazole.
- Mechanism of action: blockade of tetrahydrofolate synthesis in the sensitive microorganism.
- Indication for respiratory tract infections (RTI): acute exacerbation of chronic bronchitis (due to susceptible pathogens) and pneumonia due to *Pneumocystis jiroveci* (= *Pneumocystis carinii*).
Cotrimoxazole (2)

- SE: hypersensitivity reactions (incl. Stevens-Johnson syndrome), anemia, gastrointestinal complaints
- Bacterial resistance is a common problem today
Respiratory quinolones (1)

- **Levofloxacin**
  - Active against *S. pneumoniae, S. aureus*, and also anaerobic pathogens
  - Its bioavailability is excellent, but the achievable plasma concentration is close to the MIC of *S. pneumoniae*

- **Moxifloxacin**:
  - Active against *S. pneumoniae, S. aureus*, and also anaerobic pathogens
  - Indication: CAP
  - Interaction: with other drugs (e.g. terfenadine) which also prolong the QTc interval → *Torsade de pointes*
Respiratory quinolones (1)

- Tolerability of the respiratory quinolones:
  - In general: well tolerated
  - The most common SE: gastrointestinal irritation
  - CNS complaints: headache, insomnia
  - QTc prolongation (respiratory quinolones)
    Caution: uncorrected hypokalemia, quinidine, procainamide, amiodarone, erythromycin, tricyclic antidepressants
  - Arthropathy → avoid in general for children < 18 yrs (but there are exceptions!)
Antimicrobials used for pulmonary tuberculosis
First line drugs

- Isoniazid (H)
- Rifampicin (R)
- Pyrazinamide (Z)
- Streptomycin (S)
- Ethambutol (E)

Note: These drugs are available in single entity and in fixed dose combination (FDC) as well
Second line drugs

- Kanamycin
- Amikacin
- Fluoroquinolones
- Macrolides and co-amoxiclav
- Miscellaneous (not available in Indonesia):
  - Capreomycin
  - Cycloserine
  - Para-amino salicylic acid (PAS)
  - Rifabutin
  - Thionamides: ethionamide, prothionamide
Dose of antituberculosis drugs (ATD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose (mg/kgBW)</th>
<th>Maximal dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>10</td>
<td>600</td>
</tr>
<tr>
<td>H</td>
<td>5</td>
<td>300</td>
</tr>
<tr>
<td>Z</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>15</td>
<td>1000</td>
</tr>
<tr>
<td>Category</td>
<td>Case</td>
<td>Combination</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>I</td>
<td>Lung TB, AFR +, wide lesion</td>
<td>2RHZE / 4RH</td>
</tr>
<tr>
<td>II</td>
<td>Relapse</td>
<td>2RHZES / 1RHZE / 5RHE</td>
</tr>
<tr>
<td></td>
<td>Failure of treatment</td>
<td>2RHZES / 1RHZE / 5RHE</td>
</tr>
<tr>
<td>II</td>
<td>Drop-out lung TB cases</td>
<td>2RHZES / 1RHZE / 5R3H3E3</td>
</tr>
<tr>
<td>III</td>
<td>New lung TB, AFR -, minimal lesion</td>
<td>2RHZE / 4RH</td>
</tr>
<tr>
<td>IV</td>
<td>Chronic</td>
<td>RHZES / sens. test for 18 months</td>
</tr>
<tr>
<td>IV</td>
<td>Multi-drug resistant TB</td>
<td>Sens. test + 2nd liners for life</td>
</tr>
</tbody>
</table>

AFR = acid-fast rod
Adverse drug reactions (1)

In the majority of the patients, the tuberculostatic agents are well tolerated. The followings are the side effects of these drugs.

1. Isoniazid:
   - Peripheral neuropathy: can be prevented by the administration of $\geq 10$ mg of oral pyridoxine/day
   - Hepatitis:
     - more commonly occurs in the elderly
     - stop treatment and treat symptomatically
2. Rifampicin:
   - ‘Flu like syndrome’
   - Gastrointestinal complaints
   - Hepatitis: stop treatment
   - Hemolytic anemia, purpura, and renal failure: stop treatment
   - Red color of the urine (inform the patients in advance, this not harmful)
   - Strong enzyme inducer
Adverse drug reactions (3)

3. Pyrazinamide:
- Hepatitis (contraindication: liver disease)
- Gastrointestinal complaints
- Arthralgia and hyperuricemia
- Safety in pregnancy is not known

4. Ethambutol:
- Retrobulbar neuritis → loss of visual acuity and red-green color blindness. Uncommonly occur if the dose is 15-25 mg/kgBB/day
- Usually reversible in several weeks
- Not recommended for young children
5. Streptomycin:
- Ototoxic and vestibulotoxic
- Dose- and age-related side effect
- Tinnitus
- Reversible if the treatment is stopped early
- Predisposing factor: renal impairment
- Other side effect: temporary numbness around mouth and ear area
- Contraindicated for pregnant women
Treatment for MDR tuberculosis (1)

- This term is applied for tuberculosis caused by *M. tuberculosis* which is resistant to INH and rifampicin with or without to other agents.
- Caused by: the use of single drug, inadequate combination for local resistance pattern, patient’s incompliance.
- At least 4 drugs should be used: 2-3 of the first line drugs plus 2 second line drugs (e.g. ciprofloxacin or ofloxacin).
- Treatment is given for at least 18 months, but often for life.
Treatment for MDR tuberculosis (2)

- All drugs used must be still effective
- No standard regimen for MDR, the combination must be tailored to the report of the sensitivity test
- Drugs commonly used for MDR: aminoglycosides (streptomycin, kanamycin, amikacin), thionamides, pyrazinamide, ofloxacin, ethambutol, cycloserine, PAS
- DOTS strategy may be helpful
- Refer to specialist
Directly Observed Treatment Short Course (DOTS)

- The drug ingestion by the patients is physically observed by a health care worker, spouse, house mate, or other person

- Objectives of DOTS:
  - To achieve high cure rate
  - To reduce drop out
  - To overcome side effects
  - To prevent resistance
Fixed-dose Combination (FDC) (1)

FDC is the combination of antituberculosis drugs produced by the manufacturer

Advantages:
• Reduction of prescribing error
• Less tablets to be swallowed → compliance ↑
• The patients cannot modify treatment regimen by their own

Disadvantages:
• Prescribing error
• Trend to avoid DOTS
• Decreased bioavailability of rifampicin
Fixed-dose Combination (FDC) (2)

Examples of FDC for daily administration:

- 75 mg INH + 150 mg rifampicin
  150 mg INH + 150 mg rifampicin
- 150 mg INH + 400 mg ethambutol
- 75 mg INH + 150 mg rifampicin + 400 mg pyrazinamide
- 75 mg INH + 150 mg rifampicin + 400 mg pyrazinamide + 275 mg ethambutol
According to the American Thoracic Society, prophylaxis is given to those who have:

- contact with active cases, Mantoux (-)
- Mantoux test (+), chest X-ray abnormality typical for tuberculosis
- a positive Mantoux conversion during the last 2 years
- high risk for infection, eg. being on corticosteroid or immunosuppresant therapy, leukemia, diabetes mellitus, Hodgkin disease
Prophylaxis for children is indicated for those who:

- Have contact, appear healthy, and aged < 5 years old
- Are suckling to a mother with positive sputum

Prophylaxis (INH 5mg/BW) should be given for 6 months.

Children aged > 5 years do not need prophylaxis, but they should be monitored clinically.
Hepatotoxicity induced by antituberculosis drugs

- If clinical symptoms (+) → stop all drugs
- If clinical symptoms (-), but serum bilirubin >2 mg/dL and/or SGOT/SGPT $\uparrow \geq 5 \times$ → stop all drugs
- If clinical symptoms (-) and SGOT/SGPT $\uparrow \geq 3 \times$ → continue treatment but monitor closely
- Recognize the potentially hepatotoxic drugs: R, H, Z
- If clinical condition improves re-introduce H, then R, but not Z
- In the re-introduction, start with low dose and increase gradually (desensitization). All should be done with close monitoring
When to add a corticosteroid?

• Only indicated in very severe tuberculosis, eg. meningitis, pericarditis, miliary tuberculosis (certain cases)
• Patients should receive full protection with antituberculosis drugs
• The steroid is given at the initial phase of tuberculosis treatment and should not exceed 6 weeks
• The dosage is equal to 40 mg of prednisone per day
Thank you