Rational use of antibiotics

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Why to use antibiotics?

- Prophylaxis
- Empirical treatment
- Definite treatment
Why not to use antibiotics?

- Resistance selection pressure
- Increased risk of superinfection
- Toxicity
- Interactions with other drugs
- Costs
What is the most appropriate antibiotic?

- Narrow spectrum
- Easy to administer
- Cheap
- Least toxic
- Low selection pressure
- Oral Penicillin
Before to start treatment

- Try to identify the pathogen
  - Express tests
  - Cultures
  - Serology
  - At least to consider something in mind
- Pharmacological and pharmacokinetical considerations
  - Tissue concentrations
  - Type of bacteria
- Host factors
  - Organ failure
  - Pregnancy
  - Allergy
  - Difficulties with absorption
How to use an antibiotic?

- Relevant indications
- Epidemiological considerations
- Appropriate choice
- Appropriate dosing
Relevant indications

- **Surgical prophylaxis**
- **Definite bacterial infection with positive culture**
- **Empirical treatment**
  - Clinical features (pyrexia, tachicardia, tachipnoe, low blood pressure)
  - Pus and systemic symptoms
  - Radiological findings
  - Laboratory findings
    - Elevated or decreased WBC count, shift to left, CRP > 100 mg/l and elevated Procalcitonin (Simon L, 2004)
    - Urine dipstick for nitrite and leucocyte
Epidemiological considerations

- Most prevalent pathogens
- Local resistance pattern
- Presence of outbreaks
- Risk factors for resistance
Resistance selection pressure

Class of antibiotic

Amount of antibiotic

per

Number of patients

per

per

Geographical area
Macroepidemiological considerations

- Penicillins
- Aminoglycosides
- Nitrofurantoin, trimetroprim
- First generation cephalosporins
- Second generation cephalosporins
- Tetracyclines
- Macrolides
- Third generation cephalosporins
- Fluoroquinolones
- Carbapenems
Marketing pressure

<table>
<thead>
<tr>
<th>Cheap</th>
<th>Expensive</th>
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<tbody>
<tr>
<td>Penicillin</td>
<td>III gen cephalosporins</td>
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<tr>
<td>Ampicillin/Amoxicillin</td>
<td>Newer Macrolides</td>
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<tr>
<td>Oxacillin</td>
<td>Fluoroquinolones</td>
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<tr>
<td>Gentamycin</td>
<td>Penicillins/β- lactamase inhibitors</td>
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<td>Metronidazole</td>
<td>Carbapenemems</td>
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<tr>
<td>Nitrofurantoin</td>
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<td>Trimetroprim</td>
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Risk of superinfection

- **Clostridium Difficile infection**
  - III generation cephalosporins,
    Amoxicillin/Clavulanate, Clindamycin,

- **MRSA**
  - Macrolides (Goosens et al, 2004)
Risk of superinfection

- **Disseminated candidiasis**
  - Carbapenems
  - Cephalosporins

- **ESBL producers Gr negatives**
  - Cephalosporins (Rahal JL et al, 1998)
  - Piperacillin/Tazobactam

- **Multiresistant Pseudomonas aeruginosa**
  - Cephalosporins
  - Carbapenems (Leroy O et al, 2005)

- **Carbapenem resistant Acinetobacter Baumanii**
  - Cephalosporins
  - Carbapenems (Lee SO et al, 2004)

- **Stenotrophomonas maltophilia**
  - Carbapenems, Cephalosporins (Carmeli Y, 1997) (Hanes SD et al, 2002)
Treatment of resistant bacteria

- Choice of empirical treatment complicated
- Antibiotics with more side effects
- Combinations increase toxicity
- Risk of superinfection
- Costs
Pharmacokinetic/Pharmacodynamic (PK/PD) relationships

- Concentration independent – time dependent
  - β- lactams
    - Penicillins, Cephalosporins, Carbapenems
  - Vancomycin, macrolides, clindamycin
  - 3-6 times the MIC, with further concentration little effect
  - % of time above MIC (% $t >$ MIC) important
Time dependant strategies

- More-frequent daily doses
- Using concomitant inhibitors of antimicrobial clearance
- Continuous infusion  (Craig WA et al, 1992) (Kasiakou SK, 2005) (Frei CR, 2005)
  - Cefepime - Pseudomonas aeruginosa
    - Burgess DS et al, 2000
    - Tam VH et al, 2003
  - Meropenem – VAP
    - Lorente L et al, 2006
  - Piperacillin/Tazobactam – Gr neg abdominal
    - Buck C et al, 2005
  - Vankomicin – VAP caused by MRSA
    - Blot S, 2005
    - Kitzis MD, 2006
Pharmacokinetic/Pharmacodynamic (PK/PD) relationships

- Concentration dependent
  - Aminoglycosides
  - Fluoroquinolones
    - $C_{\text{max}}$: MIC ratio of 8-10
    - 24h AUC/MIC 100-125
- Limitations by toxicity
Concentration dependant strategies

- Aminoglycosides once daily
  - Gentamycin 7mg/kg (Nicolau DP et al, 1995)
  - Amikacin 15 mg/kg

- Fluoroquinolones in maximum dose
  - Ciprofloxacin 400mg
  - Levofloxacin 750 mg

- Dose adjustment in critically ill patient with organ failure
Combination therapy

- **Wide spectrum coverage needed**
  - β- lactams + macrolides
  - β- lactams + glucopptides
  - β- lactams + aminoglycosides + glucopptides

- **Synergic action**
  - β- lactams + aminoglycosides
  - β- lactams + fluoroquinolones (switch to oral possible)

- **Prevention of resistance acquisition**
  - *S. aureus* – rifampin, clindamycin, fluoroquinolones
  - *Pseudomonas aeruginosa* – Carbapenems
Antagonism in vivo

- Penicillin and chlortetracyclin (Lepper MH et al, 1951)
- Ampicillin and chloramphenicol (Mathies AW 1967)
- ????
- ????
- ????
- ????
- Caution needed with previously unstudied combinations
Route of administration

- Oral therapy preferable
  - Equally effective for the most indications
  - Cheaper
  - More convenient
  - Reduced catheter infection risk

- Intramuscular route is dubious

- Intravenous administration for severe disease or specific location
When to change from iv to oral

- Signs and symptoms are improving
- Patient can take oral medication
- A suitable oral agent is available as per guidelines or microbiological results
- Patient has no:
  - Meningitis
  - Osteomyelitis
  - Septic arthritis
  - Endocarditis
  - Immunosuppression
Route of AB administration in Stradins University Hospital, Riga
Length of treatment

- Early (1940-50s) use 3-5 days until fever subsides
- Later (1960-1990s) 10-14 days for registration purposes
- Today (2000-) a maximum of 5-7 days except
  - Osteomyelitis
  - Endocarditis
  - Abscess
  - Cl. Difficile infection
  - Immunocompromised (neutropenia, diabetes)
- Stop antibiotics immediately if it is not necessary to continue
If treatment does not work
(no improvement after 48 hours)

- The diagnosis is incorrect
- The choice of antibiotic is incorrect
- The antibiotic cannot reach the site of infection
- The etiological agent is resistant to the antibiotic
  - Abscess - Surgical drainage maybe needed
- There is a secondary infection
- Non – compliance of the host
- Antibiotic fever
Treatment is not effective

- Repeat the cultures
- Continue with the present regimen
  - increase the level of treatment by changing from oral to parenteral
  - Increase the dose
- Change the regimen
  - Change to more specific narrow spectrum antibiotic according to the culture
  - Change to a broader spectrum antibiotic
Treatment is effective

- decrease the level of treatment by changing from parenteral to oral
- decrease the dose or change to a more specific narrow spectrum antibiotic
- stop the antibiotic; the objective of treatment is achieved or the diagnosis has been changed.
Guidelines

- Good for people who have no idea how to use antibiotics
- Good if evidence based
- Good as consensus between specialists
- Good if local and done by professionals
- Bad if sponsored by pharm companies
- Bad if translated and adapted
- Bad if not local consensus
- Bad if not updated
Questions to answer every time

- Is an antibiotic really necessary?
- What is the most likely pathogen?
- What is the local resistance pattern?
- What is the most appropriate antibiotic?
- How it will influence the resistance selection pressure?
- What dose, route, frequency and duration are needed?
- Is the treatment effective?