Rational use of antibiotics

Uga Dumpis MD, PhD, DTM
Stradins University Hospital
Riga, Latvia
ugadumpis@stradini.lv

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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 absorbtion

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
Geographycal area

Macroepidemiological considerations

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

Marketing pressure

Cheap

- Penicillin
- Ampicillin/Amoxicillin
- Oxacillin
- Gentamycin
- Metronidazole
- Nitrofurantoin
- Trimetroprim

Expensive

- III gen cephalosporins
- Newer Macrolides
- Fluoroquinolones
- Penicillins/β- lactamase inhibitors
- Carbapenems

Risk of superinfection

- Clostridium Difficile infection
  - III generation cephalosporins, Amoxicillin/Clavulanate, Clindamycin, Ciprofloxacin ? (Pepin J et al, 2004)
- MRSA
  - Macrolides (Goosens et al, 2004)
  - Cephalosporins (Meyer En et al, 2006, Harbath S et al, 2006)
  - Fluoroquinolones (Dziekan et al, 2000, Harbath S, 2000, Charbonneau P et al, 2006)

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 maltophila
  - 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/Pharmacodinamic (PK/PD) relationships

- Concentration independent – time dependent
  - ß- 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/Pharmacodinamic (PK/PD) relationships

- Concentration dependent
  - Aminoglycosides
  - Fluoroquinolones
    - C*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
  - ß- lactams + macrolides
  - ß- lactams + glucopeptides
  - ß- lactams + aminoglycosides+ glucopeptides
- Synergic action
  - ß- lactams + aminoglycosides
  - ß- 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

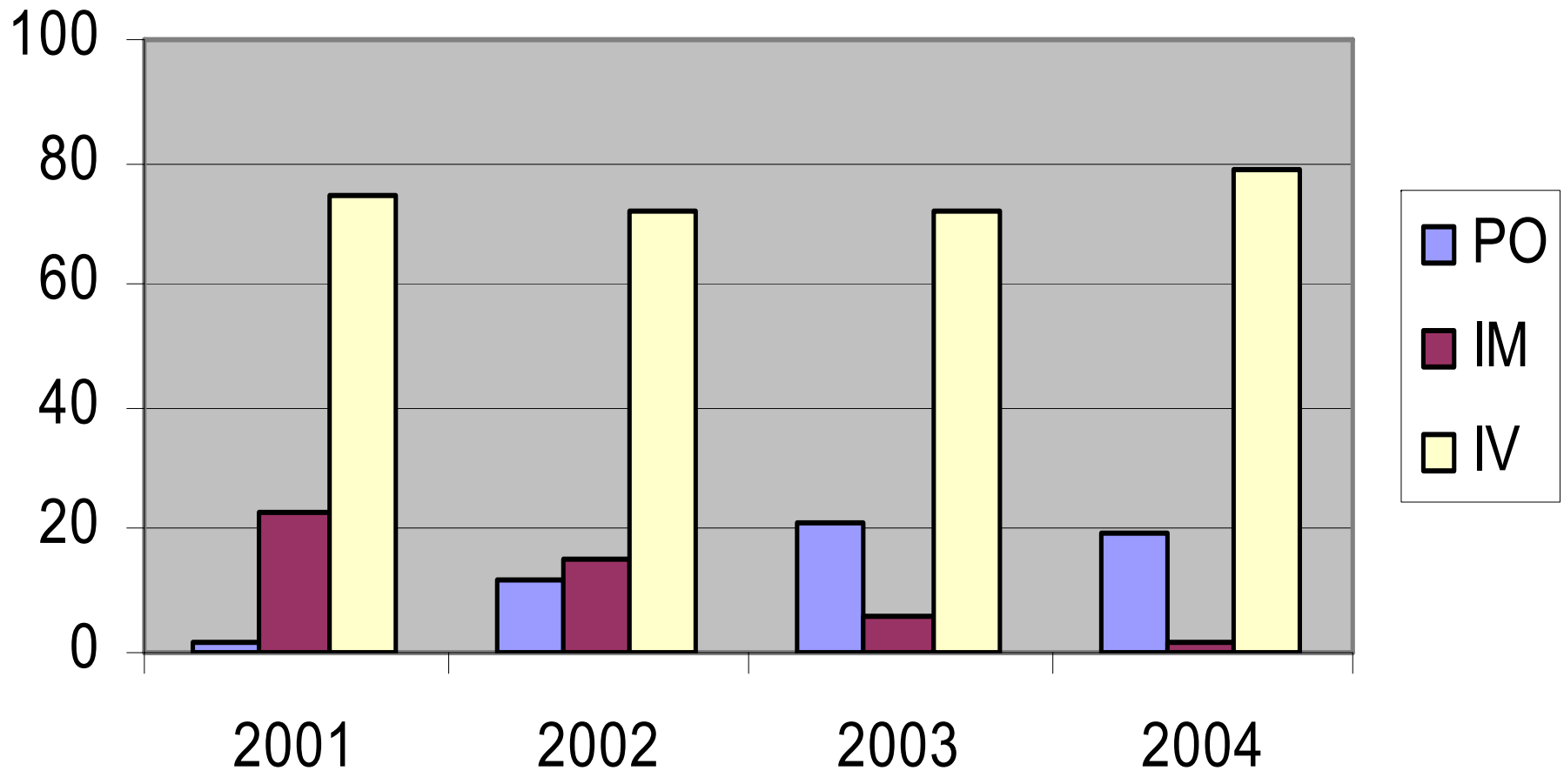
Route of administration

- Oral therapy prefferable
  - 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
  - Immunosupression

Route of AB adminstration 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
  - Osteomyelits
  - 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?