Optimizing antibiotic therapy - What is the optimal duration?

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Why optimizing antibiotic therapy?

• Antibiotics are generally very effective and safe drugs

• Threshold for empiric use is low:
  – Underuse of antibiotics leads to clinical failure
    not common after established diagnosis
    unknown rates in empiric treatment

• But: Overuse of antibiotics leads to rising rates of antimicrobial drug resistance
  – Antimicrobial resistance is a threat to the „antibiotic miracle“
Sources of overuse of antibiotics

- Overuse can result from
  - too liberal judgement in initiating empiric therapy
  - not stopping at the right time

- how can these topics be addressed?
Limiting empiric therapy

- Using PCT as a marker to guide therapy in respiratory infections in outpatient and CAP
  - Clear evidence that use of markers of inflammation can result in more focussed use or antibiotics
- Role of PCT less well established in ICU and trauma patients
Antibiotic therapy in the ICU

- one year prospective survey University hospital Maastricht, NL
- 312/ 515 (61%) admitted pts. received AB
- 74% of all intubated pts. received AB vs. 45% of non-intubated
- 49% pulmonary infections., 19% abdominal infections, 13% bacteremia with unknown focus

Antibiotics in the ICU -II

intubated (81%)    non intubated (19%)

<table>
<thead>
<tr>
<th></th>
<th>intubated</th>
<th>non intubated</th>
</tr>
</thead>
<tbody>
<tr>
<td>infection</td>
<td>51%</td>
<td>19%</td>
</tr>
<tr>
<td>suspected infection</td>
<td>31%</td>
<td>15%</td>
</tr>
<tr>
<td>prophylaxis</td>
<td>18%</td>
<td>66%</td>
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</table>

Duration of antibiotic therapy in ICUs

- 6 month survey in 2003 Regensburg: 70% of all pts with more than 48h in the ICU on AB
- 15% for more than 21d, 5% for more than 35d
Antibiotic stewardship for the ID-/Microbiology Fellow

• the problem of overuse of antibiotic therapy might be addressed by
  – limiting the initiation empiric therapy
  – limiting the length of antibiotic therapy

• to safely limit the duration of ABX we must
  – have a thorough understanding of the concepts of antibiotic therapy
  – have a thorough knowledge of the relevant clinical studies
  – promote further studies in establishing criteria for safe withdrawal of antibiotic therapy
Determinants of therapy

- drug characteristics
- bacterial characteristics
  - generation time
  - inoculum
  - biofilm production
- infection site
  - eg foreign body, necrotic tissue
- duration of infection
How do we start with an educated guess?

- apply knowledge of bacterial physiology
- apply concepts of drug pharmokodynamics
- use of animal models
- evaluate current treatment strategies, look for room for improvement
- design intelligent clinical studies
Bacterial growth

y axis = log cell number

A lag time, no growth; B exponential growth; C continuous culture time, D die off

Tc generation time is determined in phase B = doubling time of bacterial population
Bacterial Growth and Antibiotic killing dynamics

• The time to kill half of the bacteria population is designed $T_s$

• For most bactericidal agents $T_c = T_s$, in some cases $1/2 T_c \leq T_s \leq T_s$

• But is exponential growth really the appropriate assumption for concepts of antibiotic therapy?
Generation time and ABX duration

• MTb can be successfully treated within app. 180-360 generation times (6 months)

• translated to E.coli and S.aureus the ABX duration for successfully treated invasive infections would be
  - 2-4 days of treatment for E. coli
  - 4-9 days for S. aureus
# Generation time and treatment response

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>3 log kill (h)</th>
<th>Disease</th>
<th>Duration of therapy</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTb</td>
<td>INH</td>
<td>2h</td>
<td>latent Tb</td>
<td>3 months</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 year</td>
<td>93%</td>
</tr>
<tr>
<td>E. coli</td>
<td>β-lactam</td>
<td>.5h</td>
<td>UTI</td>
<td>1 dose</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 days</td>
<td>82%</td>
</tr>
<tr>
<td>S. aureus</td>
<td>β-lactam +/- Ag</td>
<td>24h</td>
<td>Bacteremia /R-endocard.</td>
<td>14d</td>
<td>92-100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L-endocarditis</td>
<td>4-6w</td>
<td>50-82</td>
</tr>
</tbody>
</table>

Connolly, PLOS Med. 2007
Bacterial killing dynamics (Mtb)

Persister populations

- persister populations are nongrowing subpopulations of bacteria not killed by antibiotics (phenotypically resistant)
- are present in nearly all bacterial populations
- rates of persisters differ between species (high rates in Mtb, low rates in E. coli (10^{exp-4} to -6))
- persister phenotypes are lost in most culture-subculture-systems
- persister phenotypes can be induced by stress (e.g. antibiotic exposure)
Other obstacles to bacterial killing

• ecological niches for bacteria
• Eagle’s effect (low rate of killing in large inocula of bacteria) might be a combination of these factors
• lower success rates with delayed therapy might be influenced by
  - larger inoculum size
  - higher rate ofpersisters, switched due to nutrient deficiency
Lessons from Mtb-Studies

- Length of therapy has been planned by concepts of different populations observed in the lab
- Modern drug therapy with a 6 months course has a cure rate of >95%
- Inoculum size is an important factor

Connolly, PLOS Med. 2007
Deficiencies in animal models of ABX in regard to persisters

- ABX mostly started before clinical establishment of infection - i.e. synchronized with symptomatic human infection
- ABX nearly exclusively in early exponential growth phase of bacteria
  - effect of antibacterial killing overestimated
  - effect of immune control underestimated
Can we improve bacterial killing?

- Recently common mechanism of bacterial killing by bactericidal drugs identified
- for all bactericidal drugs production of hydroxyl radicals precedes bacterial death
- activation of the tricarboxylic acid cycle as a part of an oxidative stress cellular death pathway
  - target for new antimicrobial substances?

Kohanski, Cell 2007
Clinical situation and ABX duration

- pneumonia
  - CAP
  - VAP
- Staph.-aureus bacteremia
- osteomyelitis

what about
- intraabdominal infections (e.g. necrotizing pancreatitis, cholangitis?)
- FUO in the ICU?
How long should you treat a patient with pneumonia?

- frequent infection - high impact for possible antibiotic overuse
- ABX therapy for CAP mostly 7-10 days established
  - in outpatients oral treatment
  - in inpatients initial IV therapy
  - longer treatment for infections due to P.aeruginosa

CAP guideline, Germany 2005
Short term ABX therapy for CAP?

- randomized study in pts. with non-severe CAP (PSI < 110)
- initial therapy with amoxicillin iv
- on improvement after three days (afebrile, improvement in respiratory symptoms and general condition) randomization
  - oral amoxicillin (n=63) vs. placebo for another 5d (n=56) (double-blind)
  - success rate (clinical resolution at 10d) 93 vs. 93% (similar with 28d evaluation, radiologic evaluation at days 10 and 28)
- for patients with mild and moderated CAP and clinical improvement on day 3, prolongation of therapy for further 5 days does not improve outcome

el Moussaouui, BMJ 2006
Shortening ABX in VAP

- Randomized study of 8d vs. 15d of ABX in VAP in pts.
- 28d Mortality: 18.8 vs. 17.2% (60d 25% vs. 28%)
- Relapse 29% vs. 26% - but higher with gram-negative bacteria: 41% vs. 25%
- Lower rate of multiresistant bacteria on relapse 42% vs. 61%

J. Chastre JAMA 2003, Am. J. Respir Crit Care Med 2003
Stopping ABX in VAP

• Pilotstudy for the evaluation of a clinical algorithm
• clinically suspected VAP (with CPIS-score)
  – high score: 10-21 d ABX
  – low score (<6): start ABX, reevaluate after 72h
    stop if score falling or constant
    continue with rising score
• Antibiotics for more than three days
  – 28% (reevaluation) vs. 90% (free choice)
• no difference in mortality and ICU stay
• signifikantly less time on antibiotic therapy (3 days vs. 9,8 days) and
  lower cost (259 US$ vs. 640 US$) in reevaluation group

Stopping ABX in VAP -II

- randomized prospective study in 290 pts with VAP (inclusion with clinical diagnosis and ABX)
- one group ABX by treating physician, one group reevaluated constantly by ID-team, treating physician was advised to stop ABX if
  - other cause for pulmonary infiltrate identified
  - symptoms were
    - temperature < 38.3 C and
    - WBC < 10,000 or drop of > 25% and
    - resolving or constant infiltrate and
    - no purulent sputum and
    - PaO2/FI O2 Ratio > 250

ST Micek, Chest 2004
Stopping ABX in VAP - II

- groups were well matched in clinical characteristics
- Outcome comparable
  - Mortality 32% with reevaluation vs. 37% in standard group
  - ICU (15,7 vs. 15,4d)
  - time on ventilator therapy (5,4 vs. 5,7d)
  - rates of relapse (37,3 vs. 32,9%)
- ABX duration significantly reduced
  - Duration of ABX 6,0 +/- 4,9d with reevaluation vs. 8,0 +/- 5,6d

ST Micek, Chest 2004
Staph. aureus bacteremia

- No clinical studies to determine length of therapy - general 14 days of IV ABX recommended
- application of results from IVDUs with right sided endocarditis: initially 4 weeks of therapy (ß-lactam +/- AG), then 2 weeks of oxacillin as well
- Mortalitiy and risk of relapse higher with bone and joint infections and endocarditis
Vertebral Osteomyelitis

- Treatment duration recommendations differ widely from 4w to >3 months
- What is the risk of relapse with different treatment schedules?
- What are the risk factors for relapse?
Vertebral Osteomyelitis

- 10 year case series of patients with VO from one center (n=120) with strictly defined and diagnosed VO (low rate of surgery (5%))
  - 36 pts. treated for 6 weeks, 84 pts. longer
  - all relapses (n=5) in the long treatment group
  - RA and endocarditis as risk factors for relapse
- Suggestion, that 6 weeks of ABX is sufficient in VO

Roblot, Sem Arthritis Rheum 2007
Necrotizing Pancreatitis

- ABX often started as prophylaxis or empirically
  - no clear evidence whether and when to start
- course often complicated by procedures as drainage and surgery
- role of infections not clear in inflammation
- no criteria established for length of therapy
  - fixed empiric course vs. safe stopping rules?
Cholangitis

• How long should you treat cholangitis after removal of an impacted duct stone?
  - no conclusive studies
  - recommendations 0-10 days

• Randomized study in uncomplicated cholangitis initiated
  - febrile cholangitis due to obstruction, initially on antibiotics
  - if afebrile 24 after removal of obstruction randomization to Moxifloxacin vs. placebo for 5d
Fever and elevated laboratory signs of inflammation in the ICU?

- frequent syndrome, high potential for antibiotic overuse (in frequency and length)
- no clear criteria established when to initiate empiric ABX (and when not)
- no clear criteria for safely stopping ABX
What are possible benefits of limiting duration of ABX?

• Mathematical modelling established as a tool for modelling resistance rates in hospitals
• Deterministic (differential equation based) and individual based model (simulation) established
• What happens if either an infection
  - a) is treated starting on day 3 until day 21
  - b) is treated starting on day 1 until day 8

D’Agata, J Theor Biol. 2007
Model representation

AV=80, AC=60, Pi=0.5, PC=0.5, Time step=5 minutes

D’Agata, J Theor Biol. 2007
Simulation of Hospital

D’Agata, J Theor Biol. 2007
Conclusions I

- Antibiotic overuse is frequent
- Killing bacteria by antibiotics is not straightforward
- Bacterial and host characteristics in infectious diseases are major obstacles to rapid bacterial killing
- The study of phenotypic resistance or persister populations has a revival after 60 years
- The concepts of persisters has not yet been applied to animal models
Conclusions II

- Stopping ABX can be more difficult than starting.
- Treatment duration has been well defined for a number of clinical situations (UTI, Pneumonia, MTB-infections) but less well for others.
- Especially in critically ill patients there may be much room for improvement in limiting overuse of ABX.
- Limiting duration of ABX is a promising candidate measure in limiting the spread of multiresistant bacteria.