Optimizing antibiotic therapy - What is the optimal duration?

B. Salzberger

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

Bergmans, J Antimicrob Chemother 1997; 39:527-535

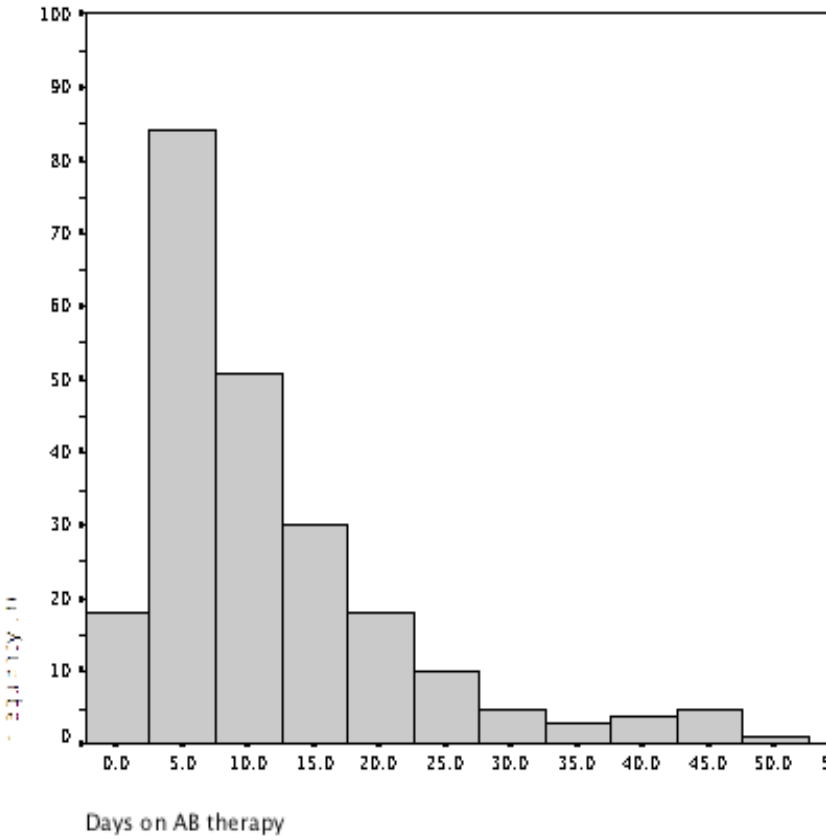
Antibiotics in the ICU -II

	intubated (81%)	non intubated (19%)
infection	51%	19%
suspected infection	31%	15%
prophylaxis	18%	66%

Bergmans, J Antimicrob Chemother 1997; 39:527-535

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



Salzberger DIVI 2006

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

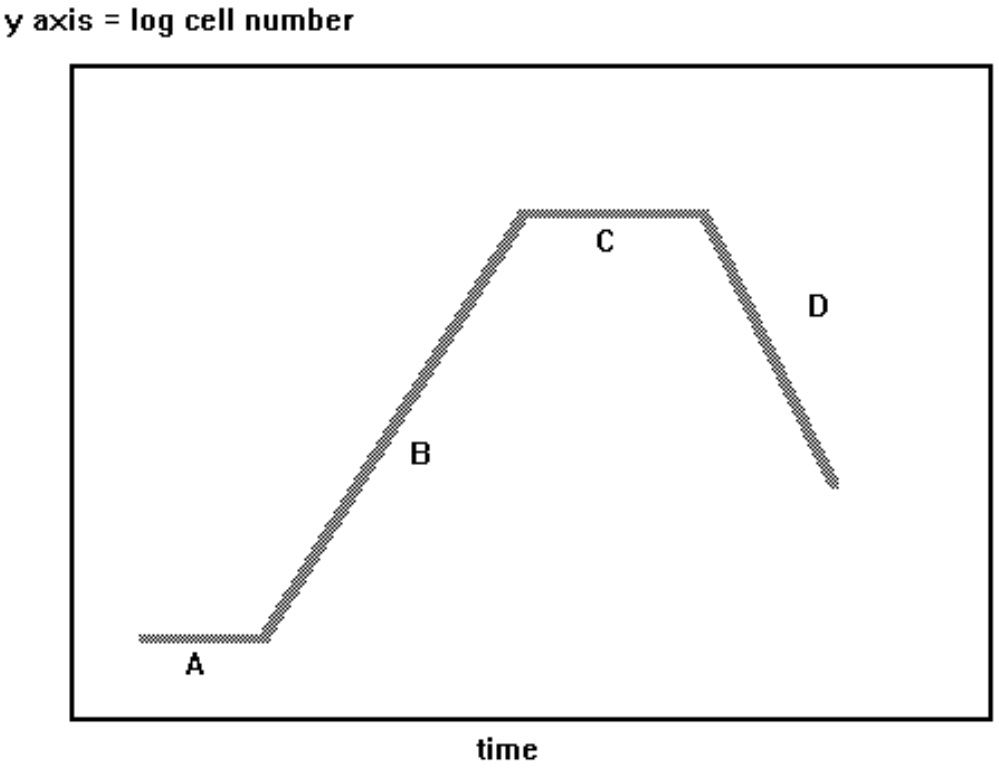
Determinants of therapy

- 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



A lag time, no growth; B exponential growth; C continous 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 Ts
- For most bactericidal agents Tc = Ts, in some cases 1/2 Tc <= Ts <= Ts
- But is exponential growth really the appropriate assumption for concepts of antibiotic therapy?

Generation time and ABX duration

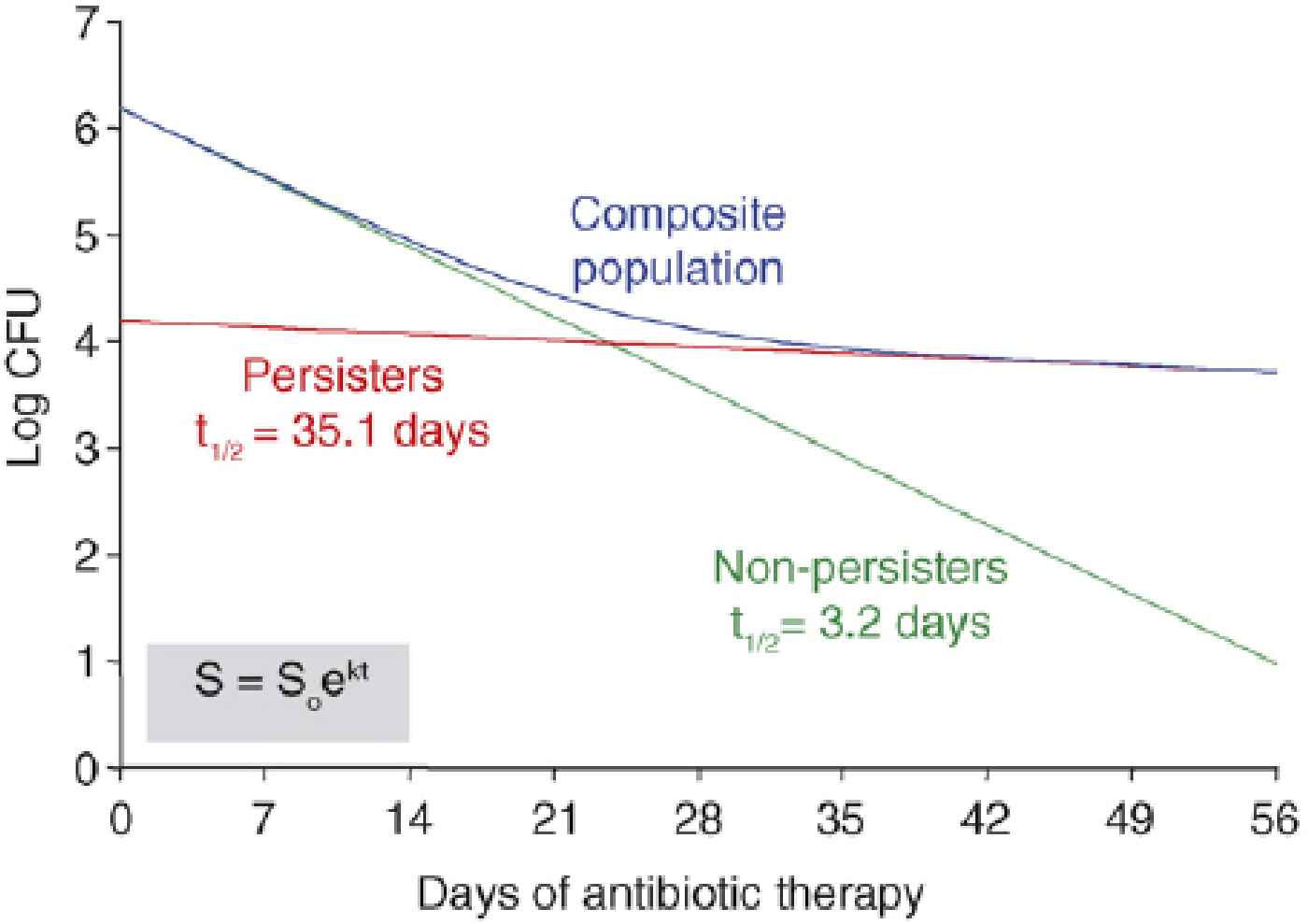
- MTb can be successfully treated within app. 180-360 generation times (6months)
- translated to E.coli and S.aureus the ABX duration for successfully treated invasive infections would be
  - 2-4 days of treatment for E. coli
  - 4-9 days for S. aureus

Generation time and treatment response

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

Connolly, PLOS Med. 2007

Bacterial killing dynamics (Mtb)



Dhar, Curr. Op. Microb. 2007

Persister populations

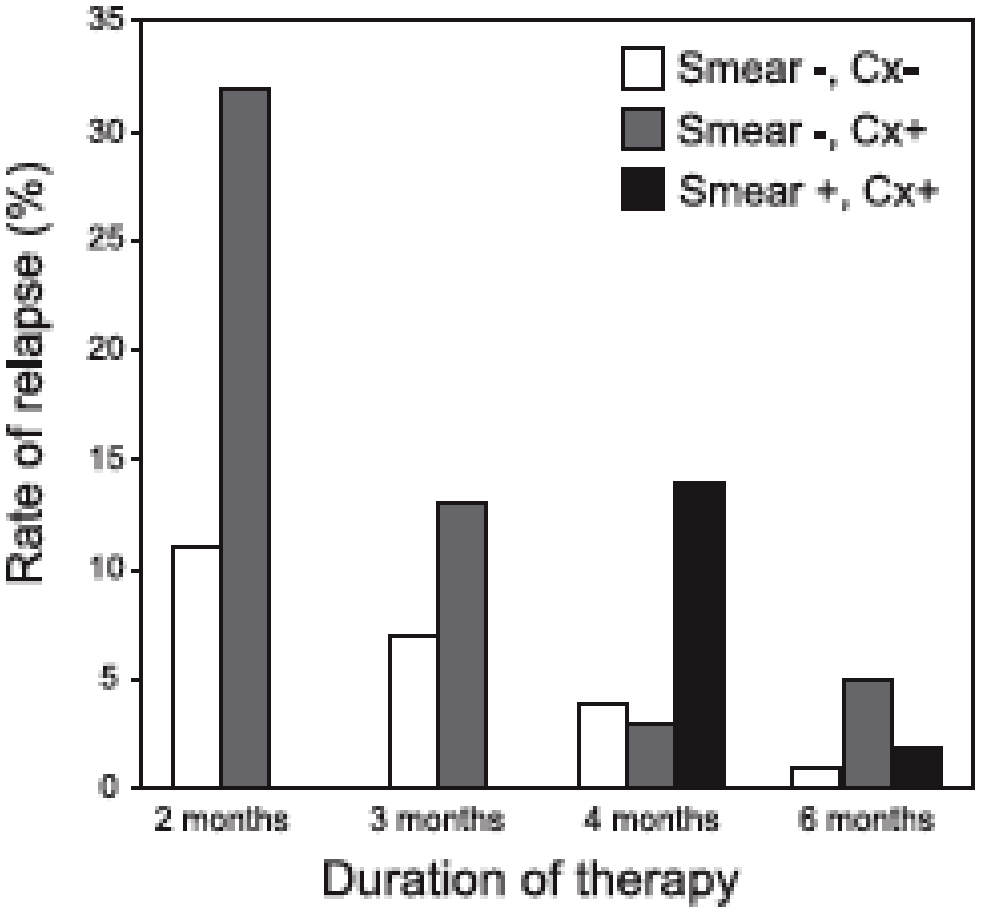
- persister populations are nongrowing subpopulations of bacteria not killed by antibiotics (phenotypically resistant)
- are present in nearly all bacterial populations
- rates of persisters differ between species (high rates in Mtb, low rates in E. coli (10exp-4 to -6)
- persister phenotypes are lost 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 of persisters, 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 establisment 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)
- inital 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 Moussauoui, BMJ 2006

Shortening ABX in VAP

- Randomized study of 8d vs. 15d of ABX in VAP in. pts.
- 28d Mortaility: 18.8 vs. 17.2% (60d 25% vs. 28%)
- Relapse 29% vs. 26% - but higher with gram-bacteria: 41% vs. 25%
- lower rater 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

N.Singh, Am.J. Resp. Crit. Care 2000

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/FIO2 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: intially 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 Osteomyelitits

- Treatment duration recommendations differ widely from 4w to >3months
- 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 diagnosted VO (low rate of surgery (5%)
  - 36 pts. treated for 6weeks, 84 pts. longer
  - all relapses (n=5) in the long treatment group
  - RA end endocarditis as risk factors for relapse
- suggestion, that 6 weeks of ABX is sufficient in VO

Roblot, Sem Arthitis 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

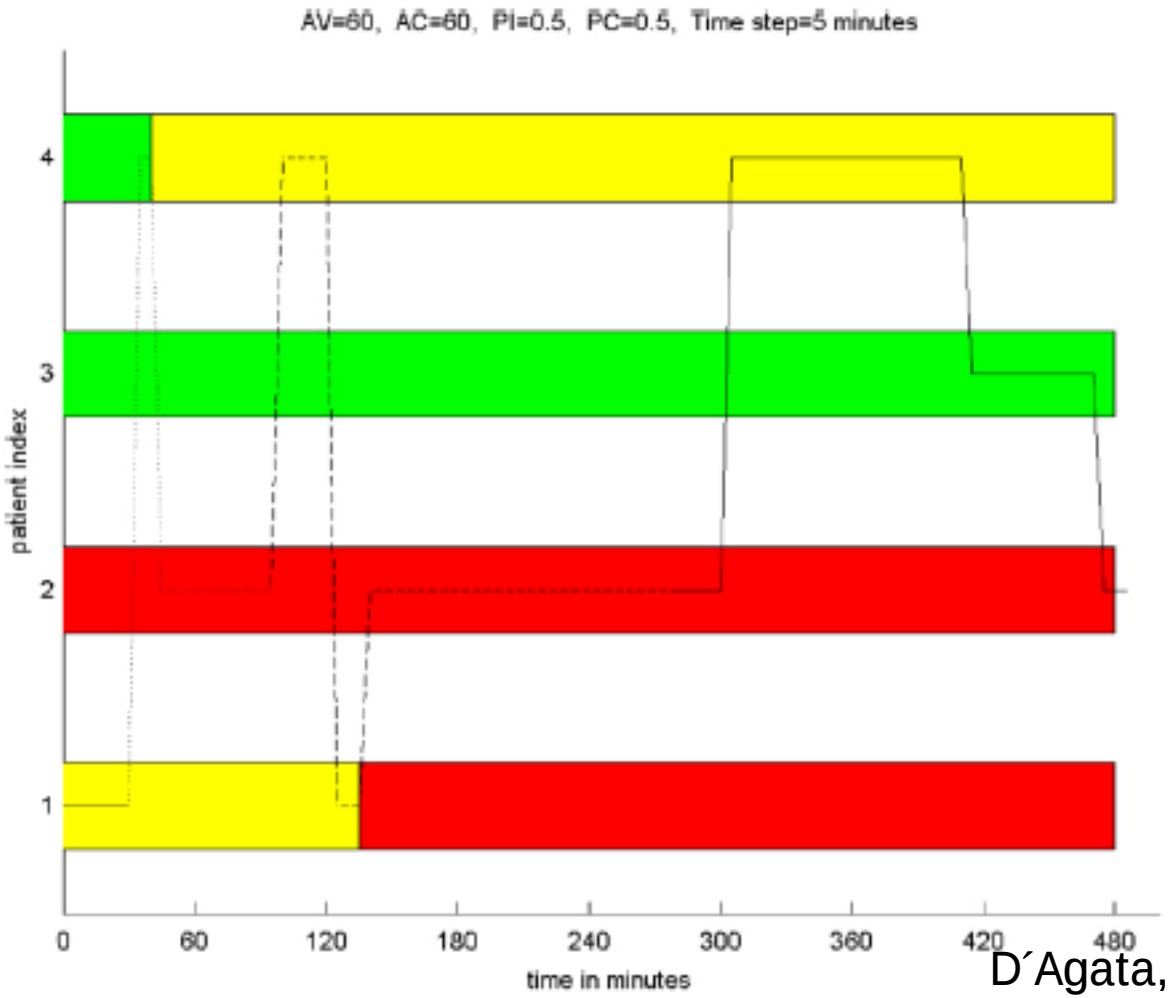
What are possible benefits of limiting duration of ABX?

- Mathematical modelling established as a tool for modelling resistance rates in hospitals
- deterministic (differential equationt 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

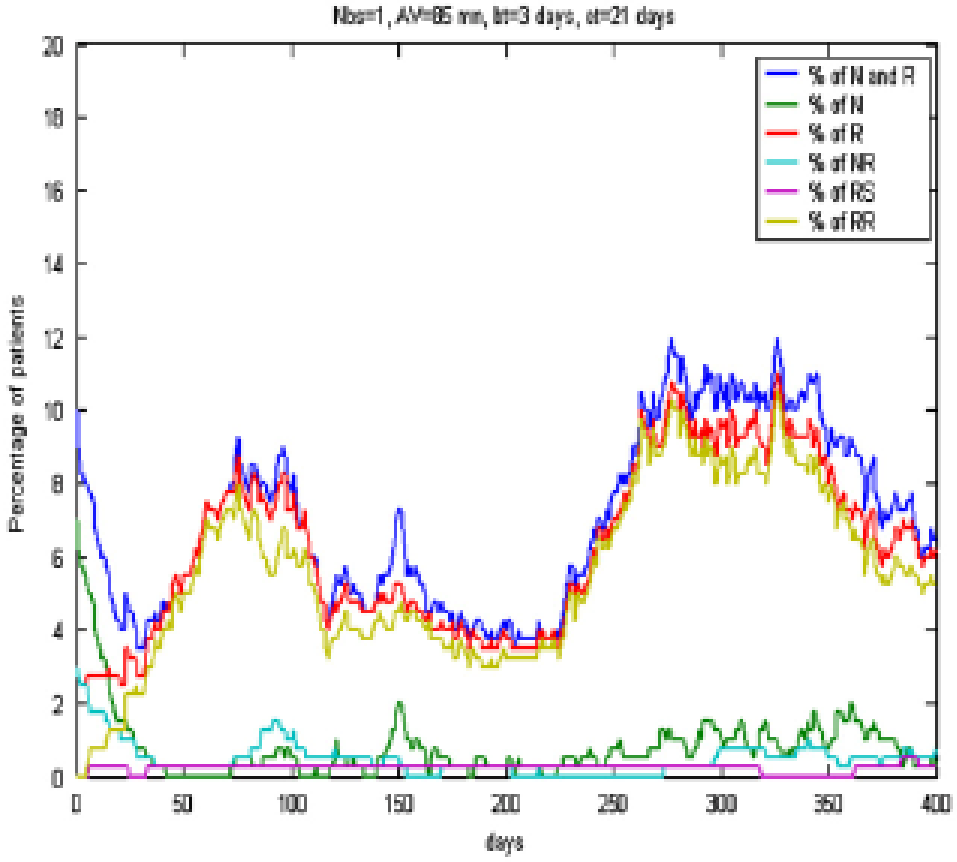
D´Agata, J Theor Biol. 2007

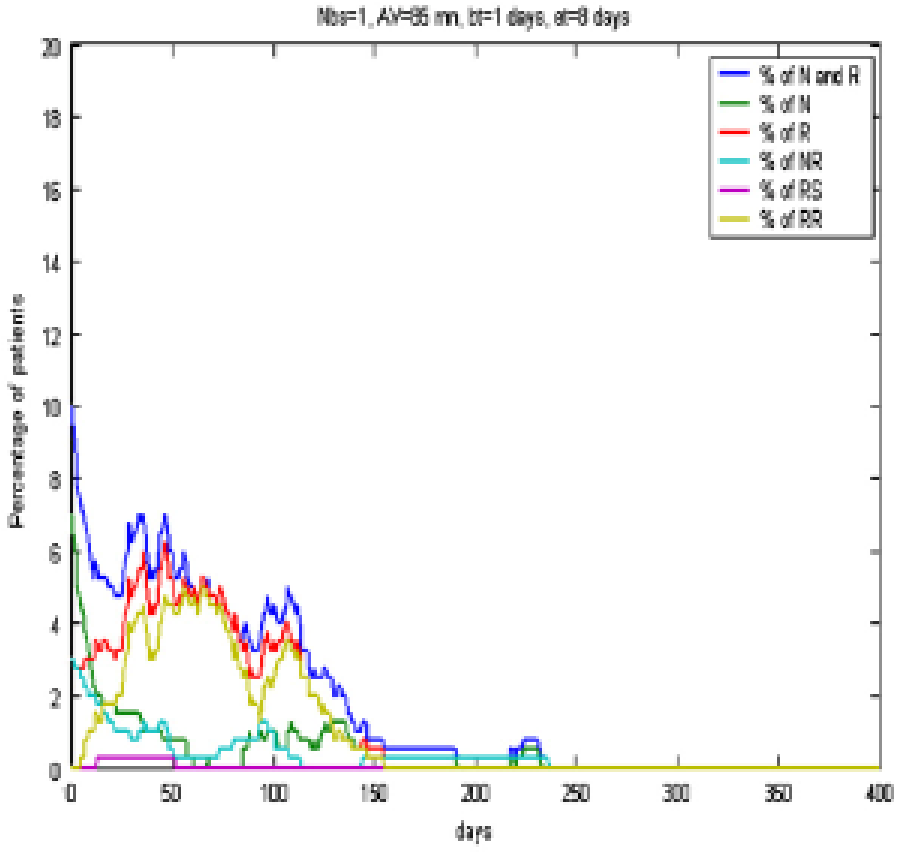
Model representation



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