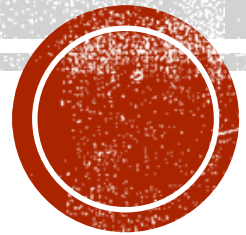
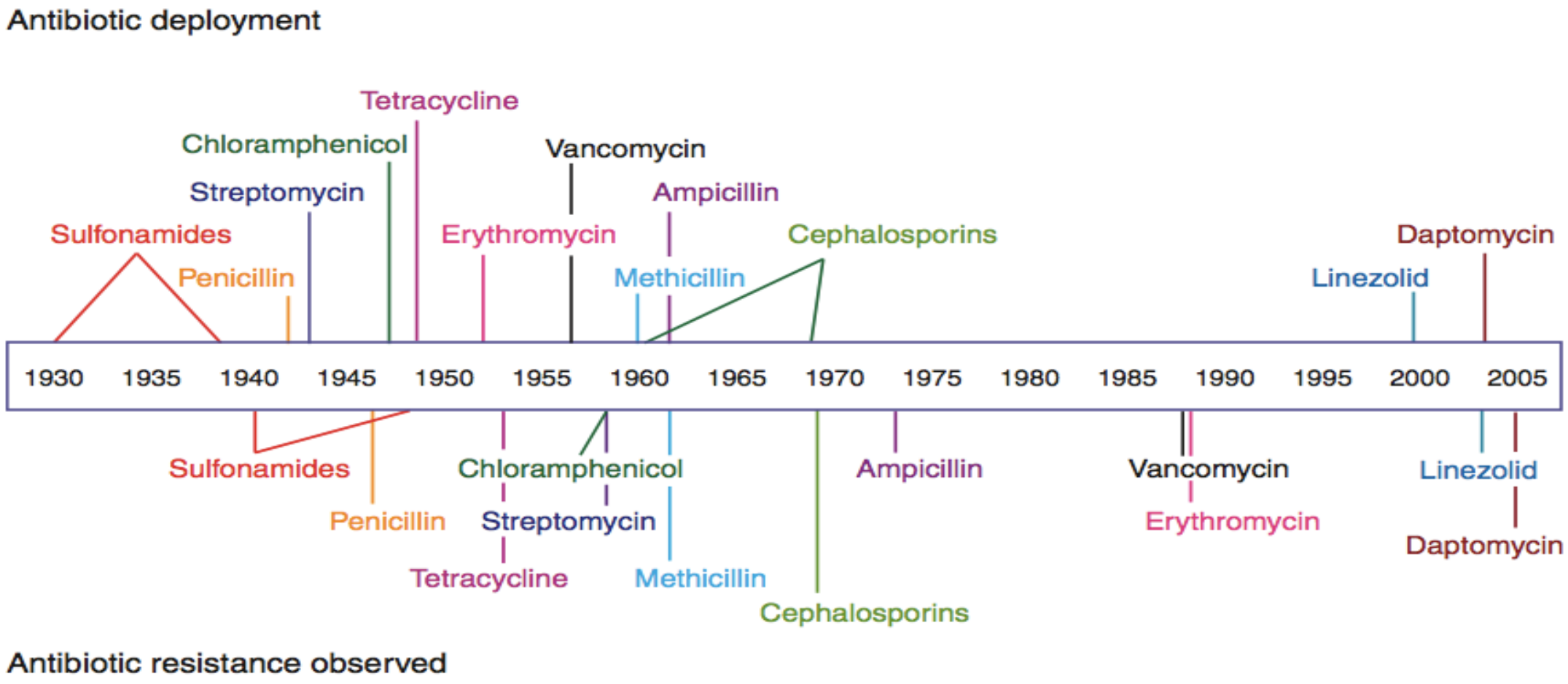
ANTIBIOTICS in ICU

Adriana Papież



FAKULTNÍ NEMOCNICE U SV. ANNY V BRNĚ

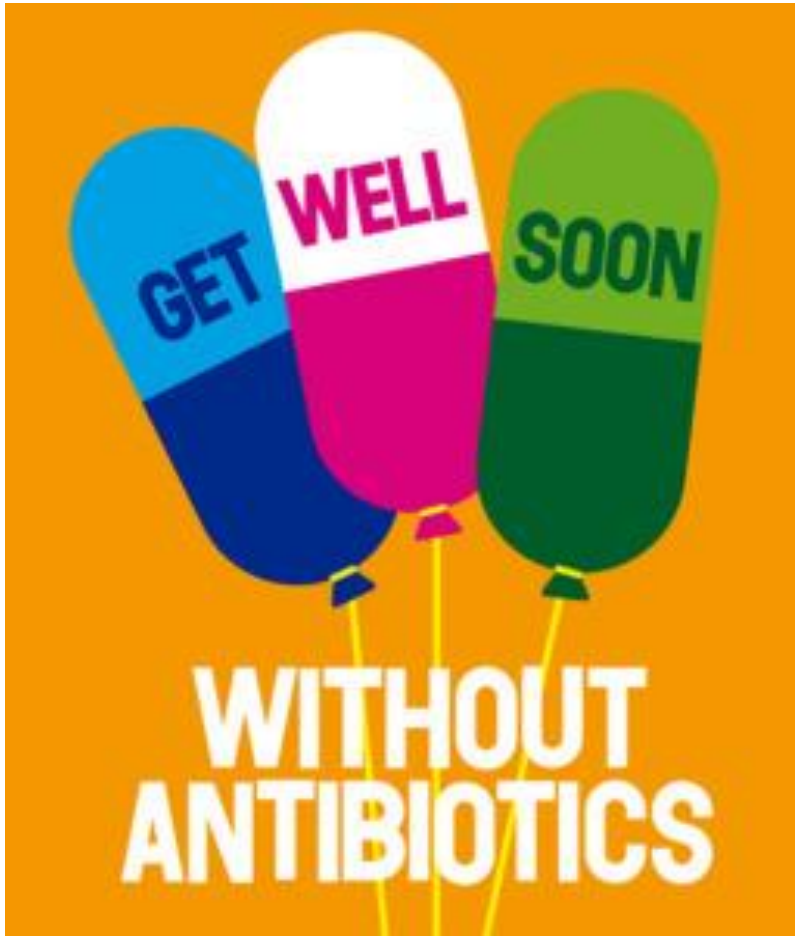
TIMELINE OF ANTIBIOTICS



Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. Nat Chem Biol. 2007 Sep;3(9):541–8

Misuse of Antibiotics

- Lack of awareness & evidence based practice
- Fear of secondary infection
- False sense of security
- Fear of losing patient
- Parental/patient anxiety & pressure



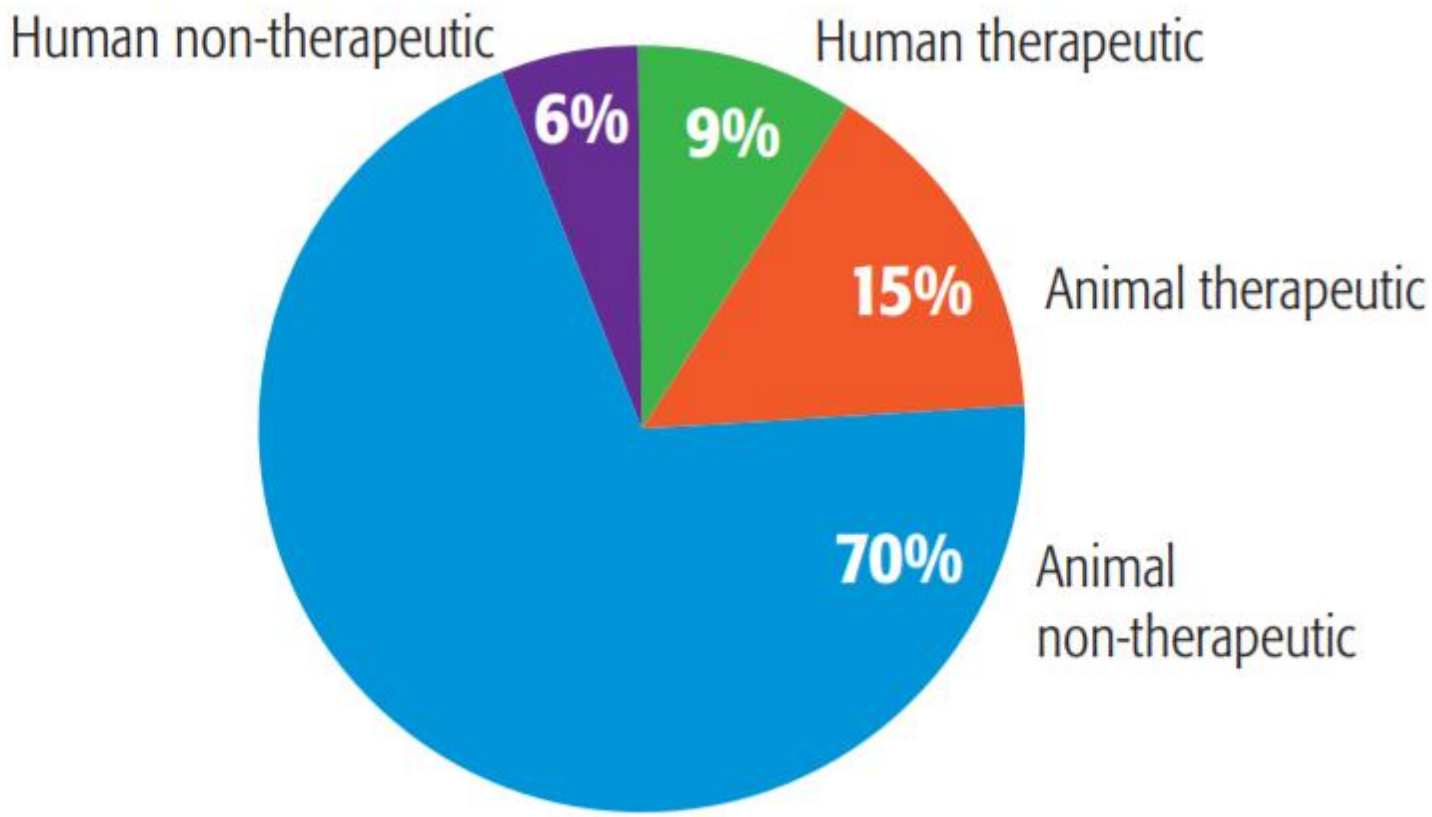
Daughter DES. Get well soon without antibiotics [Internet]. 2014 [cited 2018 Apr 15]. Available from: https://www.flickr.com/photos/diethylstilbestrol/15312609008/

Antimicrobial prescribing facts

- ~ 30 % of all hospitalised inpatients at any given time receive antibiotics
- over 30 % of antibiotics are prescribed inappropriately in the community
- up to 30 % of all surgical prophylaxis is inappropriate
- 10 – 30 % of hospital pharmacy costs can be saved by antimicrobial stewardship programs

Hoffman et al., 2007, Wise et al., 1999, John et al., 1997

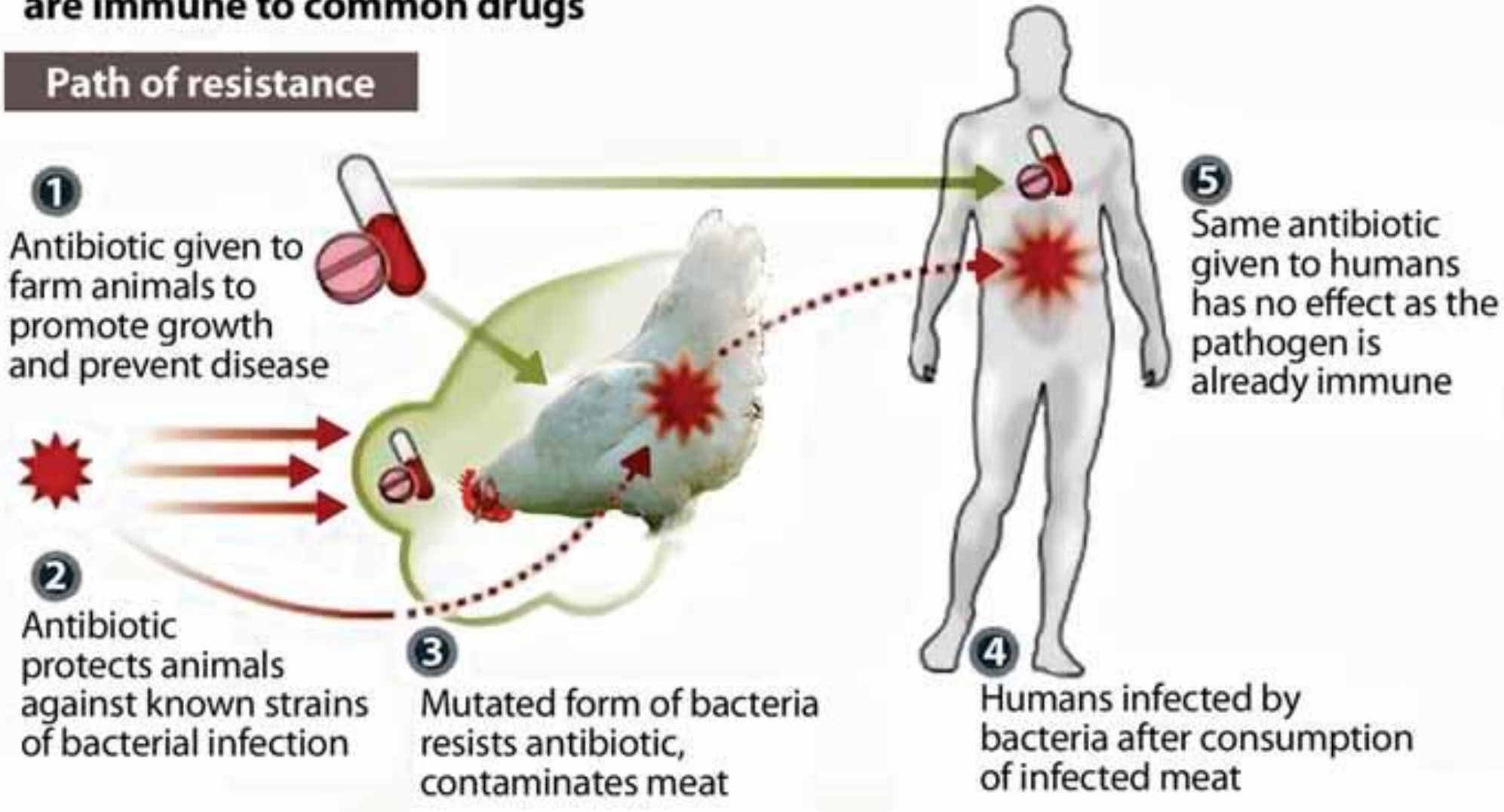
Current use of antibiotics in the United States



Source: www.pewhealth.org

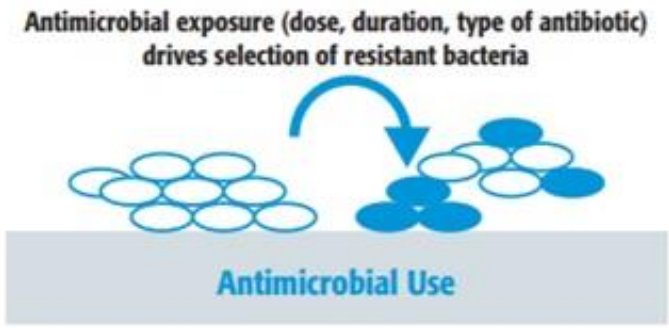
Antibiotic Drug Abuse on Our Animal Farms

Overuse of antibiotics in agriculture is widening the spread of superbugs that are immune to common drugs

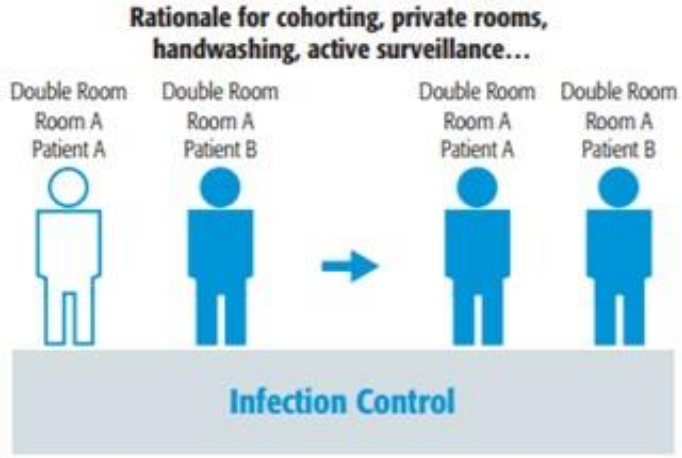


Natural Alternatives for Antibiotic Resistance and Antibiotic Treatment [Internet]. [cited 2018 Apr 15]. Available from: https://www.livehealthynaturally.info/antibiotic.htm

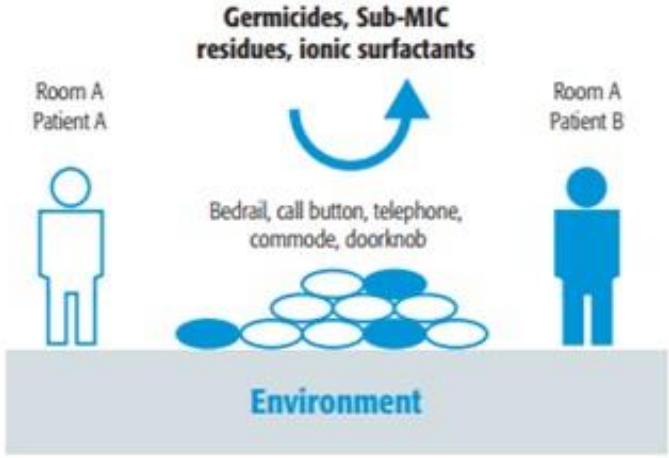
The 3 key drivers to resistance



INFLUENCERS:
- Human antimicrobial consumption
- Agriculture antimicrobial consumption



INFLUENCERS:
- Hand hygiene
- Epidemiology
- Outbreak investigations
- Cohorting
- Active surveillance



INFLUENCERS:
- Germicides
- 10% hypochlorite (sporicidal) for *C. difficile*
- Cleaning Policy & Practice (What surfaces? How often? Is terminal cleaning enough? (NO!))

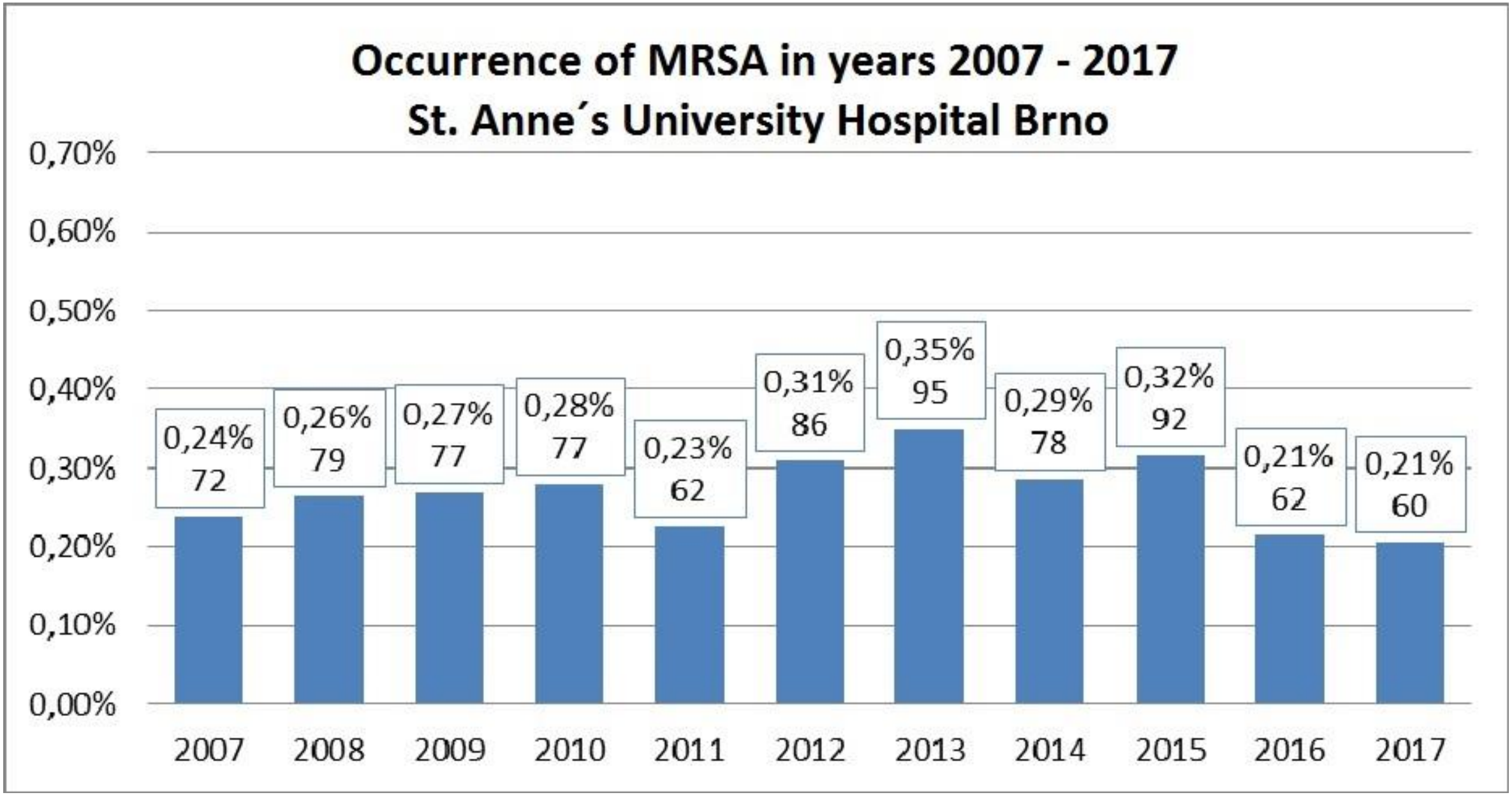
White patients = non-infected/non-colonized with MDRO

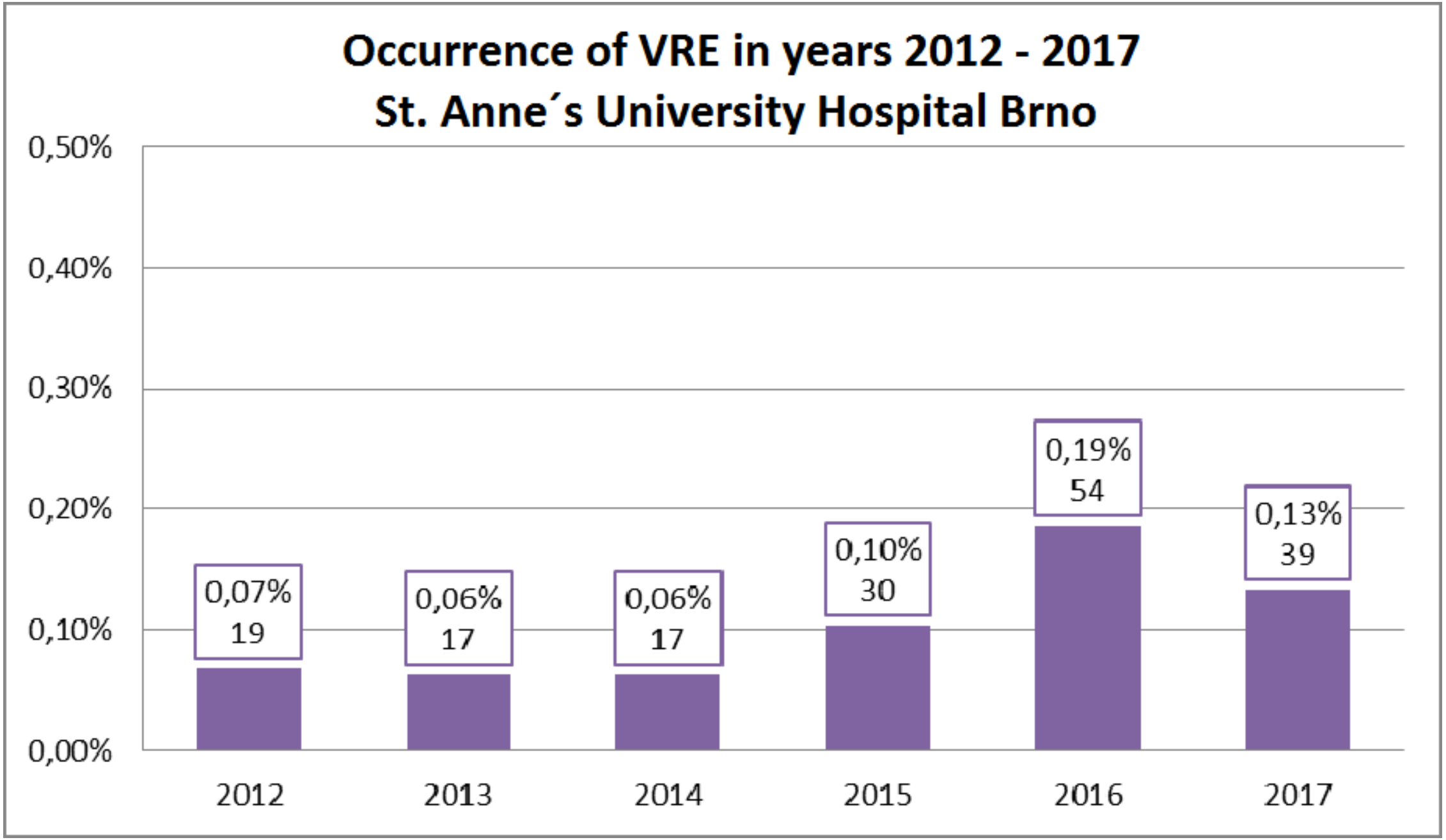
Blue patients = infected or colonized with MDRO

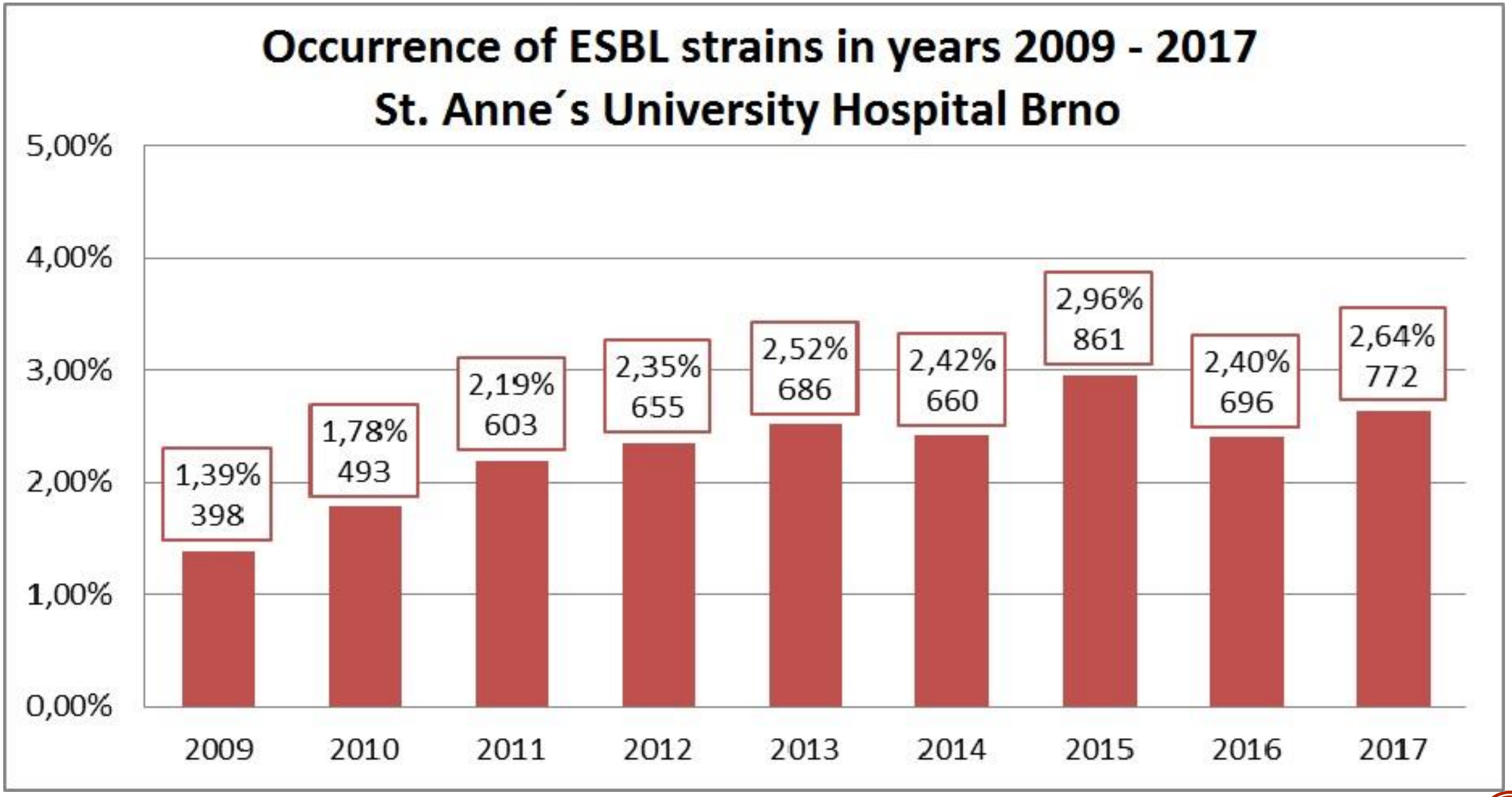
Susceptible organism

Resistant organism

Adapted from Owens RC Jr. et al. Diagn.Microbiol. and Infect. Dis. 2008; 61:110-28.


Occurrence of MRSA in years 2007 - 2017
St. Anne´s University Hospital Brno
0,70%
0,60%
0,50%
0,40%
0,30%
0,20%
0,10%
0,00%
0,24% 72
0,26% 79
0,27% 77
0,28% 77
0,23% 62
0,31% 86
0,35% 95
0,29% 78
0,32% 92
0,21% 62
0,21% 60
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017


Occurrence of VRE in years 2012 - 2017
St. Anne´s University Hospital Brno
0,50%
0,40%
0,30%
0,20%
0,10%
0,00%
0,07%
19
0,06%
17
0,06%
17
0,10%
30
0,19%
54
0,13%
39
2012
2013
2014
2015
2016
2017


Occurrence of ESBL strains in years 2009 - 2017
St. Anne´s University Hospital Brno
5,00%
4,00%
3,00%
2,00%
1,00%
0,00%
1,39%
398
1,78%
493
2,19%
603
2,35%
655
2,52%
686
2,42%
660
2,96%
861
2,40%
696
2,64%
772
2009
2010
2011
2012
2013
2014
2015
2016
2017

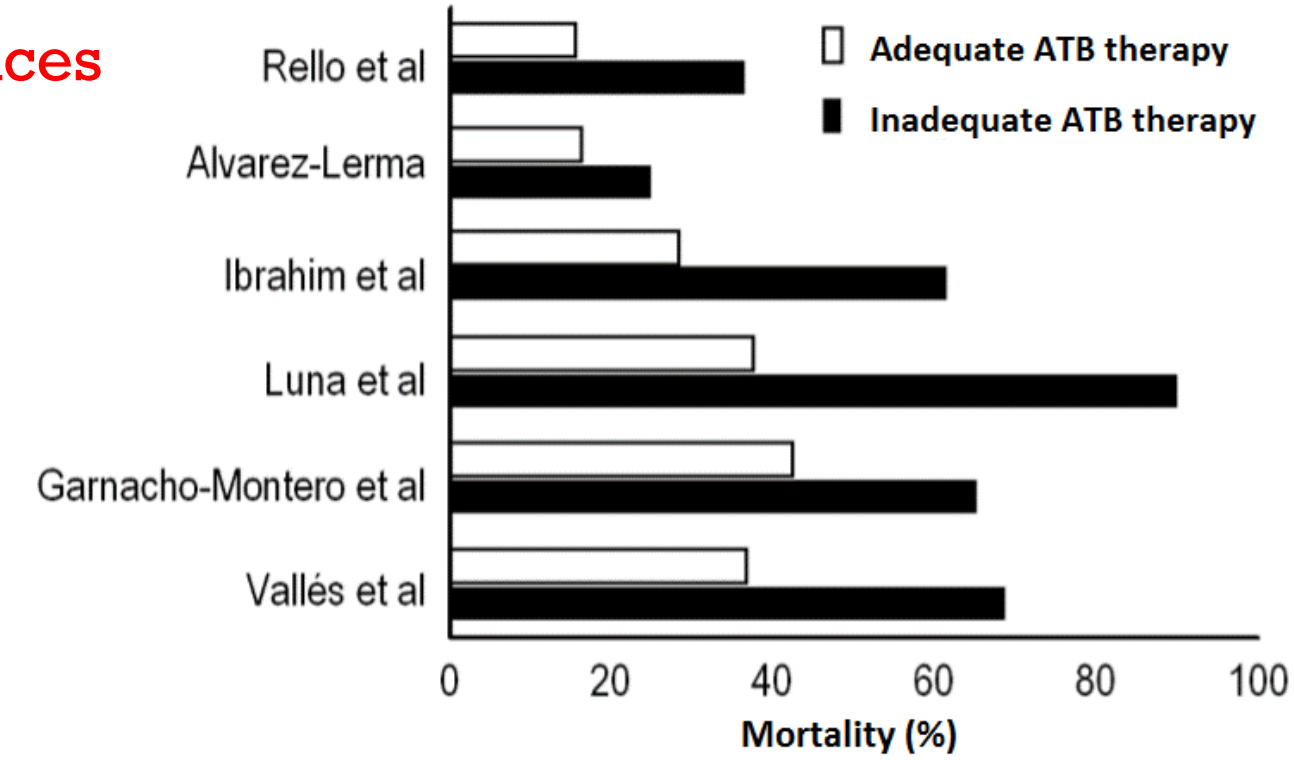
Occurrence of ESBL strains according to departments

Department	2017		
	Σ	Number of hospitalizations	% hosp.
I. IKAK	160	5260,00	3,04%
II. IK	169	3048,00	5,54%
DRO	69	711,00	9,70%
I. DVK	17	1258,00	1,35%
I. CHK	79	3310,00	2,39%
II. CHK	22	1867,00	1,18%
I. ORTK	14	2313,00	0,61%
NCHK	17	940,00	1,81%
KPECH	1	2538,00	0,04%
KOCHHK	8	1680,00	0,48%
I. NK	55	2126,00	2,59%
ARK	95	696,00	13,65%
URO	54	1990,00	2,71%
KTLR	7	693,00	1,01%
OCHO	5	835,00	0,60%
Summary	772	29265,00	2,64%

Importance of adequate antibiotic therapy

- Incidence of inadequate ATB therapy is 25.8 – 45.4 % in ICUs
  - Independent predictive mortality factor

- Adequate ATB therapy reduces the mortality of patients in
  - Sepsis (19.8 %)
  - Severe sepsis (23.1 %)
  - Septic shock (49 %)

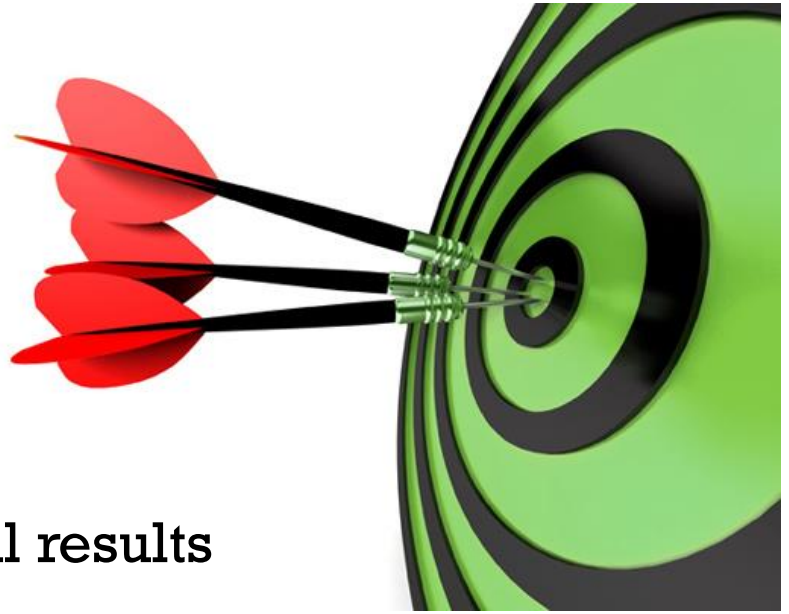


Kula R. et al.: Současné trendy antibiotické terapie v léčbě těžké sepse.

Inadequate ATB therapy

- **Infectious agent is insensitive to treatment**
- **Infectious agent is sensitive to treatment,**
  but the administration of the ATB was delayed
- **Infectious agent is sensitive to the ATB,**
  but the dose is inappropriate
- **Administration of ATB therapy in the absence of signs of infection**

TARRAGONA strategy - appropriate antibiotic therapy in ICU



- „hit early and hard“
  - high dose, broad spectrum, ASAP
- „get to the point“
  - take into account PK and PD changes
- „focus, focus, focus“
  - changes in ATB therapy according to microbiological results
- „listen to your hospital“
  - monitoring of the microbiological situation in the hospital
- „look at your patient“
  - comorbidities, previous ATB therapy, current patient status

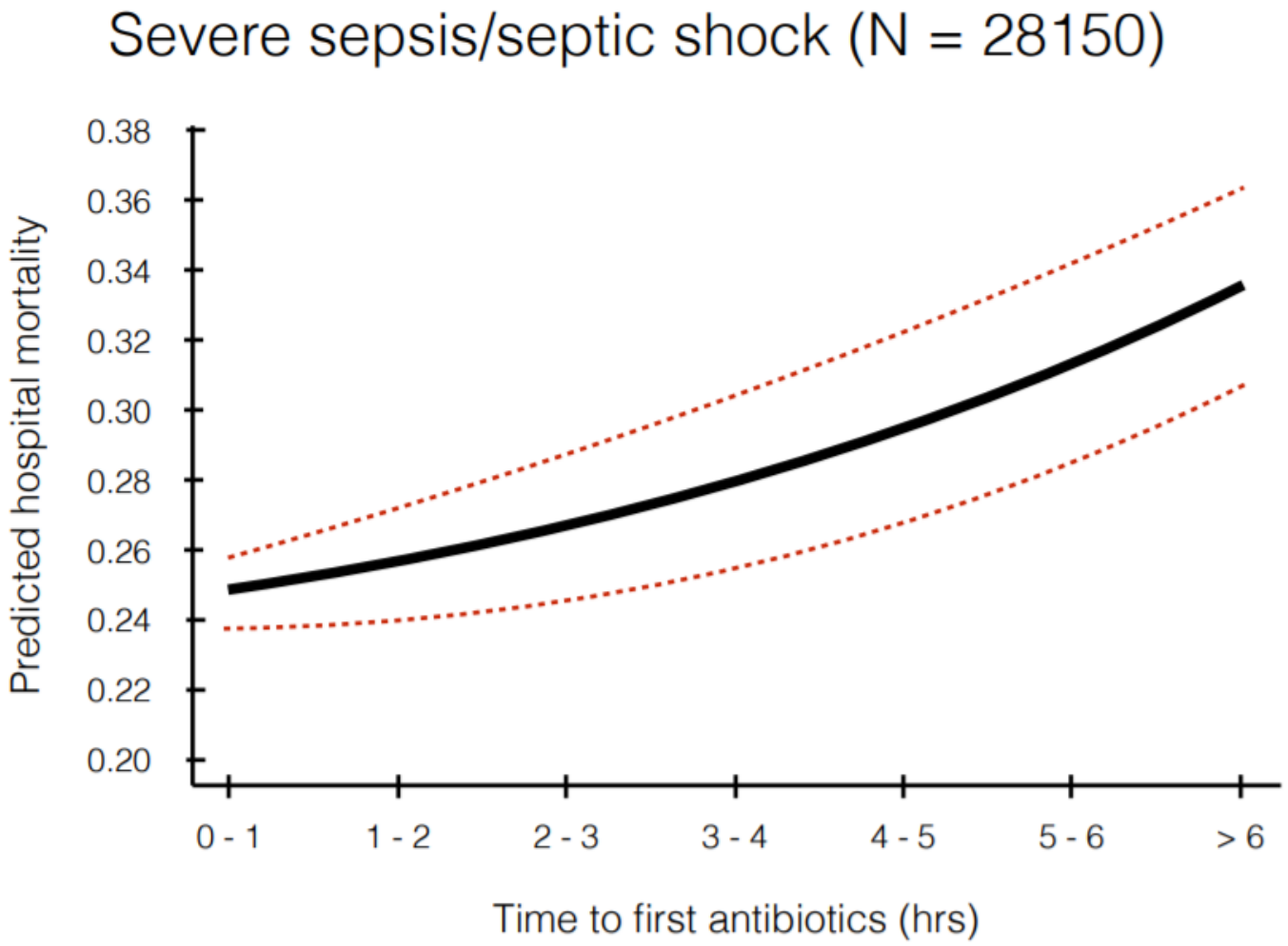
Engelmann L, Schmitt DV. [Tarragona strategy--appropriate antibiotic therapy in the ICU]. Med Klin Intensivmed Notfallmedizin. 2014 Apr;109(3):156–61.
Focus | [Internet]. [cited 2018 Apr 15]. Available from: http://www.sueurda.com/tag/focus/

Antibiotic Stewardship

How to improve ATB therapy in ICU?

- Rapid identification of patients with bacterial sepsis
- Better empirical treatment selection
- Optimized antibiotic dosing with PK-PD models
- De-escalation when culture results are available
- Shortening therapy duration

Rapid identification of patients with bacterial sepsis



Early initiating of ATB therapy is closely related to improved survival

Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589–96.

ATB selection in ICU

- Ideal situation
  - identified pathogen – ATB according to the sensitivity
- Real situation
  - need to „hit early“ – pathogen unknown

→ empiric use of broad spectrum ATBs

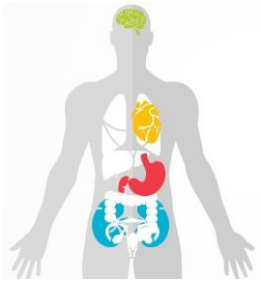
  - In 30-40 % of patients – unable to prove the infectous agent during whole hospitalization

Choice of empiric ATB therapy

According to the:

predicted pathogen

site of infection



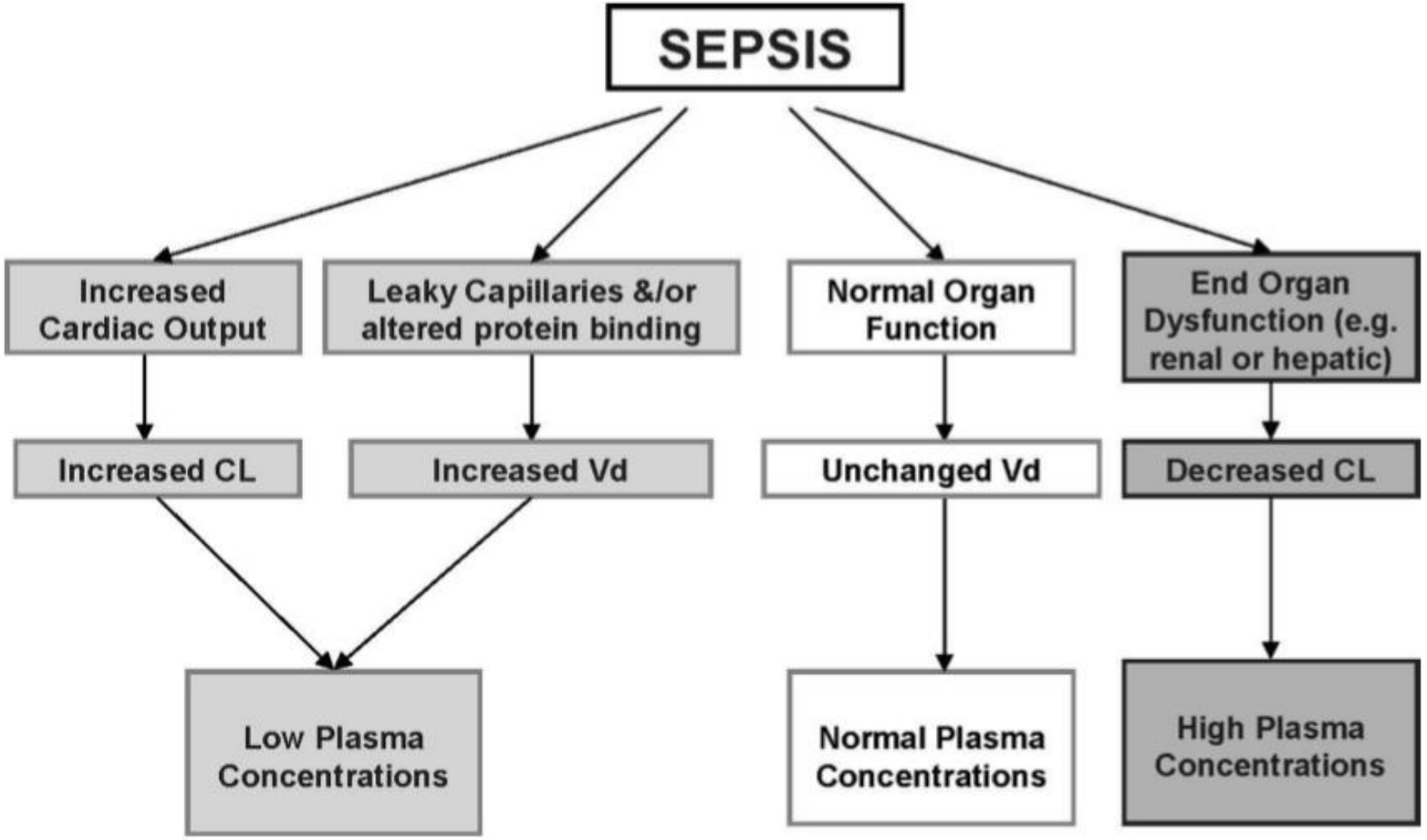
time association with the onset of infection

nosocomial / community aquired

epidemiologic situation in the locality of the hospital

Pathogen.jpg (250×199) [Internet]. [cited 2018 Apr 15]. Available from: http://phoenixrising.me/wp-content/uploads/Pathogen.jpg
Human Body Infographic Pictures to Pin on Pinterest - PinsDaddy [Internet]. [cited 2018 Apr 15]. Available from: http://www.pinsdaddy.com/human-body-infographic

Optimized antibiotic dosing based on PK/PD principles



Roberts JA, Crit Care Med 37 (3) 2009

Pharmacokinetic changes are highly variable in the ICU but may be more predictable IF...

- You know the basic ATB characteristics
  - lipophilic ATB
  - hydrophilic ATB
  - tissue penetration
- You track the changes in patients´characteristics
  - volume status
  - organ dysfunction
- You track the pathophysiologic characteristics
  - systemic inflammation
  - hemodynamics
  - site of infection

Hydrophilic or Lipophilic and Why do We Care?

Type of ATB	Pharmacokinetics	
	In healthy individuals	In critically ill
Hydrophilic ATBs beta-lactams, carbapenems, aminoglycosides, glycopeptides, colistin	Limited intracellular penetration Low Vd Predominantly renal elimination	Increased Vd resulting in decreased plasma concentration Clearance increased if augmented renal clearance or decreased if renal impairment
Lipophilic ATBs macrolides, linezolid, tigecyclinem fluoroquinolones, clindamycin	High intracellular penetration Large Vd Elimination predominantly by hepatic metabolism	Minimal change in Vd Clearance dependent mostly on hepatic function

Case 1

- 73 years old woman admitted to ICU with febrilia, oligoanuria and respiratory distress (need of intubation), need of catecholamines
- CRP 248mg/l, leucocytes 12, Urea 16 mmol/l, Kreat 140 µmol/l
- X-ray – fluidothorax on the left
- Suspected pneumonia (PN) with urinary tract infection (UTI)
- Empirically started on piperacillin/tazobactam and clarithromycin
- After 3 days in microbiological results:
  - Enterococcus faecalis resistant to penicillins from the urinary tract
  - E. faecalis and H.influenzae from the tracheal aspirate
  - CRP slightly decreased (210), leucocytes 11, patient still febrile
- Is the antibiotic treatment sufficient? Would you make any changes?

Case 1

- vancomycin added to piperacillin/tazobactam, clarithromycin after 5 days ex
- After another 4 days – results from the lab showed the presence of VRE (vancomycin resistant enterococcus)
- What is the next option for the treatment of PN and UTI caused by VRE?

nitrofurantoin, linezolid, dalbavancin, tigecycline

Per oral form, for non-complicated UTI, not for PN

30% excreted into urine, recommended as an option for UTI, excellent lung penetration

Unavailable in Czechia

Low excretion in the urine (10-15%), risk of underdosing in UTI, need of higher doses for pneumonia too

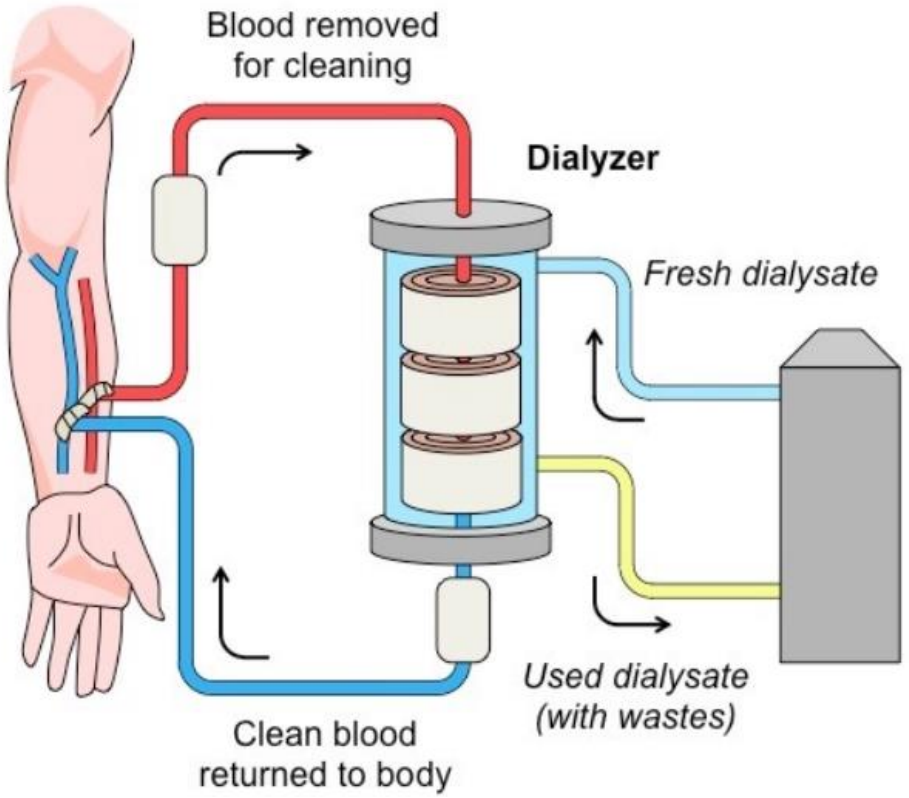
Dose adjustment for acute kidney impairment (AKI)

- Generally, in AKI dose reduction of ATB during the first 24 to 48 (72) hours is not necessary.
- In case of toxic antibiotics (vancomycin, aminoglycosides) the loading dose should be the same as for normal renal function, followed by adjusted maintenance doses according to serum drug levels.
- Suggested dose reductions for ATBs in patients with impaired renal function are mostly derived from studies in chronic (stable) renal failure - these doses may be insufficient for critically ill patients!

Blot S, Lipman J, Roberts DM, Roberts JA (2014) The influence of acute kidney injury on antimicrobial dosing in critically ill patients: are dose reductions always necessary? Diagn Microbiol Infect Dis 79:77–84

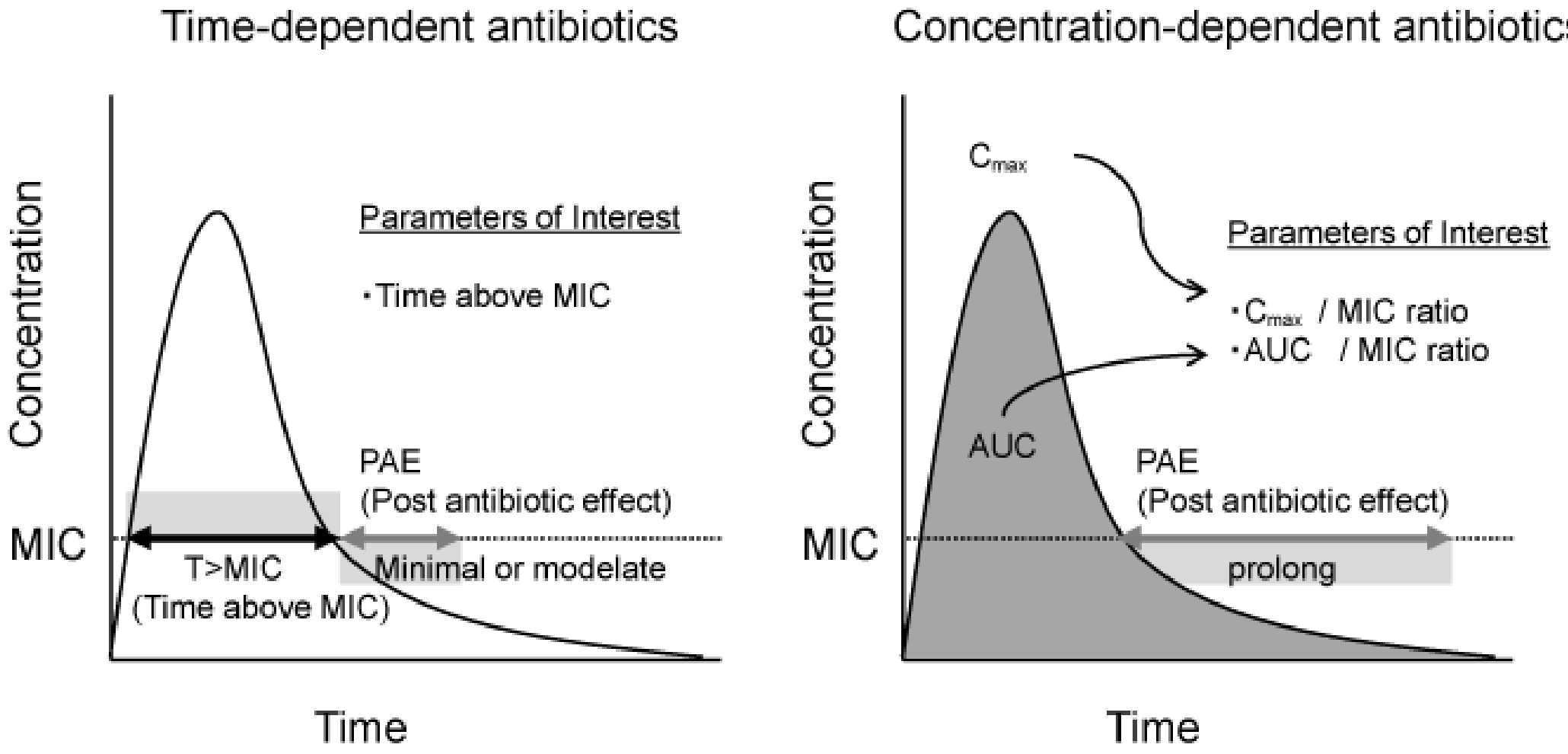
Antibiotic dosing in renal replacement therapy (RRT)

- clearance of ATB by RRT defined by
  - molecule size, solubility, plasma protein binding
  - filter permeability and porosity, blood and dialysis solution flow rate, dialysis regimen…)
  - amount of the drug in plasma (timing of dialysis)
- intermittent (IHD, SLED) vs continuous elimination methods (CVVD, CVVHD, CVVHDF)
- high-flux vs low-flux dialysis membranes
- supplemental doses after dialysis cycle in highly dialyzed ATB



Kidney Dialysis – Scott D. McDowall [Internet]. [cited 2018 Apr 15]. Available from: http://scottdmcdowallmd.com/kidney-dialysis/

Antimicrobial Killing



Silanas D oleh I, Apt., M.Kes. ANTIBIOTIK MANA YANG TERMASUK DALAM KATEGORI TIME DEPENDENT (TD) DAN CONCENTRATION DEPENDENT (CD)? [Internet]. [cited 2018 Apr 15]. Available from: https://ilmanapt.blogspot.com/2016/07/antibiotik-mana-yang-termasuk-dalam.html

Pharmacodynamic properties that correlate with efficacy of selected antibiotics

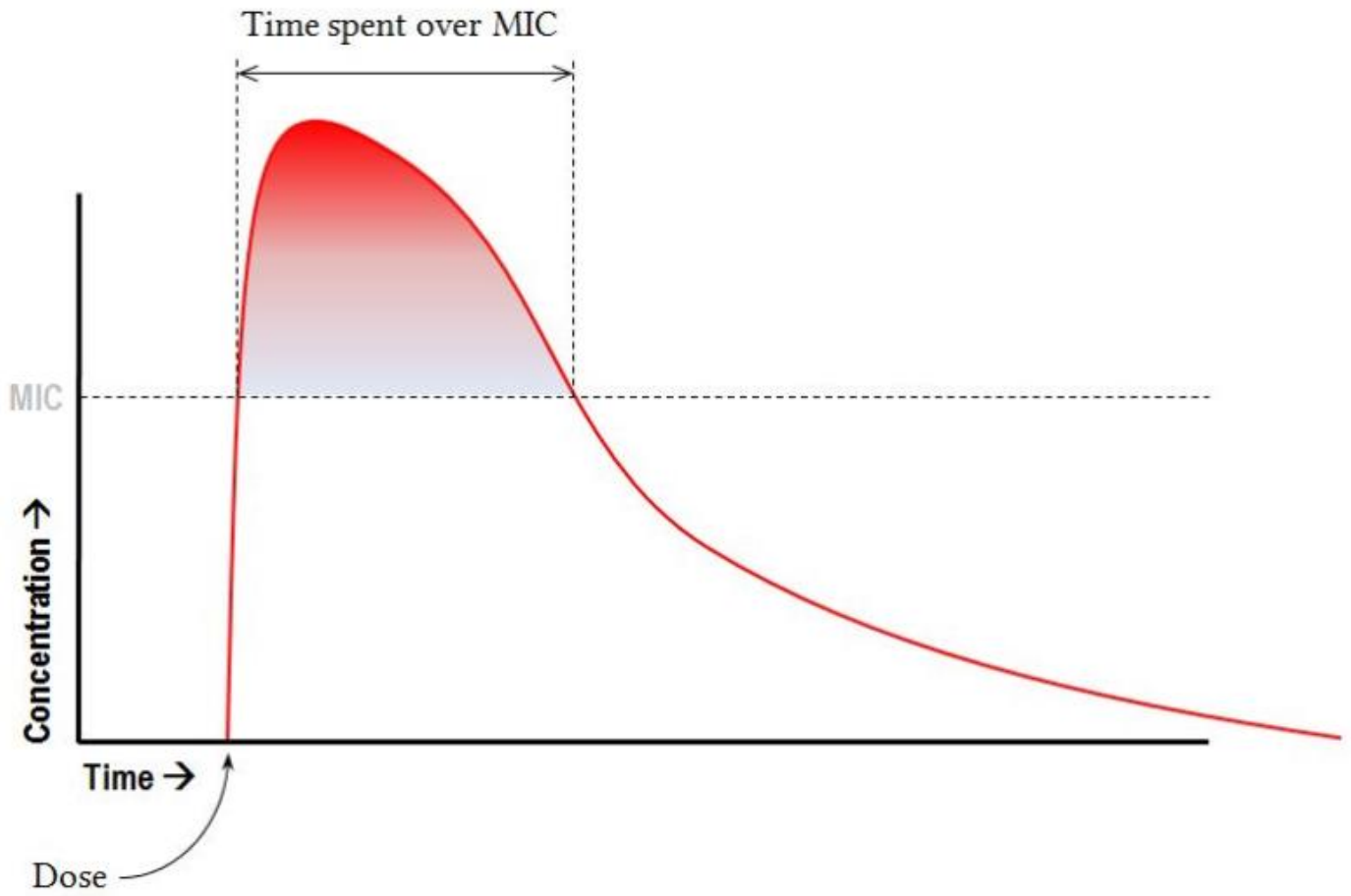
	Antibiotic	Optimal PK/PD parameter
Time-dependent ATB	B-lactams, carbapenems, clarithromycin, lincosamides	T > MIC
Concentration-dependent ATB	aminoglycosides, daptomycin, quinupristin/dalfopristin, ketolides	C_{max} / MIC
Concentration-dependent ATB with time-dependence	fluoroquinolones, glycopeptides, tetracyclines, tigecykline, linezolid	24h-AUC / MIC

DON´T FORGET

- For ATB, PD parameters are closely related to PK properties
- Each ATB has its own pharmacokinetic profile
- Different antibiotic classes have been shown to have different kill characteristics on bacteria
- Dosing regimens that maximize the rate of response in ICU patients improve patient outcomes and minimize antibiotic resistance
- Clinical status of the critically ill changes from day to day – CONSIDER DOSE READJUSTMENT REPEATEDLY

Time-dependent ATBs

- Beta-lactams
- Carbapenems
- Clarithromycin
- Clindamycin

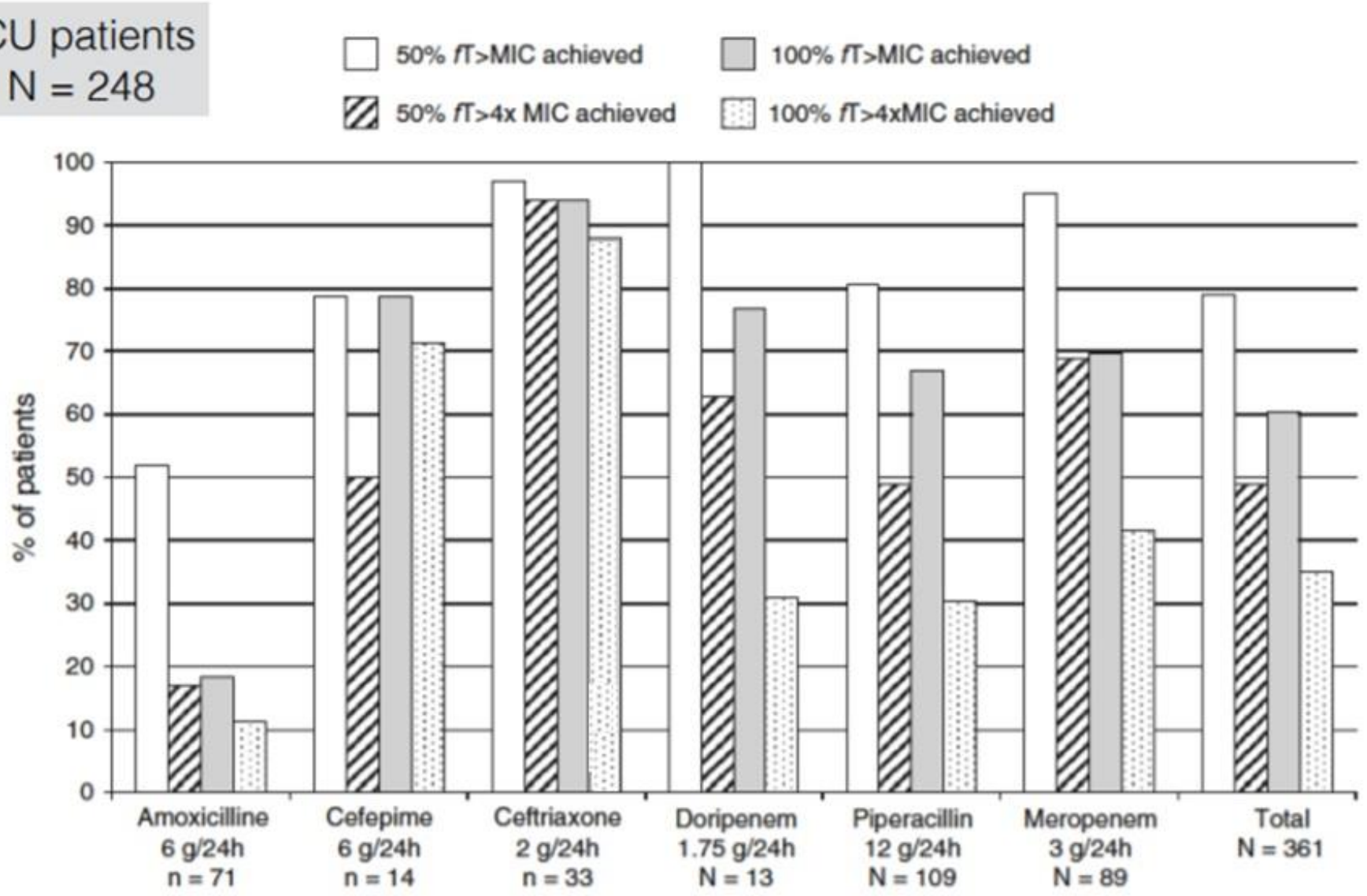


Kill characteristics of antibiotic agents - Deranged Physiology [Internet]. [cited 2018 Apr 15]. Available from: http://www.derangedphysiology.com/main/required-reading/infectious-diseases-antibiotics-and-sepsis

Time-dependent ATBs

- Maximum bactericidal/bacteriostatic effect achieved at concentrations 4-5 times above the MIC
  - Further increase in concentration doesn´t improve ATB killing, but increases the toxicity of the drug
- Maintain blood concentrations above the MIC for prolonged time periods
  - Ideally in critically ill > 80 - 90% of between-dose interval above MIC
- More frequent dosing OR
- Prolonged / continuous infusions

Inadequate B-lactam dosing in critically ill



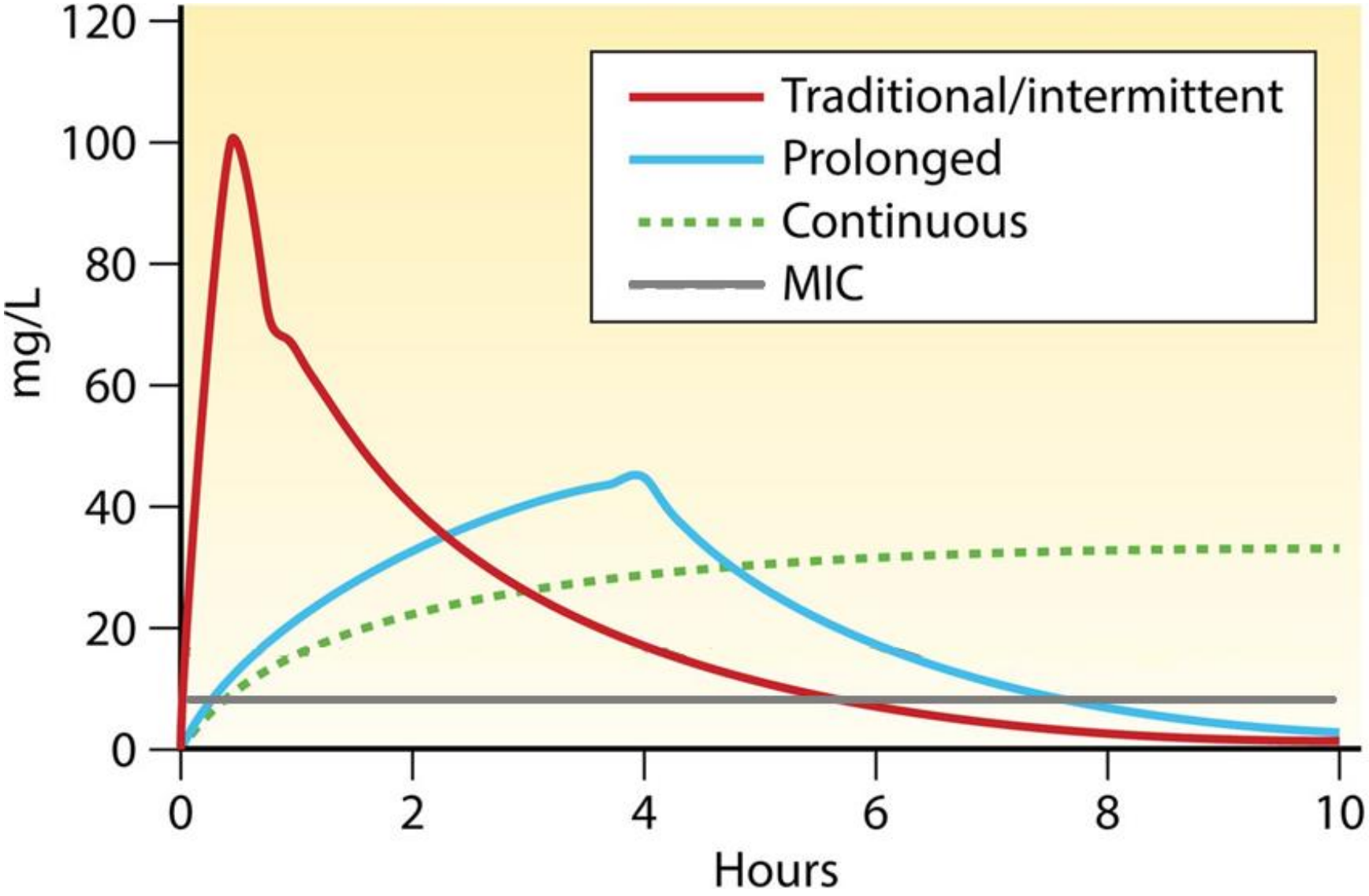
Roberts JA et al (2014) DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis Off Publ Infect Dis Soc Am 58:1072–1083

Why are the standard doses insufficient in ICU patients?

- Dosing in SPC
  - Mainly based on clinical trials with
    - healthy volunteers
    - non-critically ill patients
- Uptodate, Sanford Guide, Micromedex
  - more information, but still a gap in the dosing for ICU patients
- Pathophysiological changes in critically ill

Important to look for data in studies conducted on critically ill

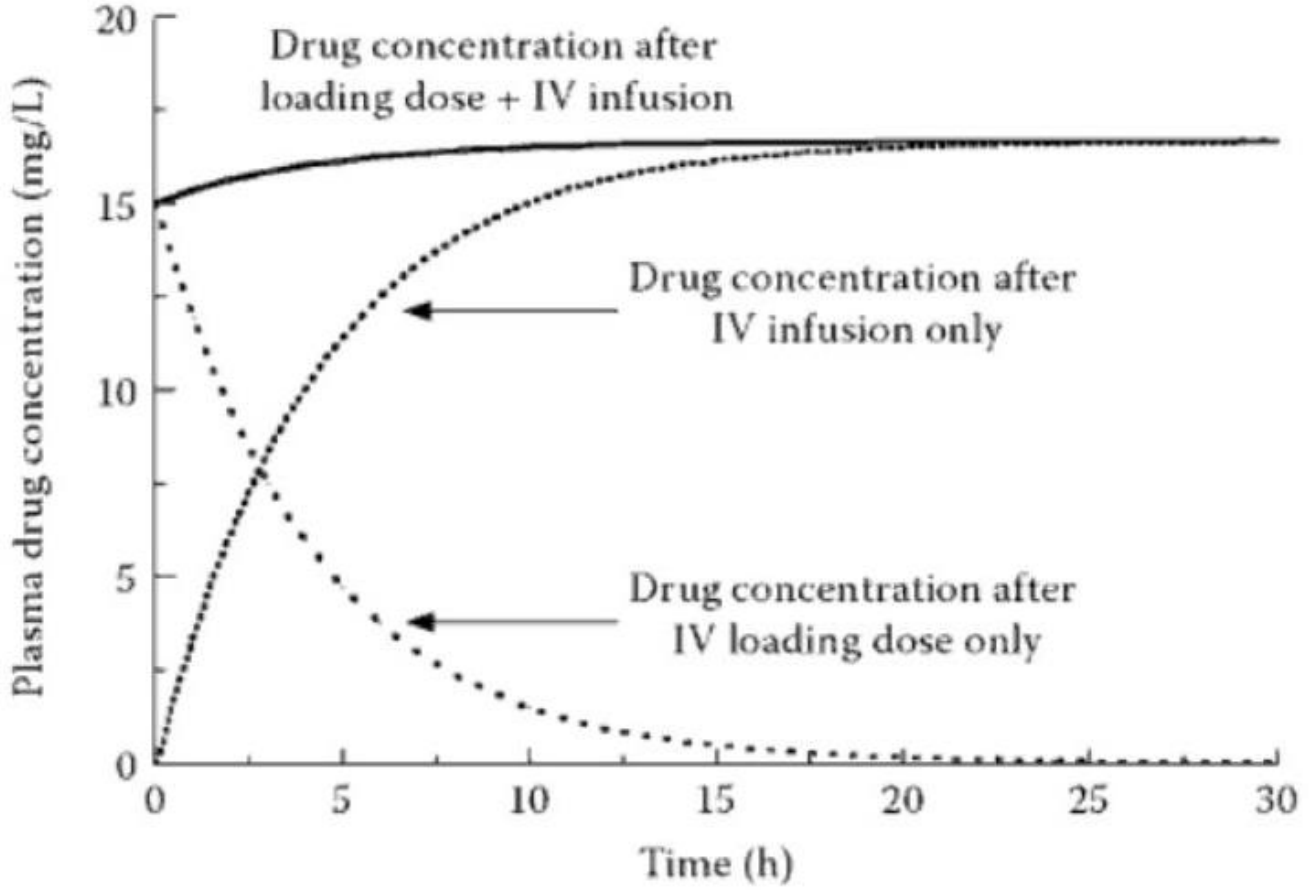
Prolonged/continuous infusions of B-lactams



Grupper M, Kuti JL, Nicolau DP (2016) Continuous and Prolonged Intravenous β-Lactam Dosing: Implications for the Clinical Laboratory. Clin Microbiol Rev 29:759–772

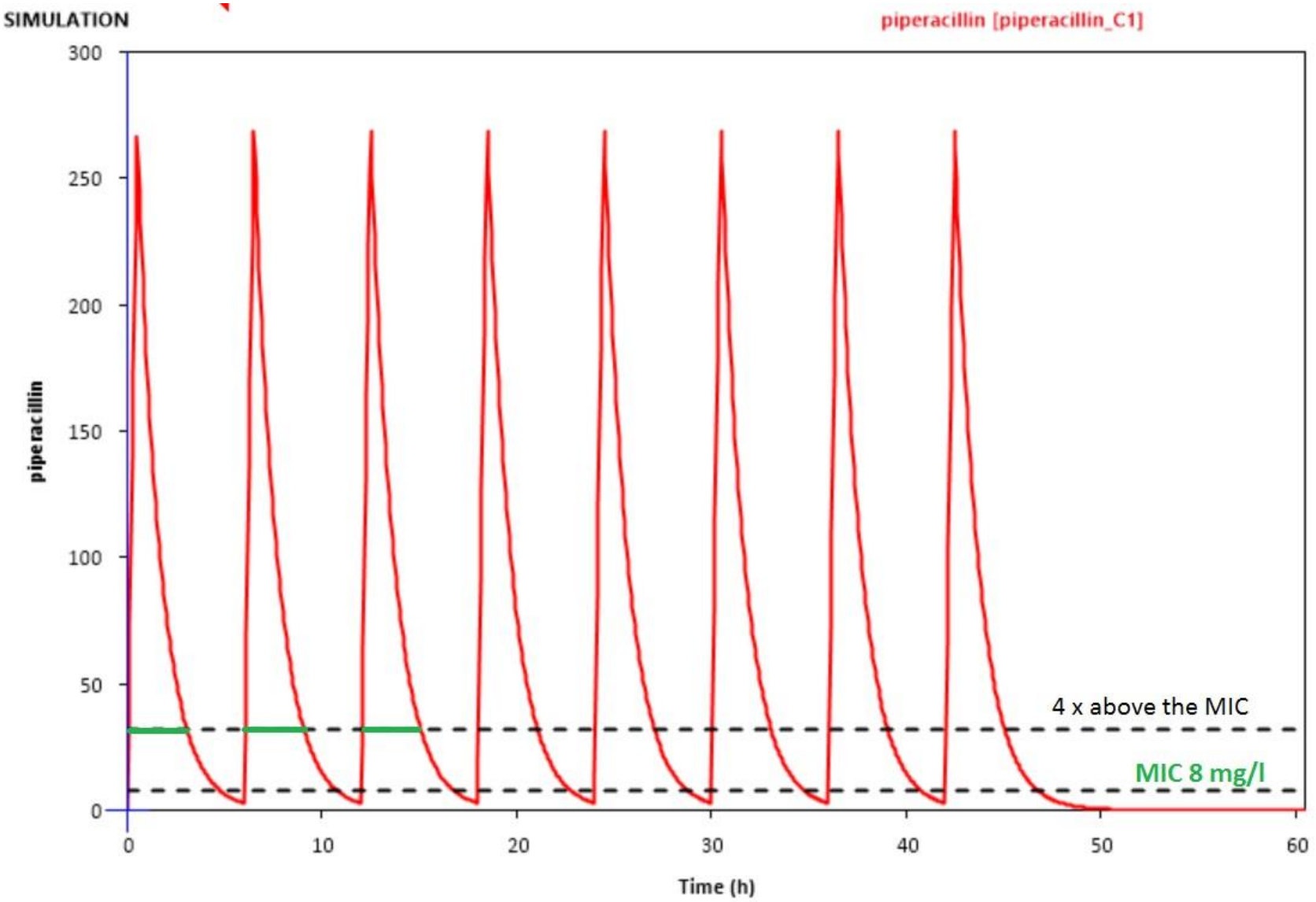
Prolonged/continuous infusions of B-lactams

- To overcome the slow onset of action of the ATB – LOADING DOSE before starting the extended/continuous infusion is advised



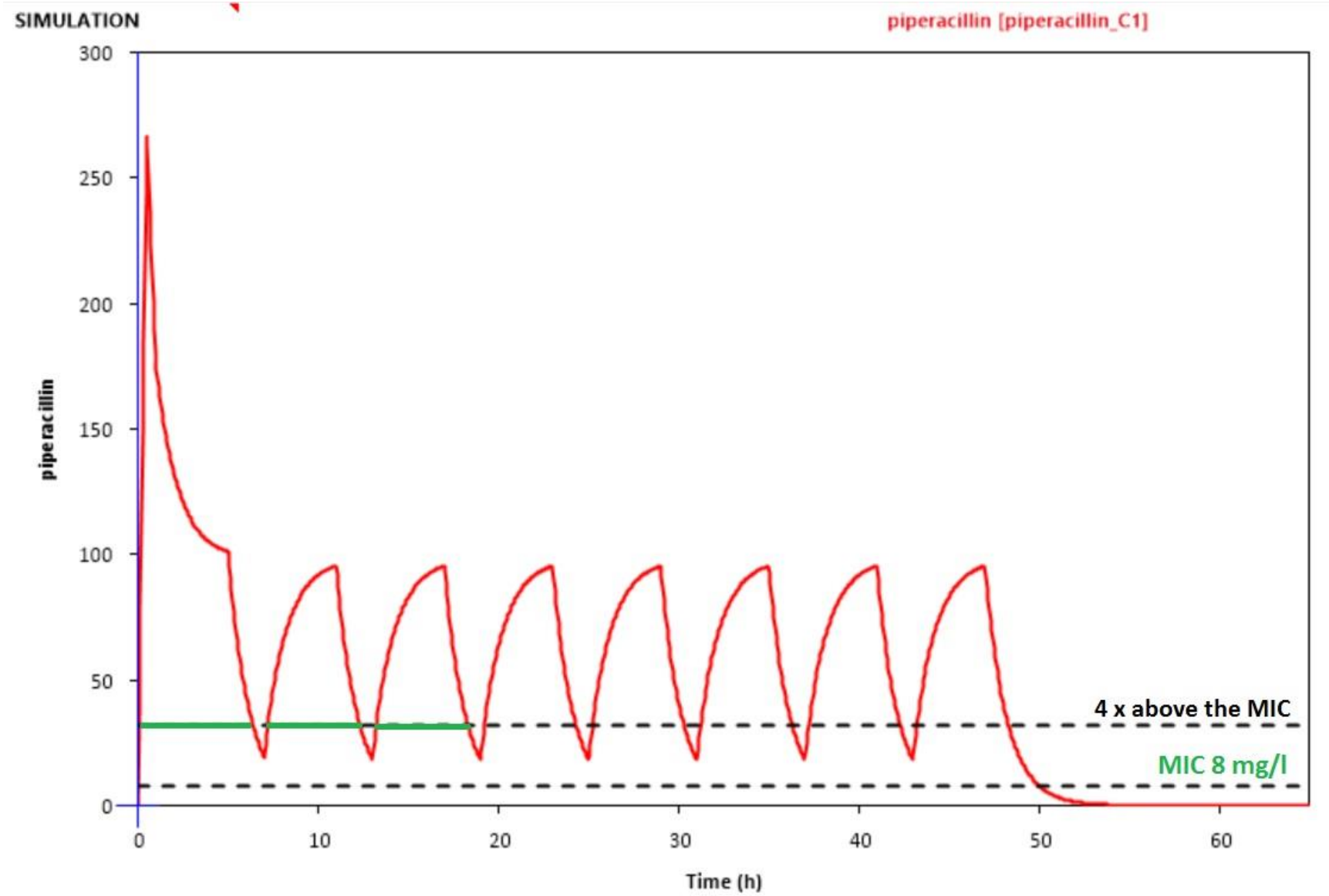
Continuous intravenous infusion (one-compartment model) - ppt video online download [Internet]. [cited 2018 Apr 15]. Available from: http://slideplayer.com/slide/9175396/

Piperacillin 30min infusion vs prolonged (4h) infusion



piperacillin 4.5 g q 6 hours administered as a 30min infusion

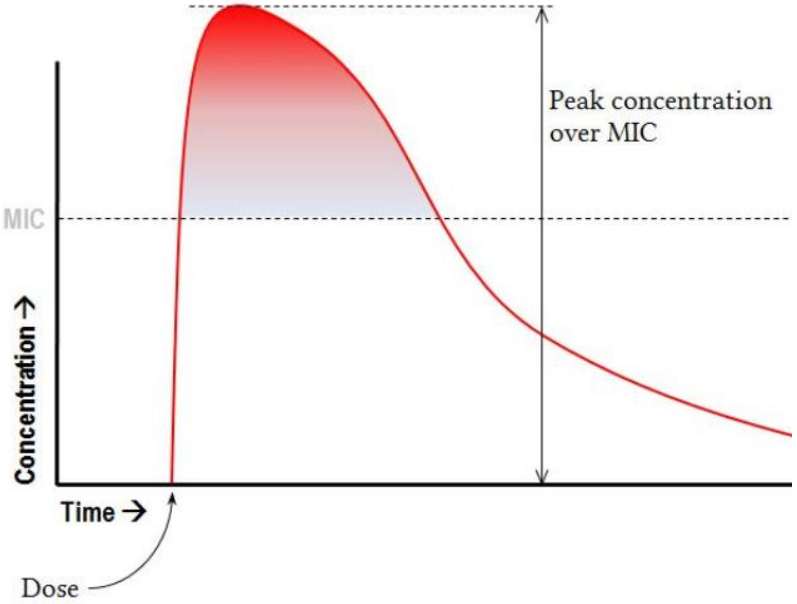
Piperacillin 30min infusion vs prolonged (4h) infusion



piperacillin 4.5 g LD followed by 4.5 g every 6 h administered as a 4h prolonged infusion

Concentration-dependent ATBs

- the rate of bacterial eradication rises with increasing concentration up to a specific level (Cmax/MIC)
- the best responses occur when the concentrations are at least 8-10 times above the MIC for their target organism(s) at the site of infection
- ideal dosing strategy is to administer high doses separated with longer time intervals
- aminoglycosides



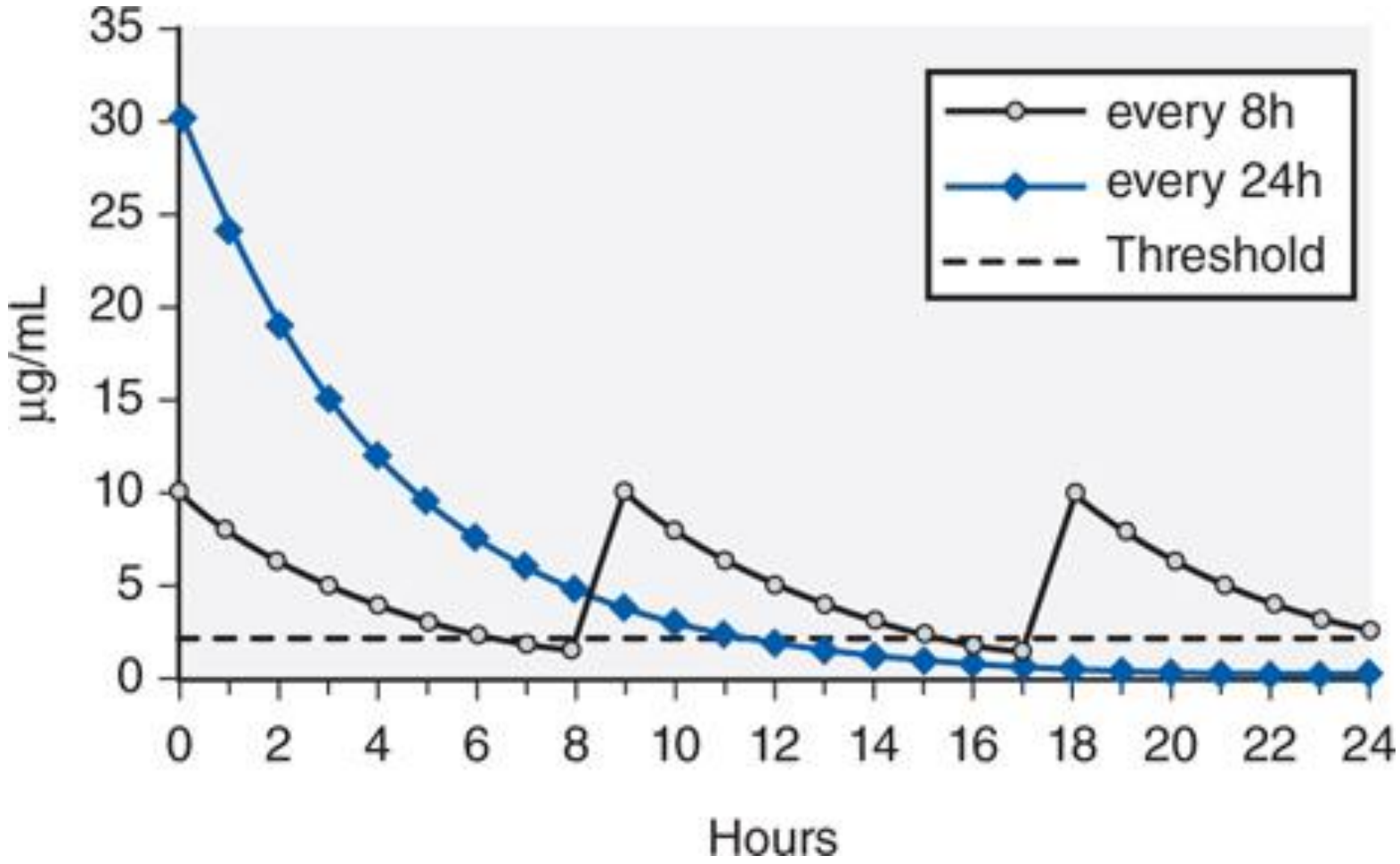
Kill characteristics of antibiotic agents - Deranged Physiology [Internet]. [cited 2018 Apr 15]. Available from: http://www.derangedphysiology.com/main/required-reading/infectious-diseases-antibiotics-and-sepsis

Aminoglycosides in ICU

- amikacin, gentamicin, (tobramycin)
- primarily used to treat aerobic G – infections (PSAE, Enterobacter)
- long post-antibiotic effect
- elimination via kidneys (85-95 % by glomerular filtration)
- nephrotoxicity
  - retention of the drug in the proximal tubular cells
  - usually reversible
- ototoxicity
  - 2-10 %
  - ireversible cochlear or vestibular damage

Aminoglycosides dosing in ICU

- Preferred once daily dosing



ONCE DAILY dosing:

- higher efficacy
- lower toxicity
- lower risk for resistance development
- less work for nurses ☺

Themes (2016) Aminoglycosides. In: Basicmedical Key. https://basicmedicalkey.com/aminoglycosides-4/. Accessed 24 Feb 2018

Aminoglycosides dosing in ICU

- Gentamicin, tobramycin 5-7 mg/kg q 24 h
- Amikacin 15 mg/kg q 24 h

- Patients with changes in distribution volume (burns, ascites) – lack of data
  - risk of under/overdosing
  - need of therapeutic drug monitoring (TDM)

- Dose reduction needed in renal impairment
  - prolonged elimination half-life
  - lack of data

TDM of aminoglycosides

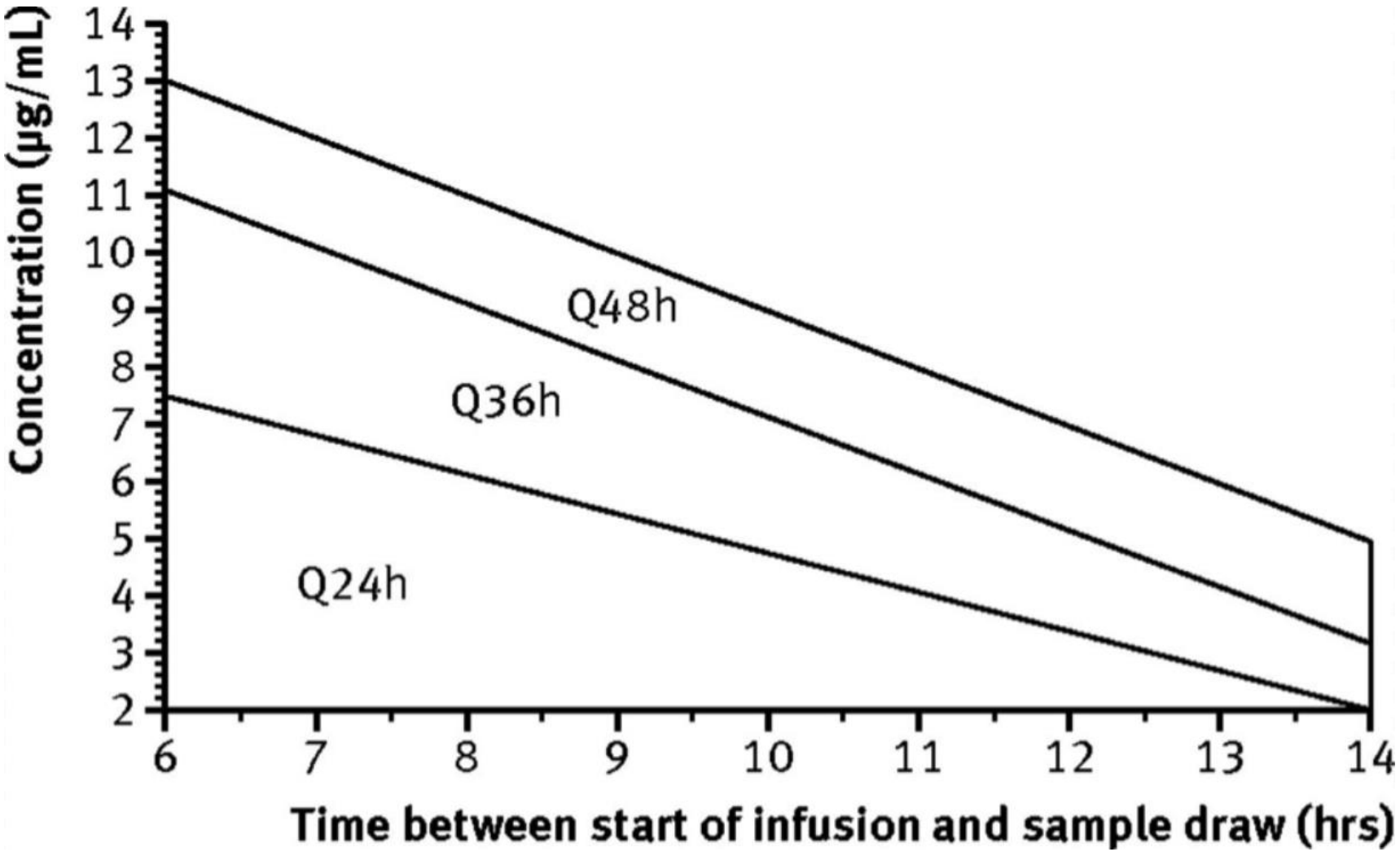
- Conventional dosing (3 x daily)

	Trough concentration	Peak concentration
Amikacin	4 – 8 mg/l	20 – 30 mg/l 25 – 35 mg/l life threatening infections
Gentamicin Tobramycin	1 – 2 mg/l	5 – 8 mg/l 8 – 10 mg/l life threatening infections

- Once daily dosing

	Trough concentration	Peak concentration
Amikacin	< 1 mg/l	40 – 60 mg/l 60 – 80 mg/l life threatening infections
Gentamicin Tobramycin	< 1 mg/l	> 10 mg/l 15 – 20 mg/l life threatening infections

Hartford nomogram for TDM of gentamicin/tobramycin



Applies for dosing
5-7 mg/kg q 24h

Nicolau DP, Freeman CD, Belliveau PP, et al (1995) Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 39:650–655

Case 2

- Septic patient in ICU with kidney impairment with the need for regular daily dialysis
- The antibiotic center recommended adding of gentamicin

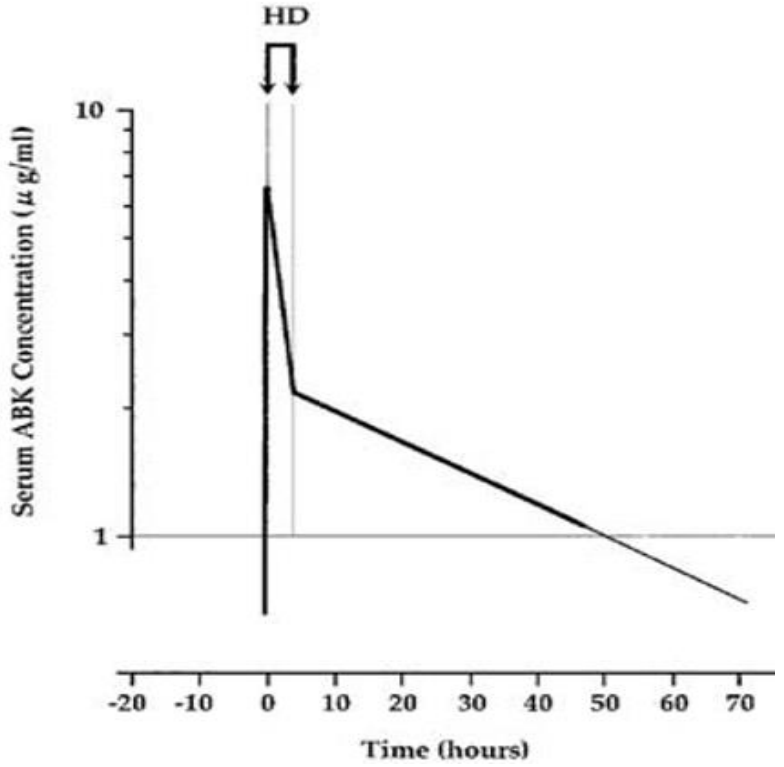
- What dosing regimen would you suggest?

- Facts:
  - Concentration dependent antibiotic
  - Elimination via kidneys (85-95 % by glomerular filtration)
  - Dialysable (cca 60 % of the administered dose)

Quality Patients: Are Yours 'Low-Quality'? - MGE: Management Experts [Internet]. MGE: Management Experts Inc. 2016 [cited 2018 Apr 15]. Available from: http://www.mgeonline.com/2016/getting-too-many-low-quality-new-patients/

Aminoglycosides dosing in hemodialysis patients

- Dosing according to SPC
  - Gentamicin 1-1,7 mg/kg after HD, amikacin 5-7,5 mg/kg after HD
  - Low Cmax and high concentrations in time between dialysis sessions
    - Risk of toxicity and insufficient concentrations for bacteria killing
- Administration of high doses before HD
  - gentamicin 4-5 mg/kg administered 1 hour before HD
  - sufficient Cmax
  - dialysis ensures rapid drop in gentamicin concentration

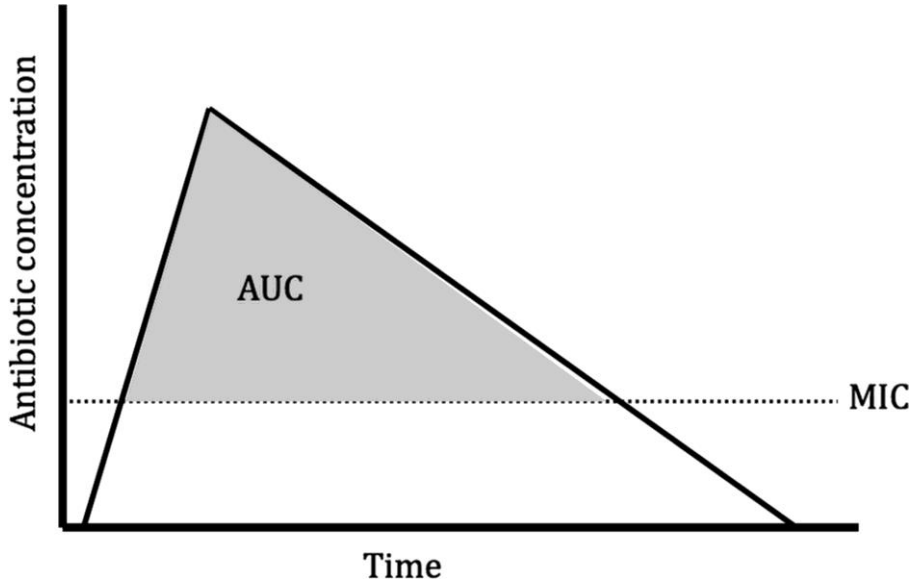


Veinstein A et al (2013) Gentamicin in Hemodialyzed Critical Care Patients: Early Dialysis after Administration of a High Dose Should Be Considered. Antimicrob Agents Chemother 57:977–982
Matsuo H et al (1997) Administration of aminoglycosides to hemodialysis patients immediately before dialysis: a new dosing modality. Antimicrob Agents Chemother 41:2597–2601

Concentration-dependent ATB with time-dependence

- optimal PK/PD parameter is the AUC-24h/MIC
- difficult to generally determine which dosing scheme is the most suitable
  - best option would be using TDM

- Glycopeptides (vancomycin, teicoplanine)
- Fluoroquinolones
- Tigecycline
- Linezolid
- Colistin



Cole TS, Riordan A (2013) Vancomycin dosing in children: what is the question? Arch Dis Child archdischild-2013-304169

Vancomycin dosing strategies in ICU

- Intermittent (traditional) dosing
  - Loading dose 25-30mg/kg (severe infections)

Patient Weight	Recommended Loading Dose	Infusion Rate
25 – 35 kg	750 mg x 1	60 minutes
36 – 45 kg	1,000 mg x 1	60 minutes
46 – 55 kg	1,250 mg x 1	90 minutes
56 – 65 kg	1,500 mg x 1	90 minutes
66 – 75 kg	1,750 mg x 1	120 minutes
≥ 76 kg	2,000 mg x 1	120 minutes

CAVE!
„red man syndrome“
-slow infusions!

Dilution:
-central line – 10mg/ml
-peripheral line – 5mg/ml

Vancomycin dosing strategies in ICU

- Intermittent (traditional) dosing
  - Maintenance dose

Creatinine clearance (ml/min)	Dose & Frequency (TBW)
> 50	15 – 20 mg/kg q 8 – 12 h
30 – 49	15 – 20 mg/kg q 12 – 24 h
15 – 29	10 – 15 mg/kg q 24 h
< 15	10 – 15 mg/kg q 24 – 48 h

Therapeutic drug monitoring - vancomycin

- goal trough concentrations in SPC are OUTDATED
- for resistance prevention higher trough level are needed

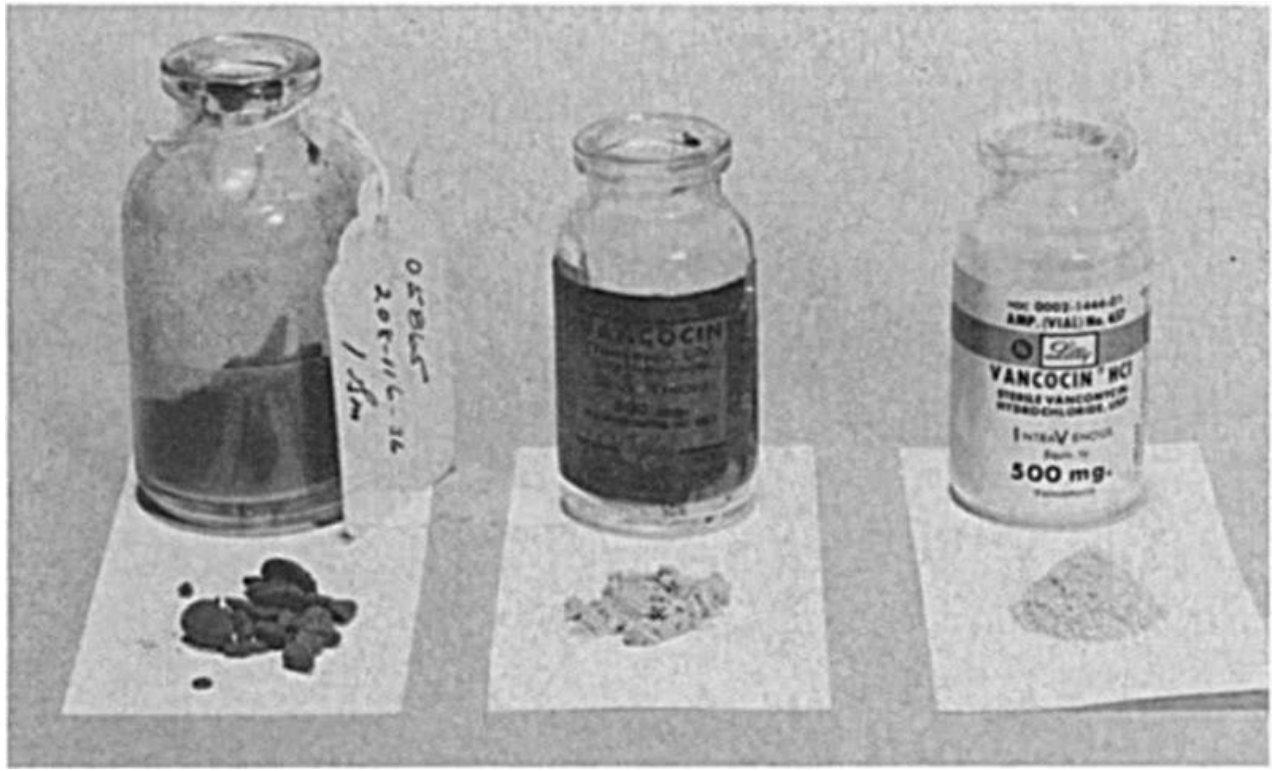
Goal Trough (mcg/mL)	Indication
10 – 15	cellulitis, skin/soft tissue infections
15 – 20	pneumonia, bacteremia, endocarditis, osteomyelitis

Recommend trough levels **>10 mcg/mL** to avoid microbial resistance

- In critically ill patients with sepsis – measure concentration of vancomycin after 24 h from therapy initiation (before 3.rd dose)
- optimum efficacy at AUC/MIC > 400

Vancomycin toxicity

- no longer nicknamed as „Mississippi mud“
- newer formulations lack high risk of ototoxicity and nephrotoxicity, so aggressive dosing is possible
- in severe infections trough levels 15-20 mg/l are needed instead of previously recommended 5-10 mg/l



Nolin TD (2016) Vancomycin and the Risk of AKI: Now Clearer than Mississippi Mud. Clin J Am Soc Nephrol CJASN 11:2101–2103
D L. Vancomycin: A History. Clin Infect Dis. 2006;42(Supplement 1):0

Vancomycin continuous infusion

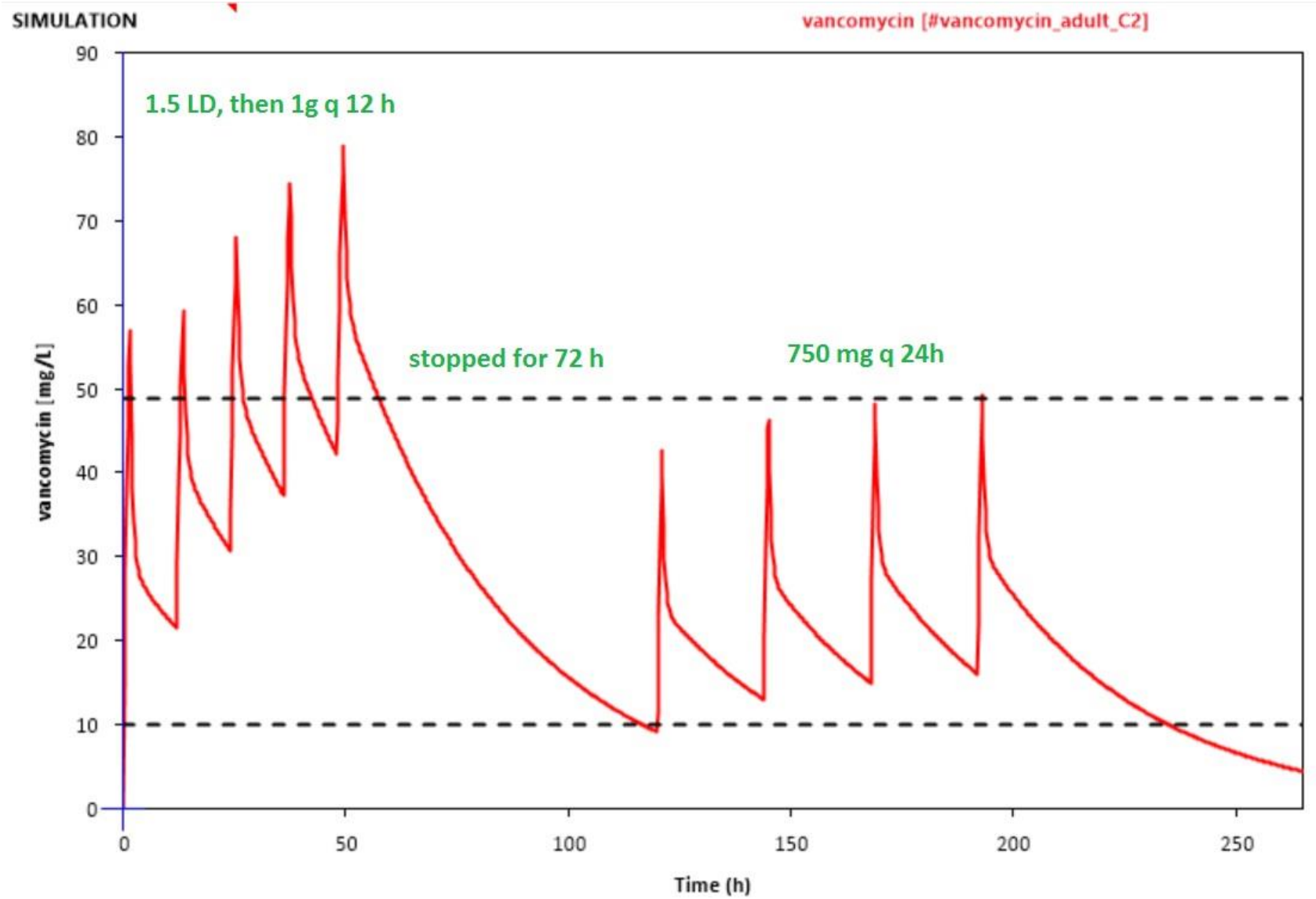
- lower daily doses needed to achieve therapeutic range
- slower onset of nephrotoxicity
- goal serum concentrations 20 – 25 mg/l
- sampling for TDM anytime during the day (lower risk of error in serum concentraction interpretation)
- possibility of prompt dose adjustment
- in patients on CVVHD the target level achieved faster
- watch out for incompatibilities!

Case 3

- Patient 56 years old, male, 72kg, admitted to ICU in septic shock, combination of vancomycin + meropenem was started
- Signs of multiorgan failure
  - Urea 14, Kreat 192
  - Elevated liver enzymes
  - Need for catecholamines and volume substitution
- Vancomycin – LD of 1500 mg, followed by 1g q 12 hours, vancomycin level measured after 48 hours

Do you agree with the dosing, plan for TDM?

Case 3



- In ICU patients – measure the level after 24h – before 3rd dose!
- Don´t wait for steady-state

- Actually, there is no steady state in critically ill

Colistimethate sodium (CMS)

- available from 1959, polypeptide ATB effective against G- bacilli
- CMS is an inactive prodrug, converted in the body to colistin (CBA)
- displaced with aminoglycosides in 70´s – 80´s for lower toxicity
- 2003 – 2009 – first PK/PD data

→ reassessment of the dosage

Li J. et al.: J chromatogr B Biomed Sci Appl, 2001 ; Li J. et al.: Antimicrom. Agents Chemother, 2002 ; Jansson B. et al.: J Pharm Biomed Anal, 2009

Colistin dosing recommendations

Table 1. Colistin Dosing Recommendations

Source	Dosing recommendations for patients with normal renal function	Daily dose for a 70-kg patient with Cl_{cr} of 70 ml/min (expressed in mg CBA)
Colomycin package insert[1] Europe	≤ 60 kg: 50,000 IU/kg/day in 3 divided doses (maximum daily dose 75,000 IU/kg) > 60 kg: 1–2 million IU (MU) 3 times/day (maximum daily dose 6 MU)	90–180 mg/day CBA in 3 divided doses 3-6MIU/day
Coly-Mycin M Parenteral package insert[2] USA	2.5–5 mg CBA/kg/day in 2–4 divided doses (maximum daily dose 300 mg CBA)	175–350 mg/day CBA in 2–4 divided doses 6-12 MIU/day
Plachouras et al[4]	Loading dose: 9–12 million IU Maintenance dose: 4.5 million IU every 12 hrs	270–360 mg CBA loading dose + 135 mg CBA every 12 h 9-12 MIU loading+ 4.5 MIU q 12 h
Garonzik et al[5]	Loading dose: colistin $C_{ss,avg}$ target × 2.0 × ideal body weight (kg)[a] (maximum dose 300 mg CBA) Maintenance dose: colistin $C_{ss,avg}$ target × ([1.50 × Cl_{cr}] + 30) in 2–3 divided doses[b]	If $C_{ss,avg}$ = 2.5 μg/ml: 300 mg CBA loading dose + 340 mg/day CBA in 3 divided doses 10 MIU loading+ 12 MIU/24h (in 3 doses q 8 h)

CBA = colistin base activity; Cl_{cr} = creatinine clearance; $C_{ss,avg}$ = average steady-state concentration.
[a]Use actual body weight if less than ideal body weight.
[b]Cl_{cr} calculated by using actual body weight and normalized to body surface area (ml/min/1.73 m^2).

1 MIU CMS = 80 mg CMS = 30 mg CBA

Ortwine JK et al.: Pharmacotherapy, 2015; *Plachouras D et al.: Antimicrob Agents Chemother, 2008*
Garonzik SM et al.: Antimicrob Agents Chemother, 2011

PK/PD mathematic model of colistin dosing

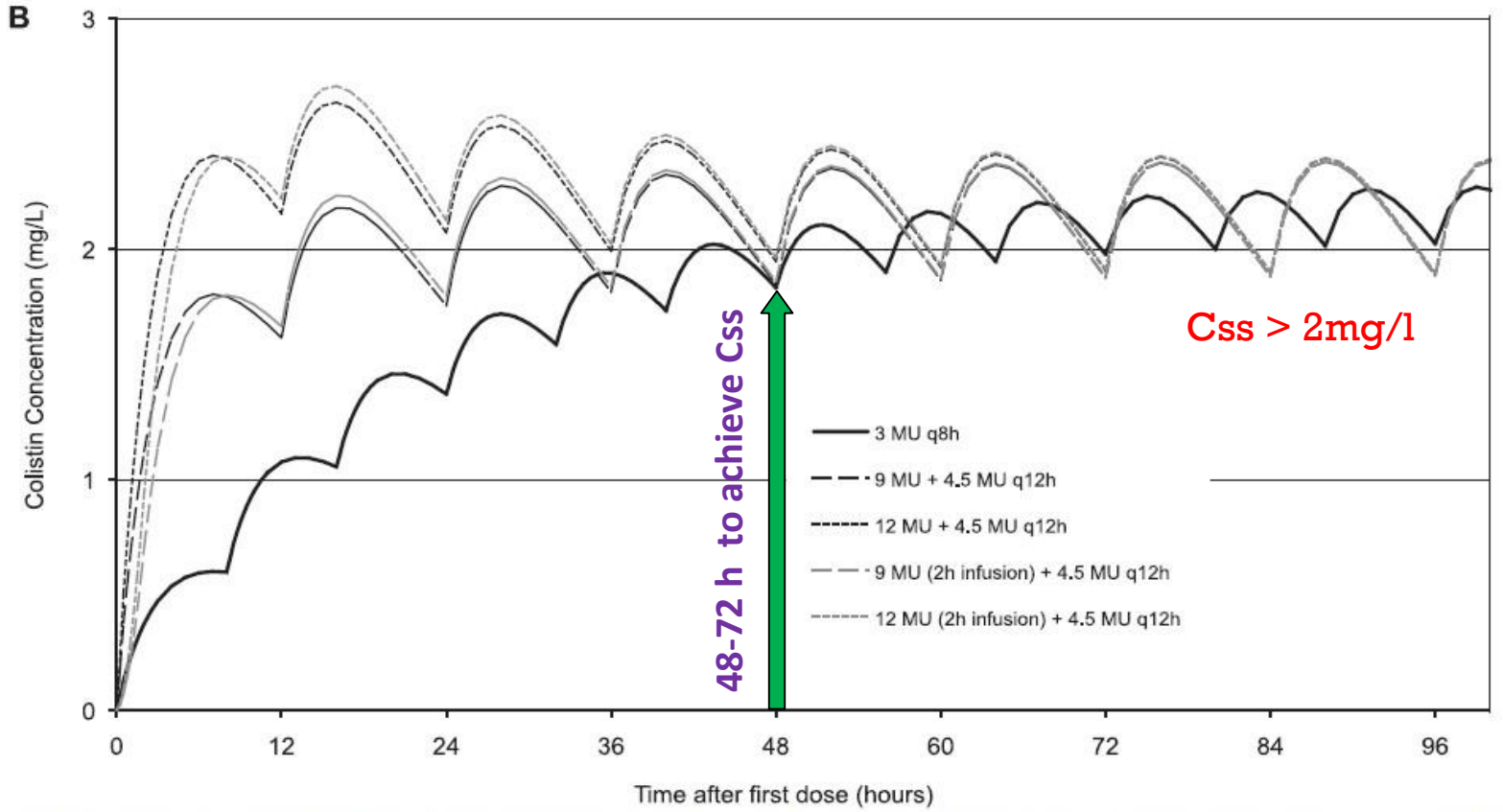


FIG. 4. Model-predicted CMS (A) and colistin (B) concentrations in a typical patient following the use of the current dosing regimen (3 MU as a 15-min infusion of CMS every 8 h [q8h]) and alternative dosing regimens with loading doses of 9 or 12 MU CMS as infusions of 15 min or 2 h and a maintenance dose of 4.5 MU CMS every 12 h (q12h).

Conclusion:

need of a LD 9 – 12 MIU, maintenance dose 4,5 MIU every 12 hours

Plachouras et al.: Antimicrob Agents Chemother, 2008

Colistin dosing in renal impairment

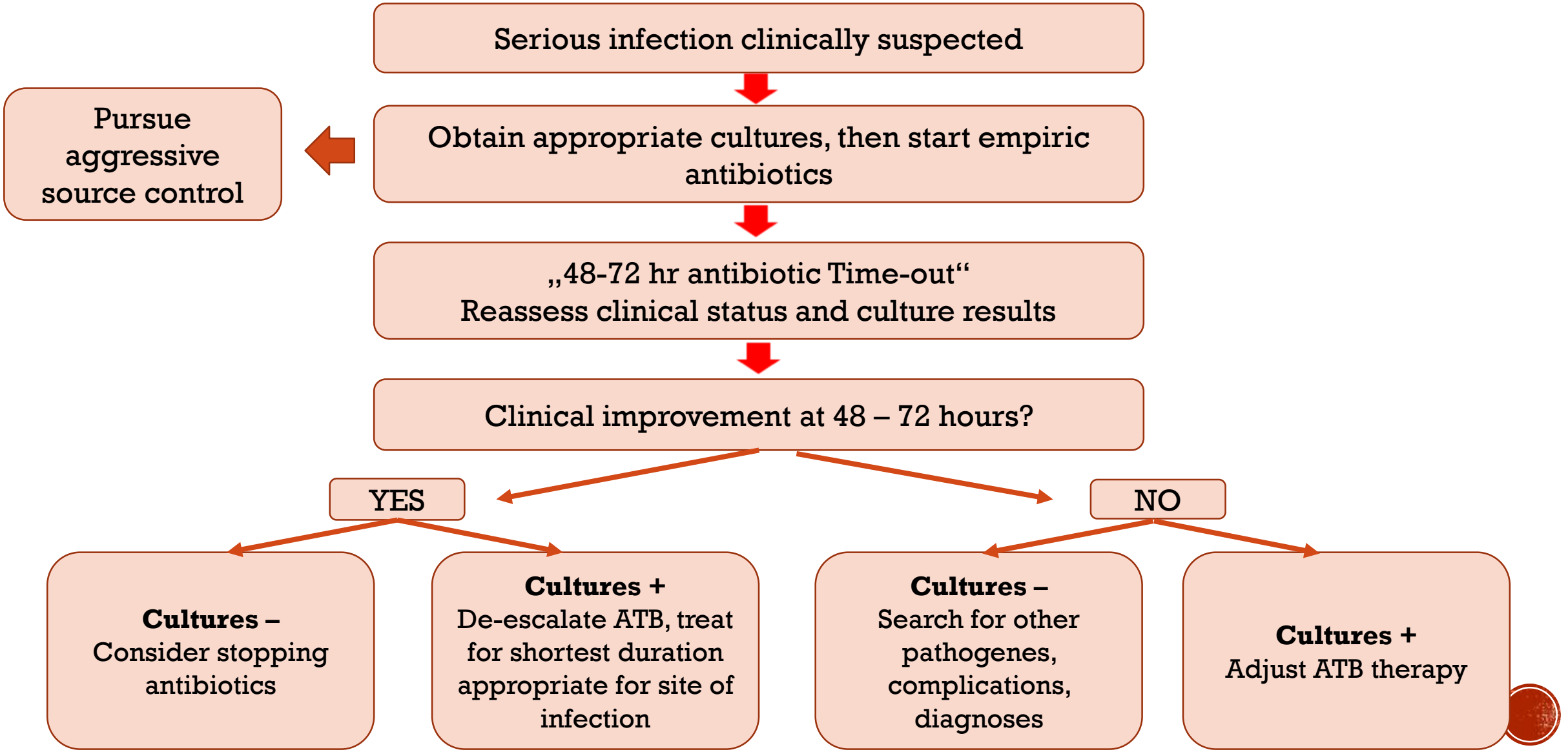
Clcr	Daily dose of CMS
30 – 50 ml/min	5,5 – 7,5 MIU
10 – 30 ml/min	4 – 5,5 MIU
< 10 ml/min	2 - 3,5 MIU

No reduction in CRRT (*Karvenen 2013*), or even higher dosing: LD 9 – 12 MIU, maintenance dose 4,5 MIU q 8h OR 6,5 MIU q 12 hours (*Karaiskos 2016*).

- elimination in CRRT greater than in patients with normal renal function

Michalopoulos et al.: Annals of intensive Care, 2011
Garonzik et al.: Antimicrob Agents Chemother,2011
Gauthier et al.: Antimicrob Agents Chemother, 2012; Dalfino et.al.: Clin Infect Dis. 2012;
Karvenen M et al.: Antimicrob Agents Chemother, 2013; Visser Kift et al.: SAMJ March 2014; EMA 2014

De-escalation when culture results are available



De-escalation of antibiotic therapy

- Application of this strategy is problematic
  - Absence of microbiological results
  - Isolation of multi-resistant pathogens preventing de-escalation
  - Reluctance of some clinicians to change antibacterials in patients with a favorable clinical course
- A systematic review of 493 studies concluded that there was not sufficient evidence to determine whether de-escalation of antibiotic agents was effective and safe for adults with sepsis
- Despite limitations, antimicrobial de-escalation therapy has been recommended
  - ATS guideline for the management of adults with hospital acquired, ventilator associated, and healthcare associated pneumonia, AJRCCM 2005;171:388-416

Shortening the duration of antibiotic therapy

- the optimal duration of ATB therapy for bacteremia is unknown
- long antibiotic courses are associated with
  - MDR pathogen selection and spread
  - increased risks of toxicity
  - higher costs
- too short courses may lead to inadequate bacterial eradication and relapse
- current guidelines advise a 7–10 day course, unless poor prognosis predictors are present (e.g., initial clinical failure, undrainable foci of infection)

Vincent J-L, Bassetti M, François B, et al (2016) Advances in antibiotic therapy in the critically ill. Crit Care 20:133

Shortening the duration of antibiotic therapy

- A systematic review of 24 studies that compared a shorter (5–7 day) regimen versus a longer (7–21 day) antibiotic course for critically ill patients with various infections identified no differences in terms of clinical cure, microbiological eradication, or survival.

Study or Subgroup	Short Duration Events	Total	Long Duration Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chaudhry	5	6	7	8	29.3%	0.95 [0.61, 1.48]
Runyon	9	9	15	17	54.1%	1.10 [0.87, 1.39]
Siegel	1	2	4	4	16.5%	0.56 [0.17, 1.79]
Total (95% CI)		**17**		**29**	**100.0%**	**0.97 [0.76, 1.23]**
Total events	15		26			

Heterogeneity: Chi² = 2.07, df = 2 (P = 0.36); I² = 3%
Test for overall effect: Z = 0.26 (P = 0.79)

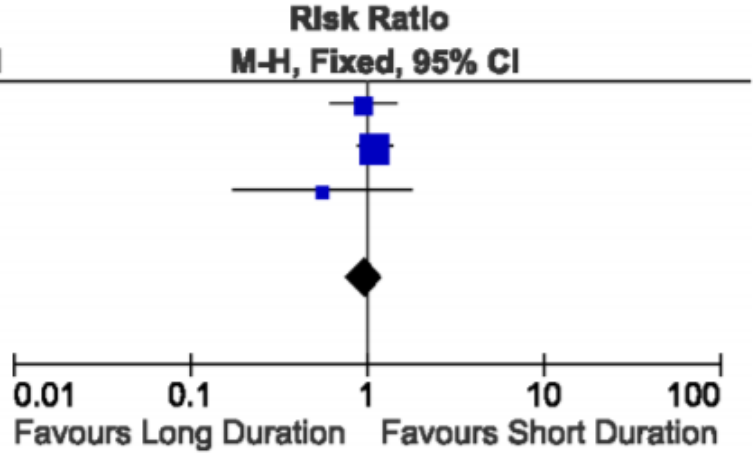
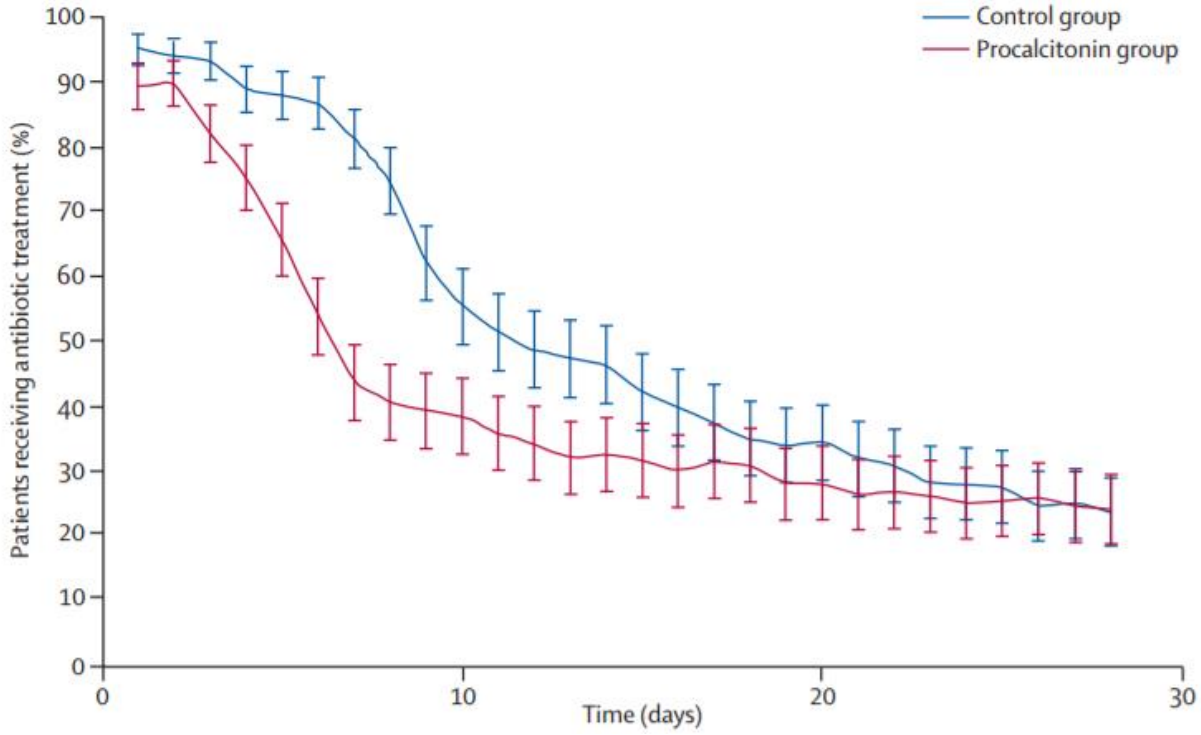


Figure 4 Forest plot for outcome of survival among bacteremic subgroups of randomized trials of shorter versus longer antibiotic treatment. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

Havey TC, Fowler RA, Daneman N (2011) Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care Lond Engl 15:R267

PRORATA trial – PCT guided duration of ATB therapy

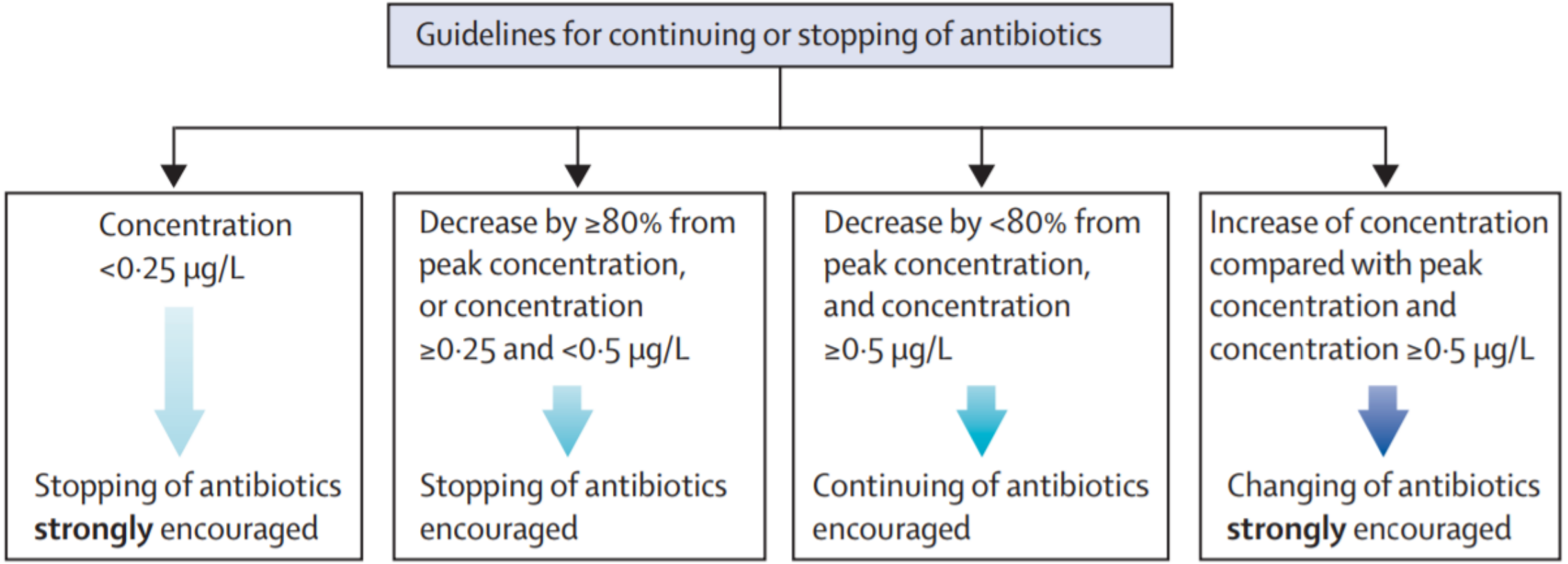
	Procalcitonin group (n=307)	Control group (n=314)	Between-group absolute difference	p value
Primary endpoints				
28-day mortality*	65 (21·2%)	64 (20·4%)	0·8% (–4·6 to 6·2)	NA
60-day mortality*	92 (30·0%)	82 (26·1%)	3·8% (–2·1 to 9·7)	NA
Number of days without antibiotics	14·3 (9·1)	11·6 (8·2)	2·7 (1·4 to 4·1)	<0·0001



- significantly fewer patients assigned to the PCT group received ATB than did those assigned to the control group
- no significant difference in survival between the two groups

Bouadma L et al (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. The Lancet 375:463–474

PCT guided duration of ATB therapy



Bouadma L, Luyt C-E, Tubach F, et al (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. The Lancet 375:463–474

Antibiotic combinations

- irrational use can worsen the already alarming scenario of antibiotic resistance
- appropriate in empirical regimens (organism unknown) to cover all possibble pathogens
- used in critically ill patients due to widespread emergence of multidrug resistant organisms (MDRO)
  - MDRO = resistant to at least 1 agent in 3 or more ATB categories
- fixed dose ATB combination?

trimetoprim/sulfamethoxazole = Cotrimoxazole

  - sulfamethoxazole -> inhibits bacterial synthesis of dihydrofolic acid
  - trimethoprim -> blocks production of tetrahydrofolic acid
  - blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to bacteria

Rationale for combination therapy

- synergy or additivity
- decrease resistance
- broaden spectrum

- Synergy:
  - Penicillin + Gentamicin
    - penicillin is bacteriostatic against enterococci
    - aminoglycosides are inactive against enterococci
    - combination is bactericidal
    - issues with administration (incompatibility)

Rifampicin

- **no indication for monotherapy**

Adding rifampicin to combinations

- PROs
  - highly active against S.aureus
  - excellent tissue penetration
- CONs
  - Significant adverse effects (increased transaminases & drug interactions)
  - Rapid resistance development (21% of patients with S. aureus native-valve endocarditis)

Levine DP, Intern Med 1991;115:674-80.
Cosgrove S, Clin Infect Dis. (2008) 46 S386-S393.

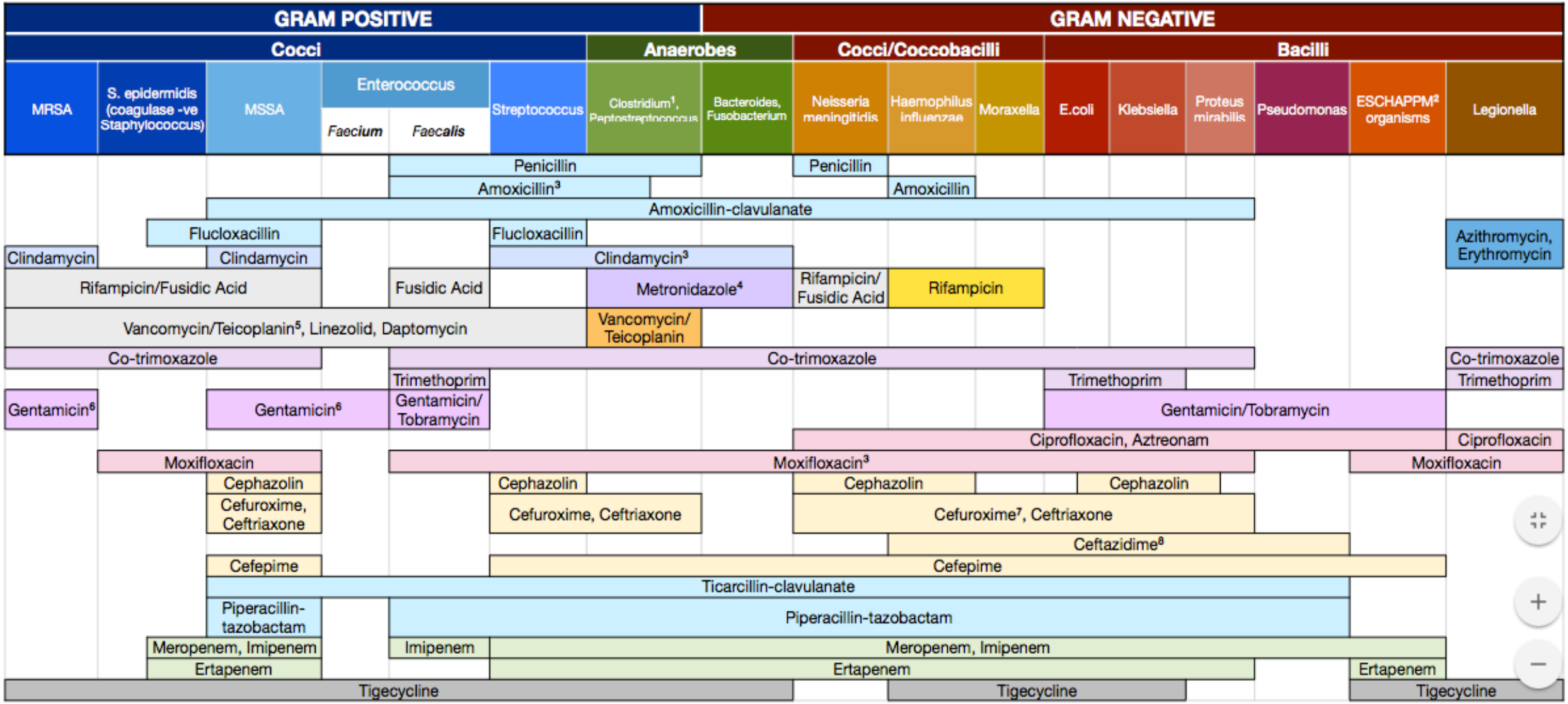
Case 4

- Patient 86 years, male, admitted to the ICU for respiratory failure
- Suspected pneumonia and flu – empiric ATB treatment started: amoxicillin/clavulanate + clarithromycin + oseltamivir
- 3rd day – Staph. aureus (MSSA) in hemocultures
  - PCR positive for FLU
- ATB center recommended oxacillin + linezolid, continue with oseltamivir

Do you agree with the combination of ATB?

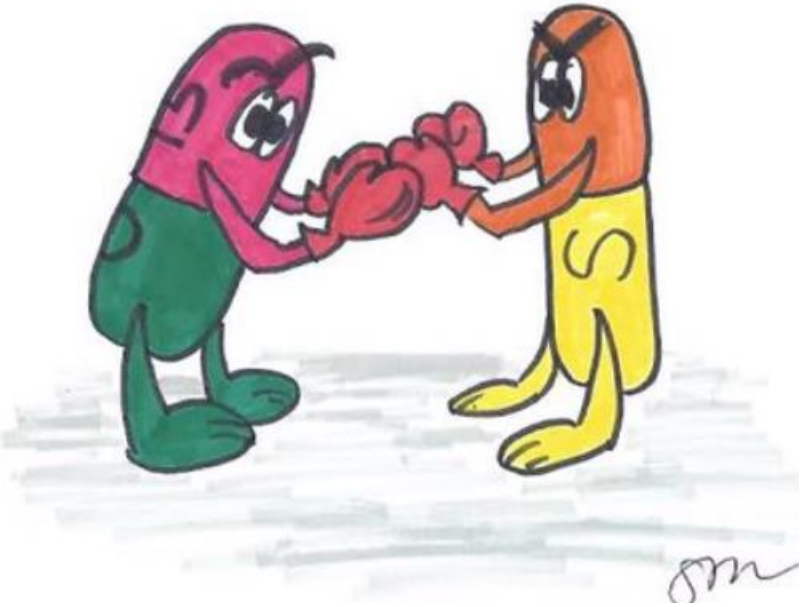
Do you have different suggestion?

ANTIBIOTIC SUSCEPTIBILITIES IN INTENSIVE CARE*



Wellington ICU Antibiotic Summary. In: Scribd. https://www.scribd.com/document/360193700/Wellington-ICU-Antibiotic-Summary. Accessed 17 Mar 2018

Drug interactions with antibiotics



- linezolid x serotonergic drugs
  - linezolid is an IMAO
  - increased risk of serotonin syndrome
- clarithromycin x CYP3A4 and P-gp substrates
  - increase in drug levels (statins, warfarin, ticagrelor…)
  - decrease the formation of active substance in case of clopidogrel (prodrug)
- Rifampicin x CYP3A4 and P-gp substrates
  - decrease in drug levels (statins, warfarin, ticagrelor, clarithromycin, valproate…)

Drug interactions – What you should know. [cited 2018 Apr 15]. Available from: https://thedrugcode.wordpress.com/2016/07/12/drug-interactions-what-you-should-know-%F0%9F%92%8A/

Case 5

- 63 years old man with a history of stroke and COPD admitted to the hospital for pneumonia empirically treated with
  - ampicillin/sulbactam + clarithromycin
  - theophylline, salbutamol + ipratropium for spasticity
- transferred to ICU for status epilepticus

What might be the cause of the seizures?

Case 5

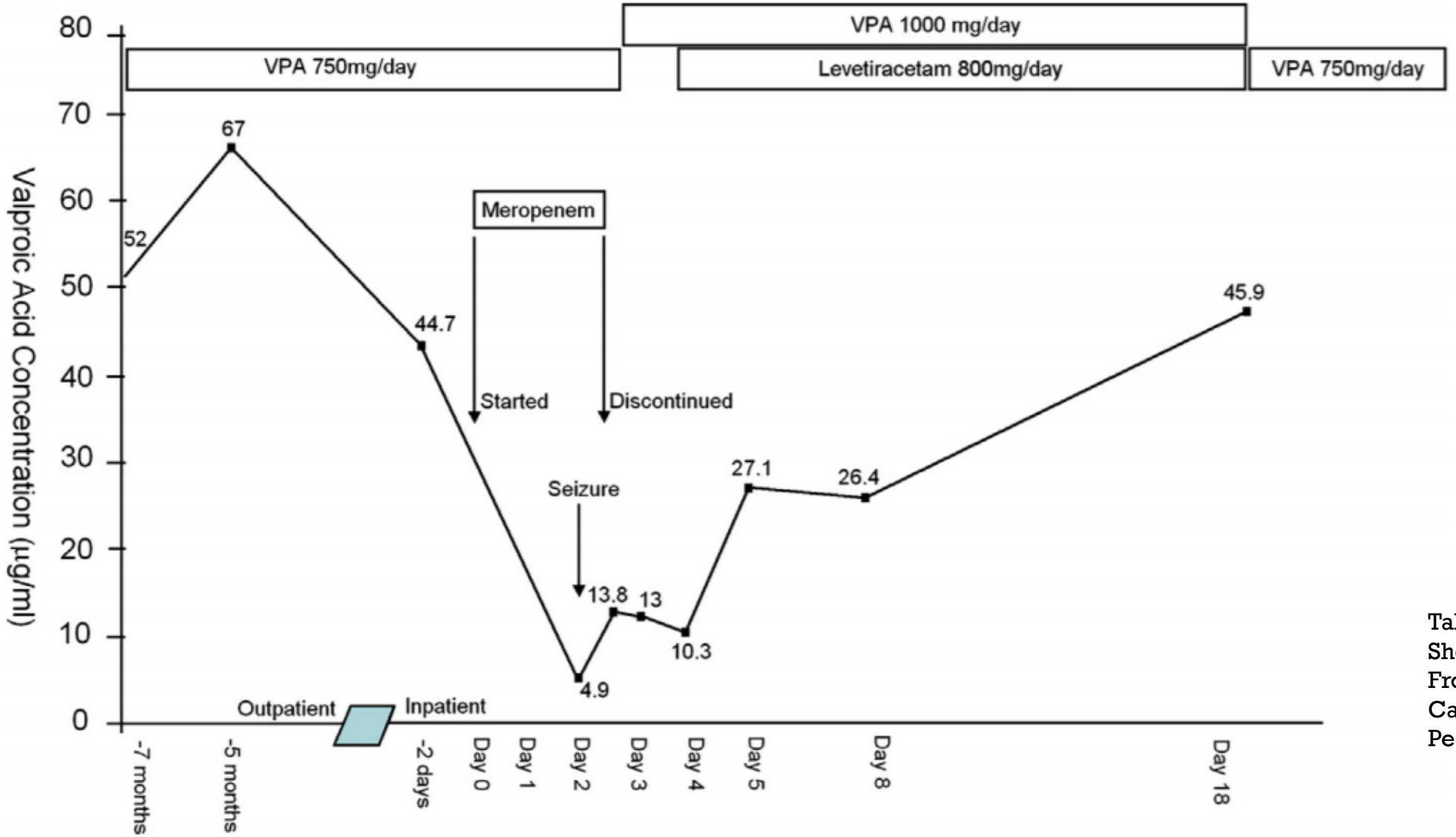
- 63 years old man with a history of stroke, admitted to the hospital for pneumonia empirically treated with ampicillin/sulbactam + clarithromycin, theophylline, salbutamol + ipratropium
- transferred to ICU for status epilepticus
  - level of theophylline in therapeutic range
  - antibiotic doses suitable for the patient
- valproate was initiated with good response
- after 2 days ATBs switched to meropenem (KLPN ESBL in cultures)
- 2 days later there was a rapid drop in valproate serum concentrations, subtherapeutic levels even after doses of 5g/day of valproate

What was the cause and how to deal with it?

Valproate x carbapenems interaction

- significant reduction in valproate serum concentration
- Possible mechanisms of the interaction
  - induction of the formation of valproate-glucuronide in the liver and inhibition of its hydrolysis to active valproate?
  - increasing the renal elimination of VPA-glucuronide?
- Management of the interaction
  - stopping the carbapenem is not enough
  - it may take 5 to 14 days to achieve therapeutic drug concentrations of valproate after carbapenem discontinuation
  - switch to another antiepileptic drug (levetiracetam)

Valproate x carbapenems interaction



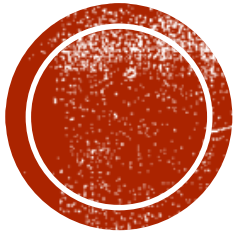
Taha FA, Hammond DN, Sheth RD (2013) Seizures From Valproate–Carbapenem Interaction. Pediatr Neurol 49:279–281

Take home message

- Early administration of adequate ATB at sufficient dose is crucial for the treatment of sepsis and positively influences the outcome of the patient
- Given that most antibiotic regimens have been derived from trials with patients who are not critically ill, there are often required higher doses of ATBs in the critically ill
- To optimize dosing, the antibiotic's pharmacodynamic properties, as well as the potential altered antibiotic pharmacokinetics, need to be considered by the clinician
- Do not reduce the antibiotic dose within the first 24 – 48 hours in case of acute renal or hepatic failure
- Therapeutic drug monitoring based on the serum levels, if possible, should be attempted.

Recommended literature

- Gilbert DN MD, Eliopoulos GM MD, Chambers HF MD, et al (2017) The Sanford Guide to Antimicrobial Therapy 2017, 47 edition. Antimicrobial Therapy
- Blot SI, Pea F, Lipman J (2014) The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 77:3–11
- Roberts JA, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37:840–851; quiz 859.
- Blot S, Lipman J, Roberts DM, Roberts JA (2014) The influence of acute kidney injury on antimicrobial dosing in critically ill patients: are dose reductions always necessary? Diagn Microbiol Infect Dis 79:77–84.
- Lewis SJ, Mueller BA (2014) Antibiotic dosing in critically ill patients receiving CRRT: underdosing is overprevalent. Semin Dial 27:441–445.



THANK YOU FOR YOUR ATTENTION

adriana.papiez@fnusa.cz