Interactive Part – clinical cases – PK/PD

Optimal dosing of antibiotics: insights anno 2019

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EAHP Academy Seminars
20-21 September 2019

CONFLICT OF INTEREST

THERE ARE NO CONFLICTS OF INTEREST TO DECLARE

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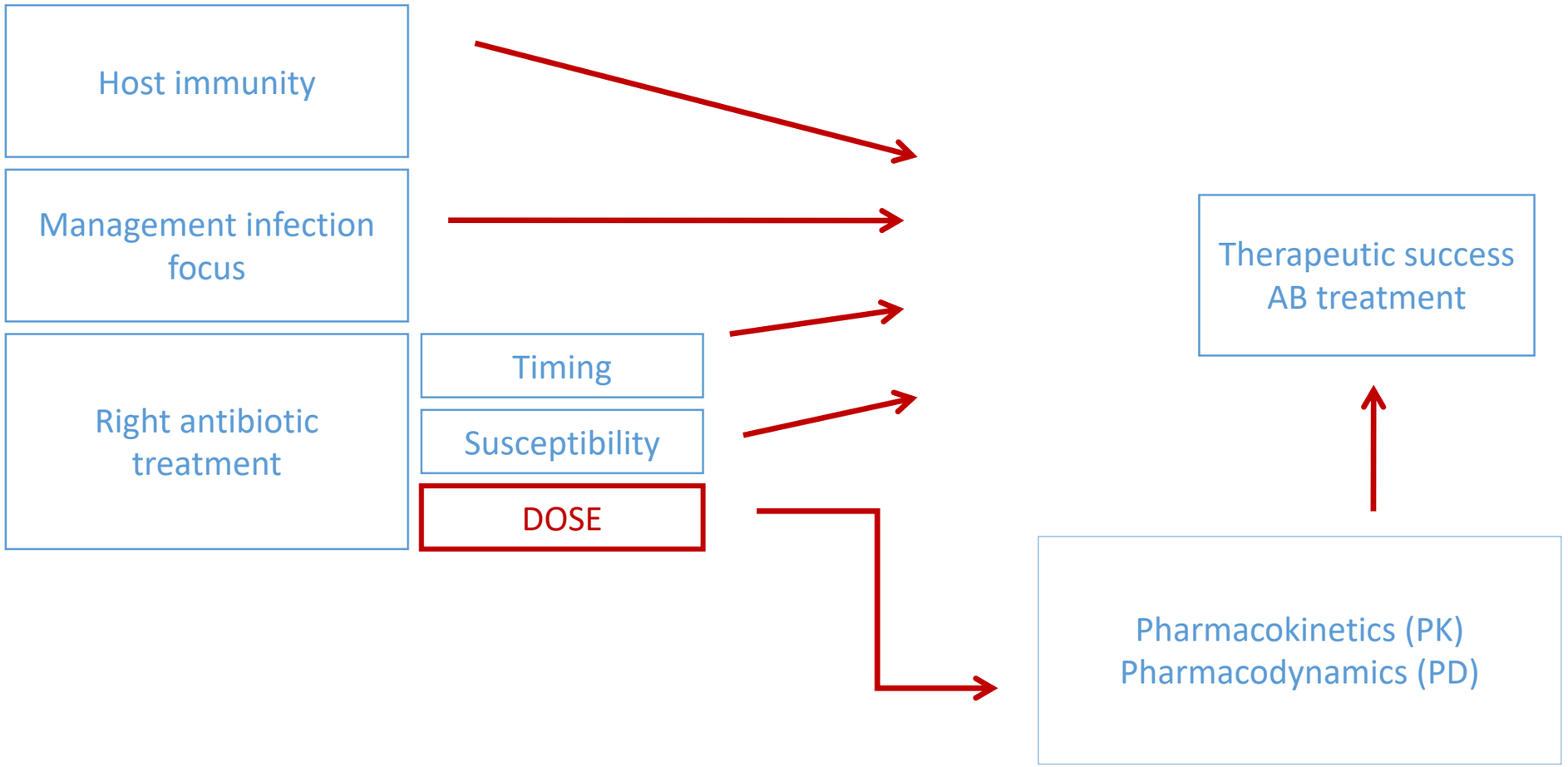
Voting

- Log on to PollEv.com/isabelspriet326

Content

- **Introduction**
- Applying AB dosing in clinical practice: case-based discussion

Introduction



Introduction: the special case of antibiotics

Host + Pathogen = Infection

AB concentrations should be

- ✓ **sufficient <u>to kill the bug</u>**
- ✓ **sufficient <u>to attain the infected tissue</u>**
  (e.g. lung, brain, abdomen…)
- ✓ **not to be too <u>high to avoid toxic effects</u>**

Introduction: current challenges in antibiotic prescribing

DE ANTIBIOTICACRISIS

Valt resistentie in de geneeskunde en de landbouw nog te bestrijden?

En op het einde winnen de bacteriën

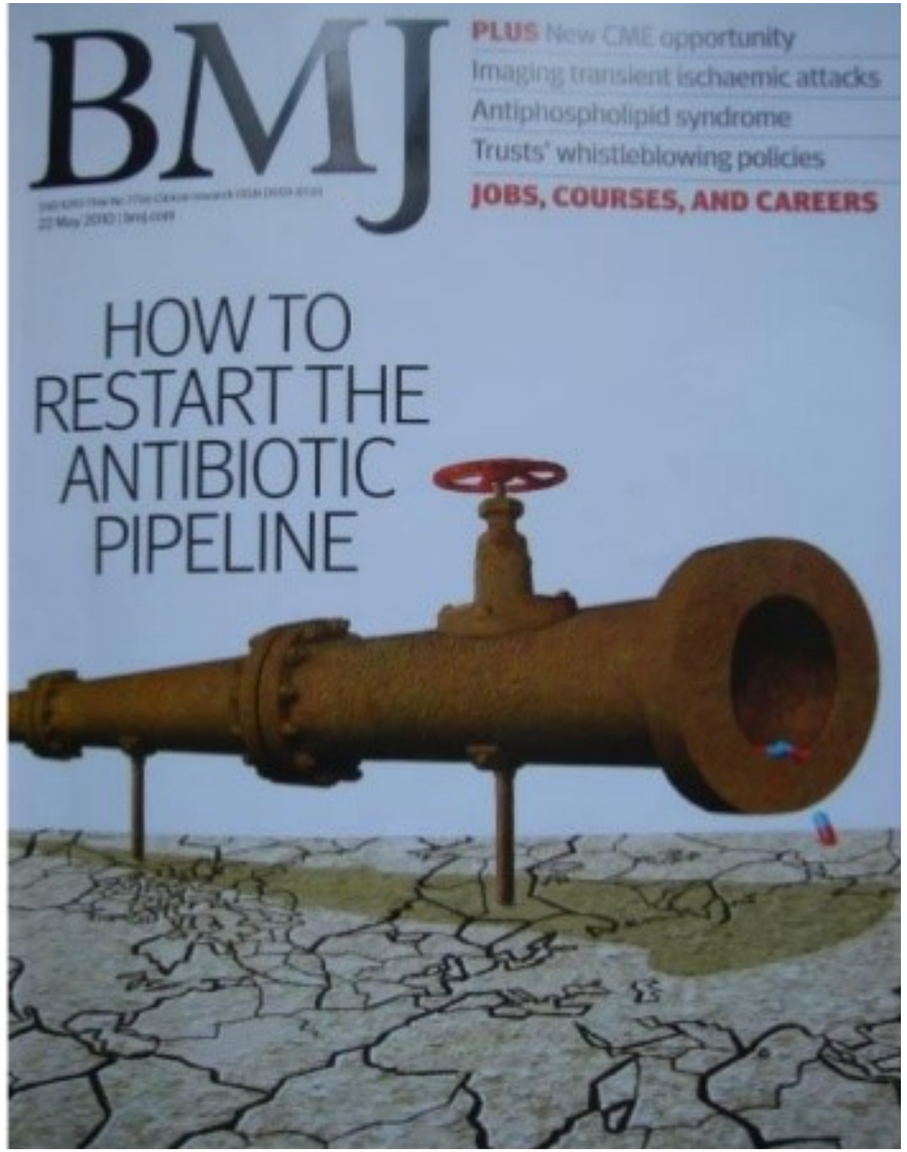
Door menselijke overmoed is het helaas de regel geworden: bacteriën, schimmels, insecten en zogenaamde onkruiden die resistent worden tegen bestrijdingsmiddelen. Nu de farmaceutische industrie de handdoek in de ring lijkt te gooien, dreigen infectieziektes vrij spel te krijgen.

Door *DIRK DRAULANS*

Knack

>> Increasing bacterial resistance

Introduction: current challenges in antibiotic prescribing

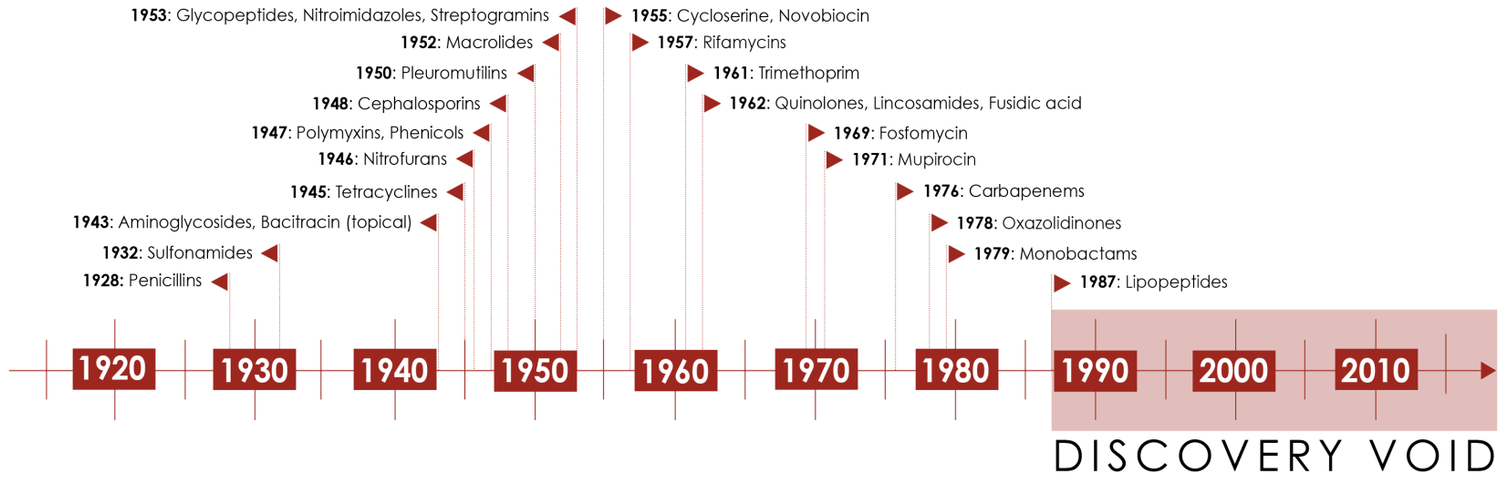


>> “Lack” of new antibiotics

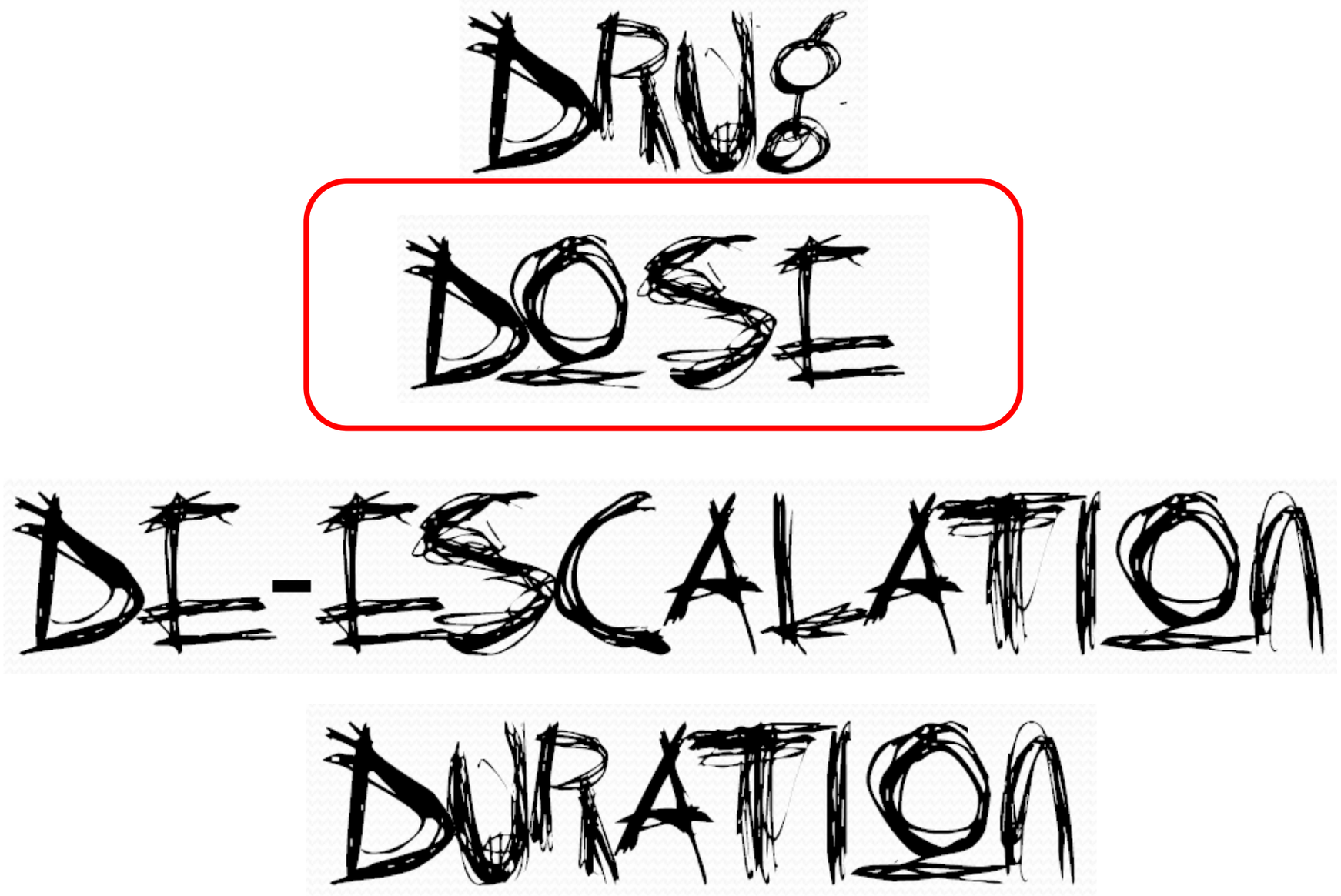
2009-2019:

- **Fidaxomycin**
- **Ceftaroline**
- **Ceftazidim-avibactam**

- Ceftolozane-tazobactam
- Isavuconazole

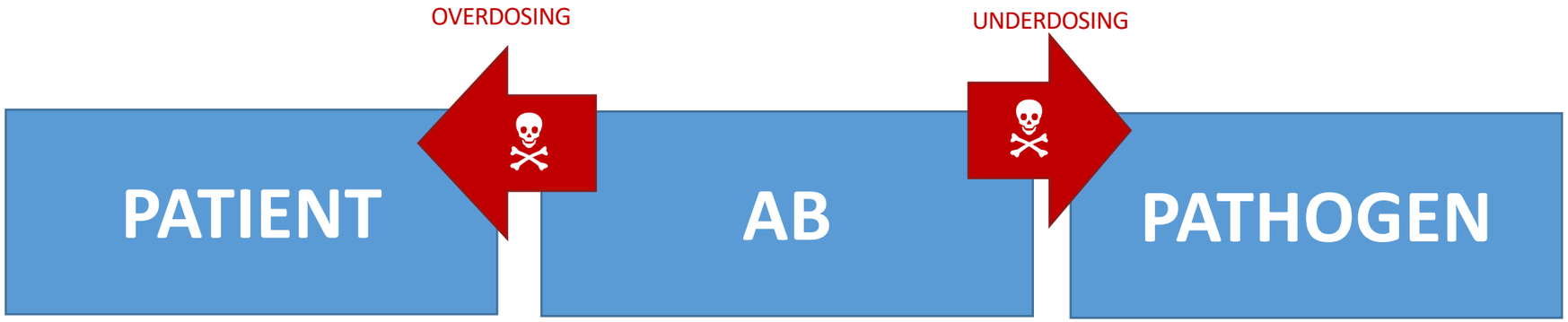


Introduction: correct use of antimicrobials: the “4D strategy”



Slide Courtesy Dr. Niels van Regenmortel, ZNA

Introduction: “4D strategy”: the right dose

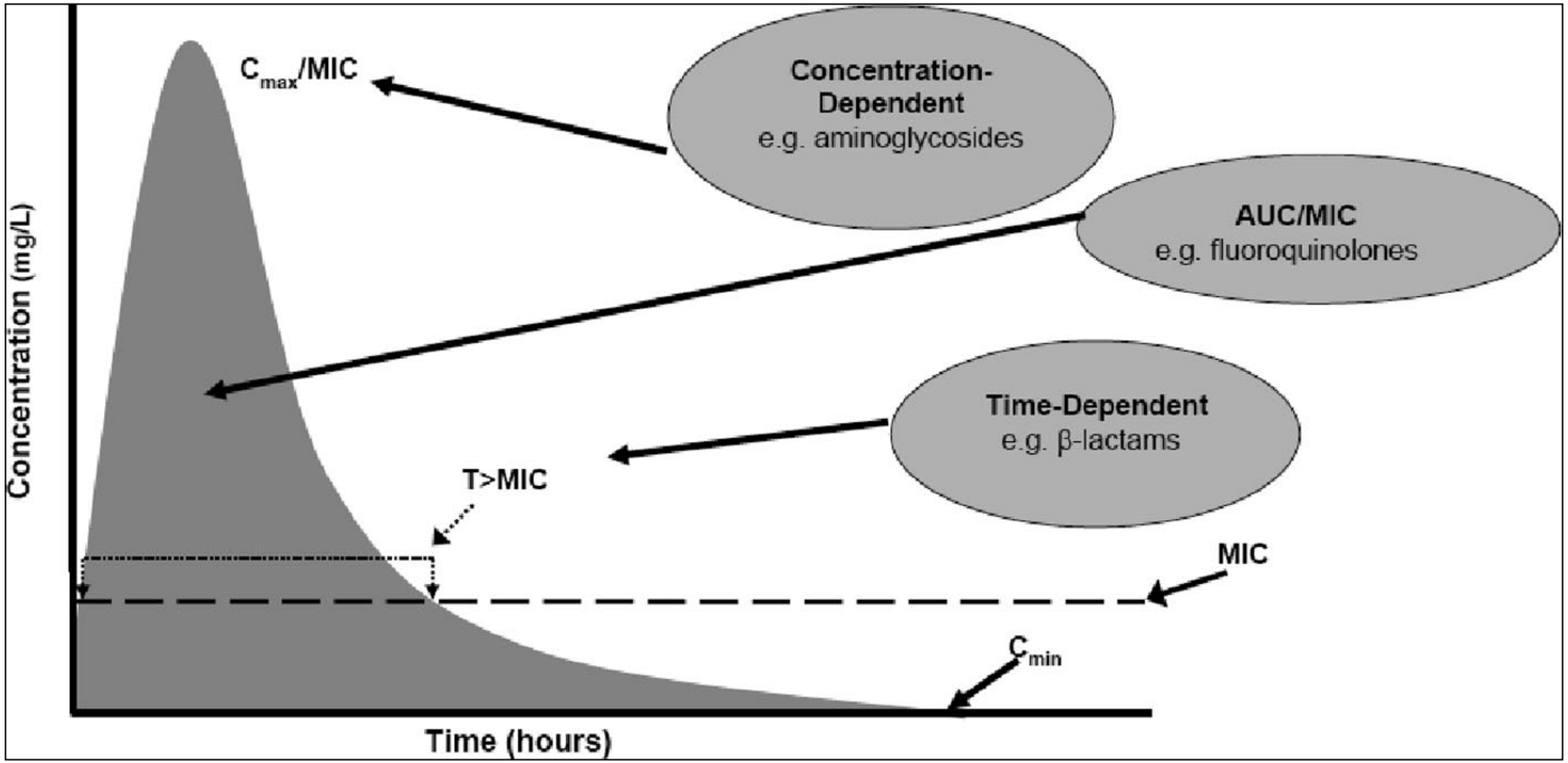


Volume of distribution
Clearance
Tissue penetration
Protein binding

Minimal inhibitory Concentration (MIC)
“Kill characteristics”

Defining the dose =
finding a balance between
overdosing **(toxicity) vs.** ***underdosing*** **(therapeutic failure and resistance development)**

Introduction: “4D strategy”: the right dose



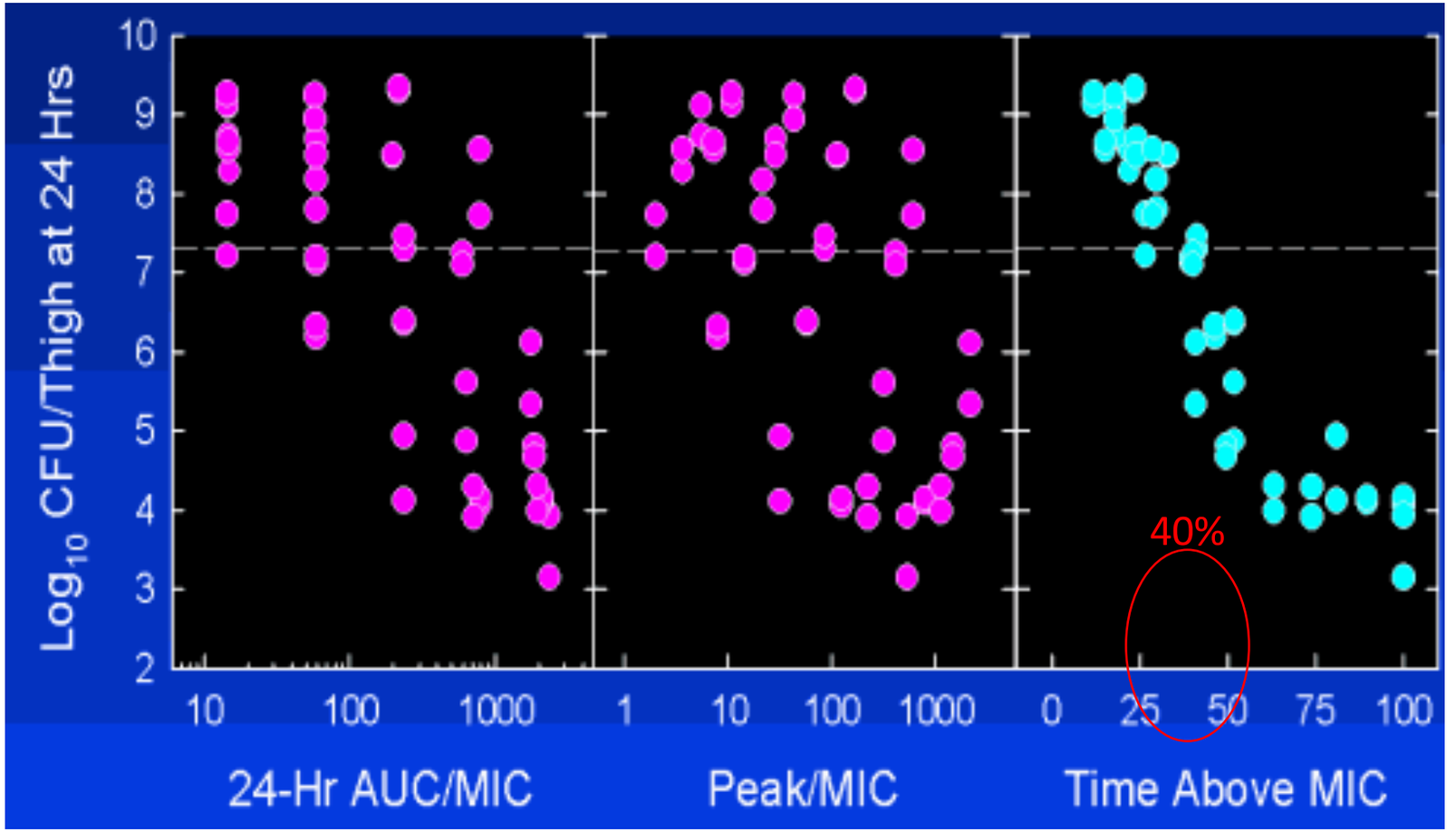
Antibiotics are classified in function of PK/PD target

Figure is adapted from Roberts et al. (2009). *Crit Care Med*

Introduction: “4D strategy”: the right dose

Which PK/PD target? Magnitude of the PK/PD target?

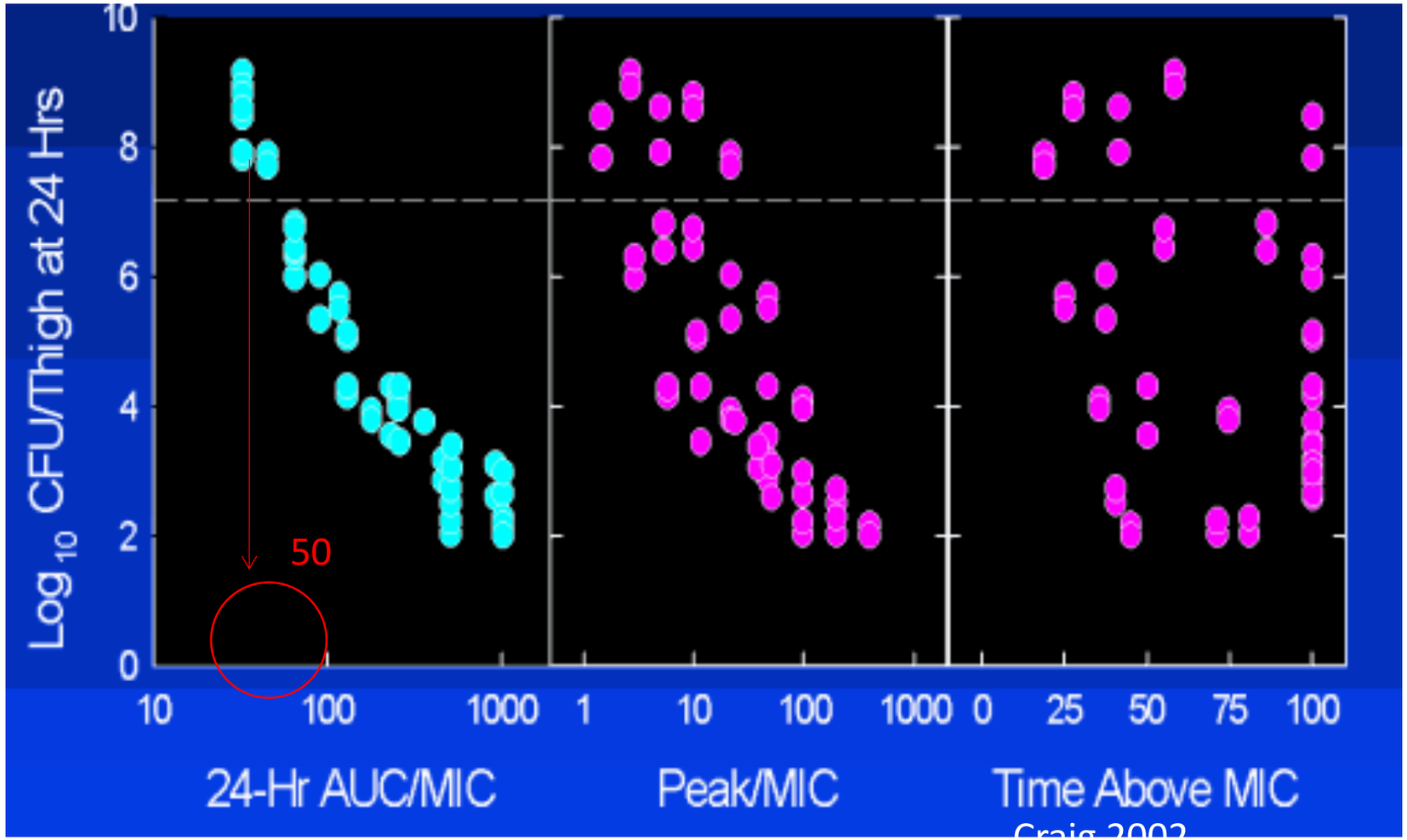
Bacterial eradication & **ceftazidime** dose (mouse -pneumonia model - *K. pneumoniae)*



Introduction: “4D strategy”: the right dose

Which PK/PD target? Magnitude of the PK/PD target?

Bacterial eradication & **temofloxacin** dose (neutropene mouse - *S. pneu* thigh abces)



Craig 2002

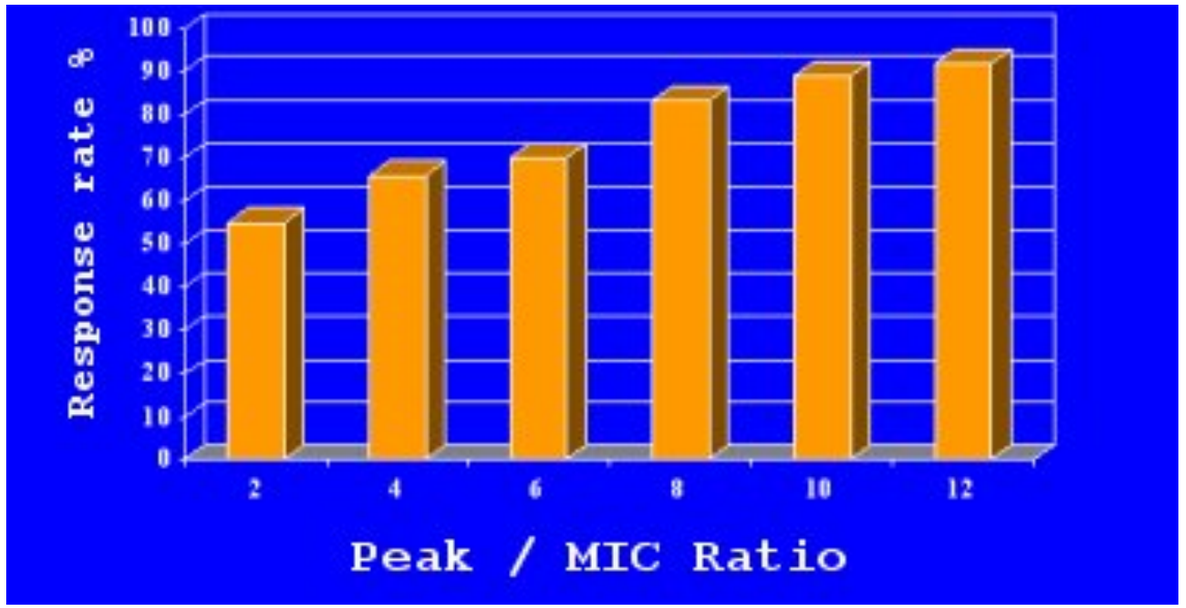
Introduction: “4D strategy”: the right dose

These findings in animal models were confirmed in patients…

J Infect Dis. 1987 Jan;155(1):93-9.

Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration.

Moore RD, Lietman PS, Smith CR.



Relation between Cmax/MIC and clinical response: Cmax/MIC ~10

→ Switch 3 x 1 mg/kg per day to 1 x 5 mg/kg per day

Introduction: “4D strategy”: the right dose

Antimicrobial PKPD – targets & magnitude - knowledge anno 2019

	Preclinical studies		Clinical studies	
Concentration-dependent				
Aminoglycosides	Maximum killing[43]	AUC_{0-24}/MIC 80–100	Clinical cure[82-86]	C_{max}/MIC 8–10; AUC/MIC >70
	Resistance suppression[87]	C_{max}/MIC 10–30	Microbiological cure	..
Time-dependent				
Carbapenems	Maximum killing[88]	40% $T_{>MIC}$	Clinical cure[89]	75% $T_{>MIC}$; C_{min}/MIC 5
	Resistance suppression[90, 91]	16 × MIC; C_{min}/MIC >6·2	Microbiological cure[17]	54% $T_{>MIC}$
Cephalosporins	Maximum killing[11]	60–70% $T_{>MIC}$	Clinical cure[92]	100% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[16,93]	60–100% $T_{>MIC}$; 95% $T_{>4·3×MIC}$
Penicillins	Maximum killing[11]	40–50% $T_{>MIC}$	Clinical cure	..
	Resistance suppression[94]	40–50% $T_{>MIC}$	Microbiological cure[95]	40–50% $T_{>MIC}$
Concentration-dependent and time-dependent				
Fluoroquinolones	Maximum killing[11,96]	AUC_{0-24}/MIC >30–100	Clinical cure[15,86,96,97,98]	AUC_{0-24}/MIC ≥125–250; C_{max}/MIC ≥8
	Resistance suppression[99,100,101]	AUC_{0-24}/MIC >160; AUC_{0-24}/MPC ≥22	Microbiological cure[14,86,102]	AUC_{0-24}/MIC ≥34–125; C_{max}/MIC ≥8
Vancomycin	Maximum killing[103]	AUC_{0-24}/MIC 86–460	Clinical cure[20,21]	AUC_{0-24}/MIC ≥400–450
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure[20]	AUC_{0-24}/MIC ≥400
Linezolid	Maximum killing	..	Clinical cure[22]	AUC_{0-24}/MIC ≥85; 85% $T_{>MIC}$
	Resistance suppression	..	Microbiological cure[22]	AUC_{0-24}/MIC 80–120; 85% $T_{>MIC}$
Tigecycline	Maximum killing[105]	50% $T_{>MIC}$	Clinical cure[106,107,108]	AUC_{0-24}/MIC >12·8–17·9; *f* AUC_{0-24}/MIC ≥0·9
	Resistance suppression	..	Microbiological cure[109,110]	AUC_{0-24}/MIC 6·9–17·9
Daptomycin	Maximum killing[111,112]	AUC_{0-24}/MIC 38–442	Clinical cure	..
	Resistance suppression[104]	AUC_{0-24}/MIC >200	Microbiological cure	..
Colistin	Maximum killing[113,114]	AUC_{0-24}/MIC 7–23	Clinical cure	..
	Resistance suppression	..	Microbiological cure	..

AUC_{0-24}/MIC=ratio of area under the concentration time curve from 0 to 24 h to minimum inhibitory concentration. C_{max}/MIC=ratio of maximum concentration of antibiotic in a dosing interval to minimum inhibitory concentration. $T_{>MIC}$=percentage of dosing interval that the antibiotic concentration is maintained above the minimum inhibitory concentration. AUC_{0-24}/MPC=ratio of the AUC_{0-24} to the concentration that prevents mutation. C_{min}=minimum concentration of antibiotic in a dosing interval, *f*=free concentration or fraction of drug not bound to plasma proteins. *Where the index is reported as a range, data included might have been derived from different infection models with different bacteria. Specific data for the contributing values can be found in the associated references. Data for the various indices has been reported in different studies according to total and free (unbound) concentrations of drug.

***Table 1*: Studies reporting pharmacokinetic/pharmacodynamic indices from preclinical and clinical assessments, by antibiotic class**

Adapted from Roberts JA et al. (2014). *Lancet Infect Dis*

Introduction: “4D strategy”: the right dose

- ‘one dose fits all’ → PERSONALIZED DOSING
  - Infection focus (e.g. musculoskeletal vs. urinary tract infection)
  - Patiënt characteristics (renal function, volume of distribution (capillary leak), …)

- ultimate personalized dosing = TDM-based dosing
  - Vancomycin, aminoglycosides, voriconazole, posaconazole
  - Increasing interest: beta-lactams, colistin, …

Introduction: “4D strategy”: the right dose

Shift from standard “one size fits all dose” to “personalized dosing”

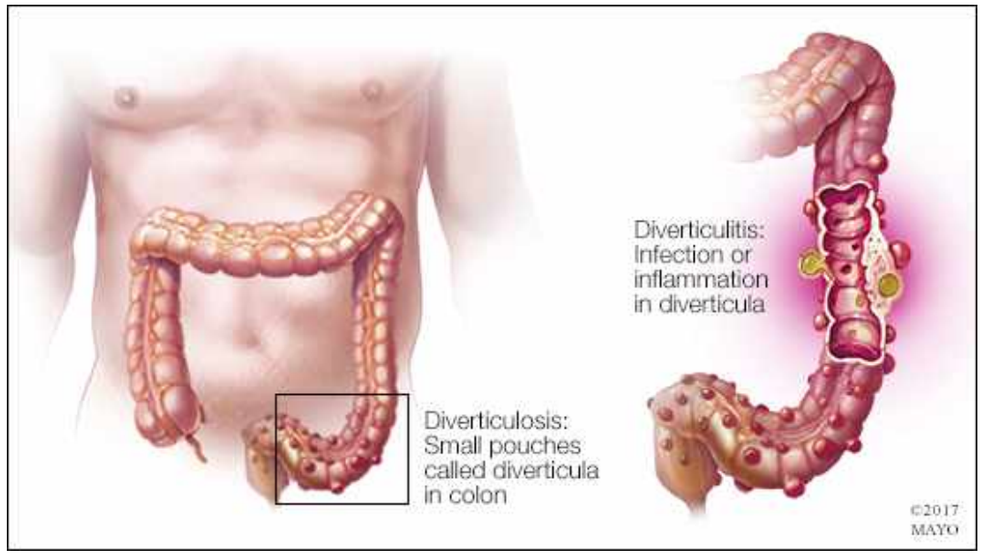
WHICH ANTIBIOTIC DOSE SHOULD BE USED?

Content

- Introduction
- **Applying AB dosing in clinical practice: case-based discussion**

Case 1: dosing amoxicillin-clavulanic acid in intra-abdominal infections (IAI)

- Man, 60 yrs old; 75 kg; 1,78m; BMI: 23,6 kg/m²
- eGFR (CKD-EPI): 93 ml/min/1,73m²
- Reason for admission: colon-diverticulitis



- R/ **amoxicillin-clavulanic acid IV**

Which dose and dosing frequency should be applied for IV amoxicillin-clavulanic acid?

Case 1: Dosing amoxiclav in IAI?

Amoxicillin-clavulanic acid 1.2g q6h

Amoxicillin-clavulanic acid 1.2g q4h

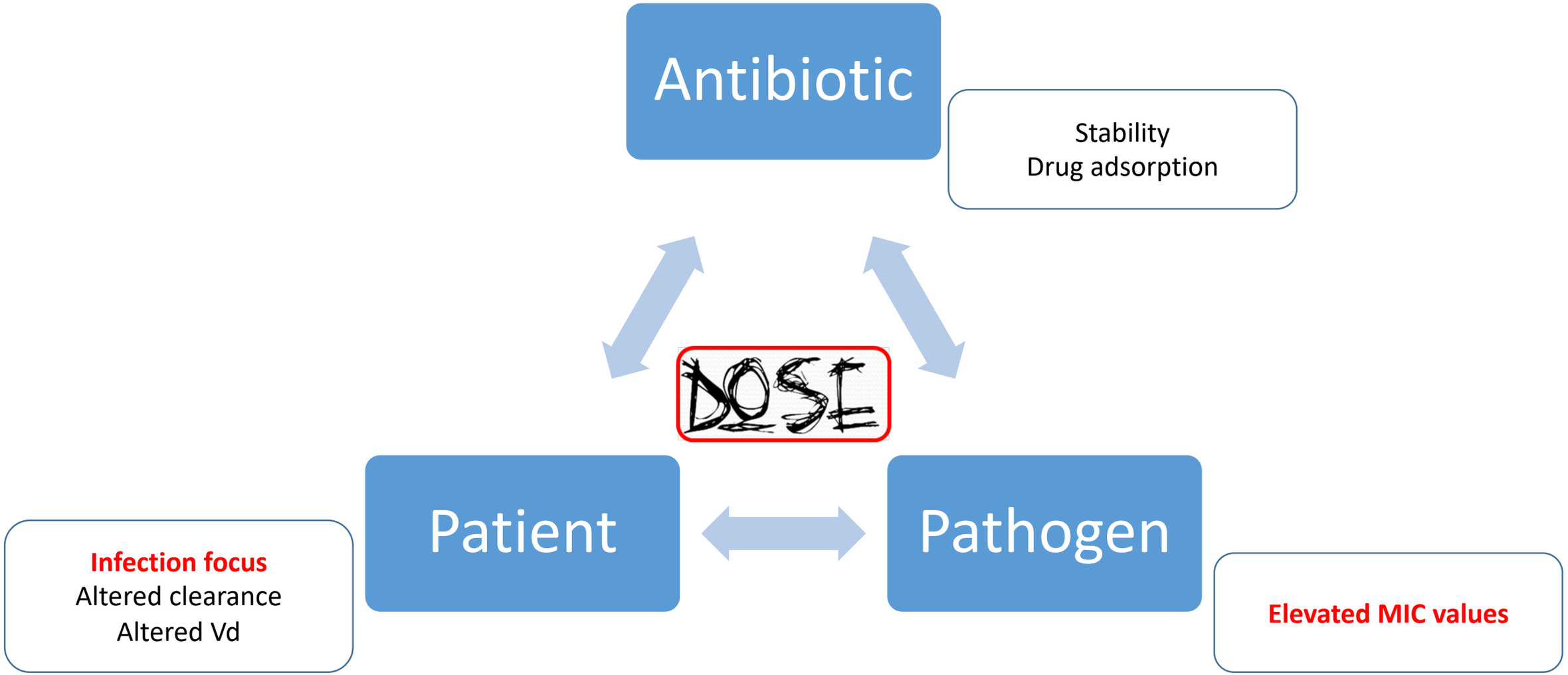
Amoxicillin-clavulanic acid 2.4g q6h

All of the above are possible

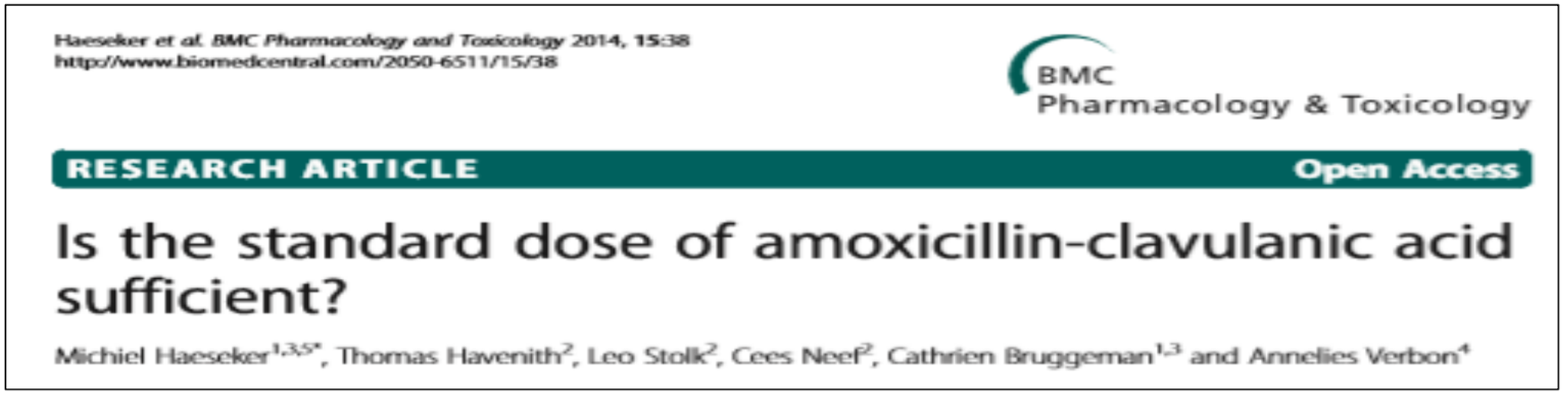
Case 1: dosing of amoxicillin-clavulanic acid in IAI

1. amoxicillin-clavulanic acid 1,2g q6h
2. **amoxicillin-clavulanic acid 1,2g q4h**
3. amoxicillin-clavulanic acid 2,4 g q6h
4. all of the above are possible

Case 1: AB dosing in function of infection focus / pathogen (MIC)



Case 1: AB dosing in function of infection focus / pathogen (MIC)



Haeseker et al. BMC Pharmacology and Toxicology 2014, 15:38
http://www.biomedcentral.com/2050-6511/15/38

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

Is the standard dose of amoxicillin-clavulanic acid sufficient?

Michiel Haeseker[1,3,5*], Thomas Havenith[2], Leo Stolk[2], Cees Neef[2], Cathrien Bruggeman[1,3] and Annelies Verbon[4]

Methods and patients:

Amoxicillin-clavulanic acid 1,2 g IV q6h in hospitalised patients
(n=58; majority of intra-abdominal infections (n=28))

Outcome:

% of PKPD target attainment of amoxicillin (at least 40%T>MIC) by applying the EUCAST susceptibility breakpoint for Enterobacterales (8 mg/l)

Haesaker et al. BMC Pharmacology and Toxicology 2014, 15:38
http://www.biomedcentral.com/2050-6511/15/38
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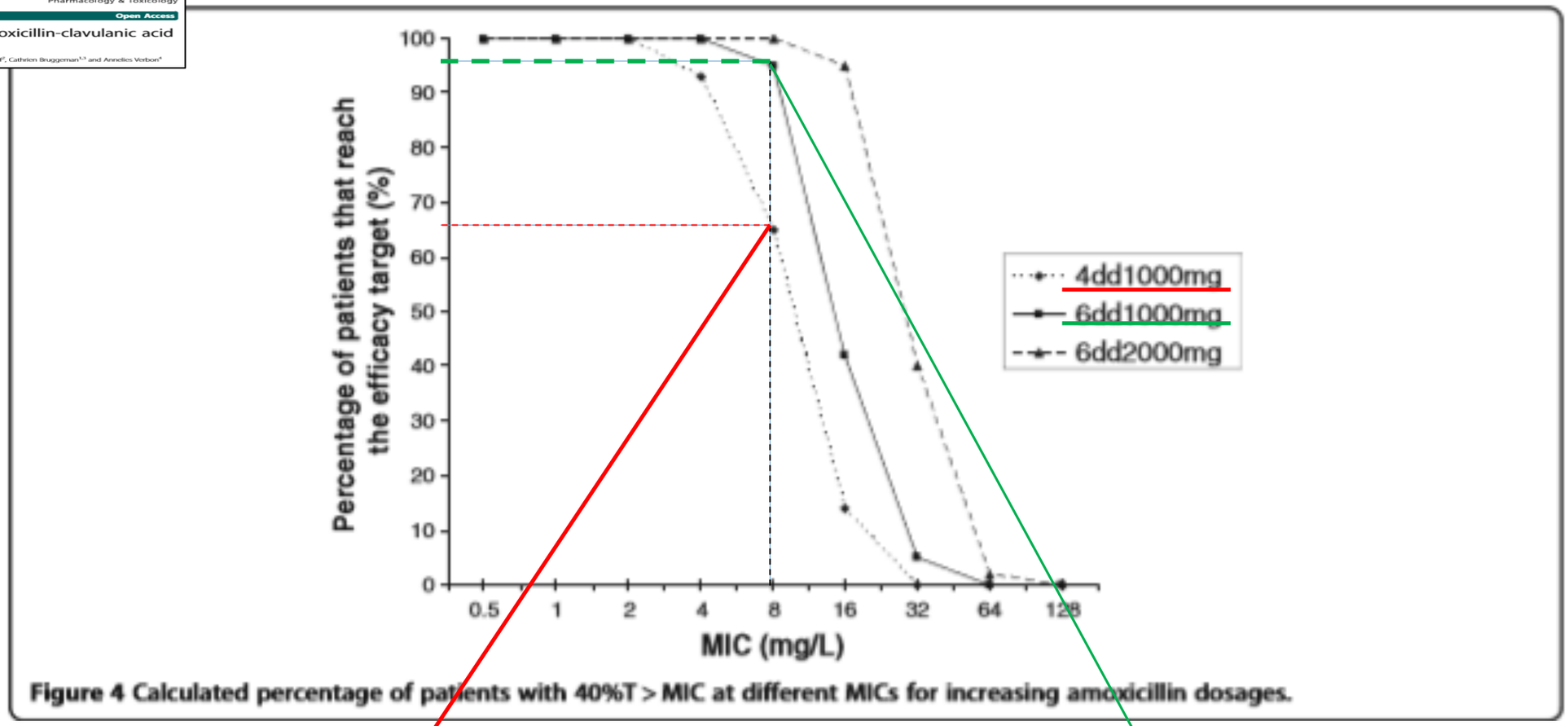


Figure 4 Calculated percentage of patients with 40%T > MIC at different MICs for increasing amoxicillin dosages.

1000 mg q6h: PD efficacy TA: only 65%

When increasing the frequency to 1000 mg q4h: 95%

UZLeuven: MIC50 *E. coli*: 8 mg/L

- IAI: amoxicillin-clavulinic acid IV 1200mg q6h → q4h (CKD-EPI ≥ 80 ml/min/1,73m²)

Cave: amoxicillin-clavulinic acid induced liver injury (in 1-1,7/10.000 users)

Case 1: AB dosing in function of infection focus / pathogen (MIC)

→ Amoxicillin-clavulanic acid 1,2g q4h (high dose)

*Intra-abdominal infections (**pathogen (MIC): Enterobacterales**)*

*Musculoskeletal infections (**infection focus**)*

→ Amoxicillin-clavulanic acid 1,2g q6h (normal dose)

*Urinary tract infections (**pathogen (MIC): Enterobacterales, but with impaired renal function**)*

*Respiratory tract infections (**pathogens with lower MICs**: H. influenzae, M. catharalis and S. pneumoniae)*

*Skin and soft tissue infections (**pathogens with lower MICs**: streptococci and anaerobes)*

Case 1: AB dosing in function of infection focus / pathogen (MIC)

→ Meropenem high dose (2g q8h)

Lung Tx with
P. aeruginosa or MDR gram negative pathogens in donor lung (***higher MIC***)

Infection with *Pseudomonas spp.* (***higher MIC***)

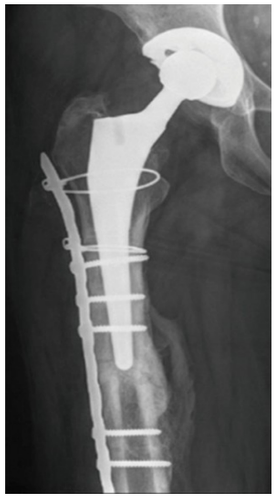
Bone- and joint infections ***(infection focus)***

Meningitis ***(infection focus)***

Cystic fibrosis ***(higher MIC , infection focus, altered clearance)***

Case 2: rifampicin dosing in musculoskeletal infection (MI)

- Woman 60 yrs old, COPD, +- 36 kg
- Total hip prosthesis (THP) right
- 6 months ago: periprosthetic fracture femur → internal fixation procedure



- Reason for admission: fracture-related infection with MSSA from internal fixation material

R/ flucloxacillin IV 1g q4h + **rifampicin PO 300 mg q12h**

Case 2: rifampicin dosing in MI

During the daily "***check of medication appropriateness***" by the pharmacist

Recentste zorgregistraties die voldoen aan deze criteria:
Zorgregistratie van FPgewicht{ FPgewichtW = 38.0 } voor patient 17 uitgevoerd door uitvoerder: cquint3 op 2019-03-05 21:17:12.

- Custom criteria for [MANUEEL_NA_TE_KIJKEN] are not (yet) implemented: Indicatie van rifampicine
- Voorschrift voor RIFADINE uit te voeren op 2019-03-06 20:00:00 en gevalideerd door validator: cquint3 op 2019-03-05 21:21:19.
  In de periode van 2019-03-06 00:00:00 tot 2019-03-06 23:59:59 waren er elke dag voorschriften
  effectieve dosis 600.00mg in periode van 2019-03-06 00:00:00 tot 2019-03-06 23:59:59

Required actions for rifampicin:

- **Check the indication**
- **Check the dose and frequency**

→ Should the rifampicin dose/posology be adapted?

Case 2: Would you change the dose of rifampicin?

No, the prescribed dose is OK

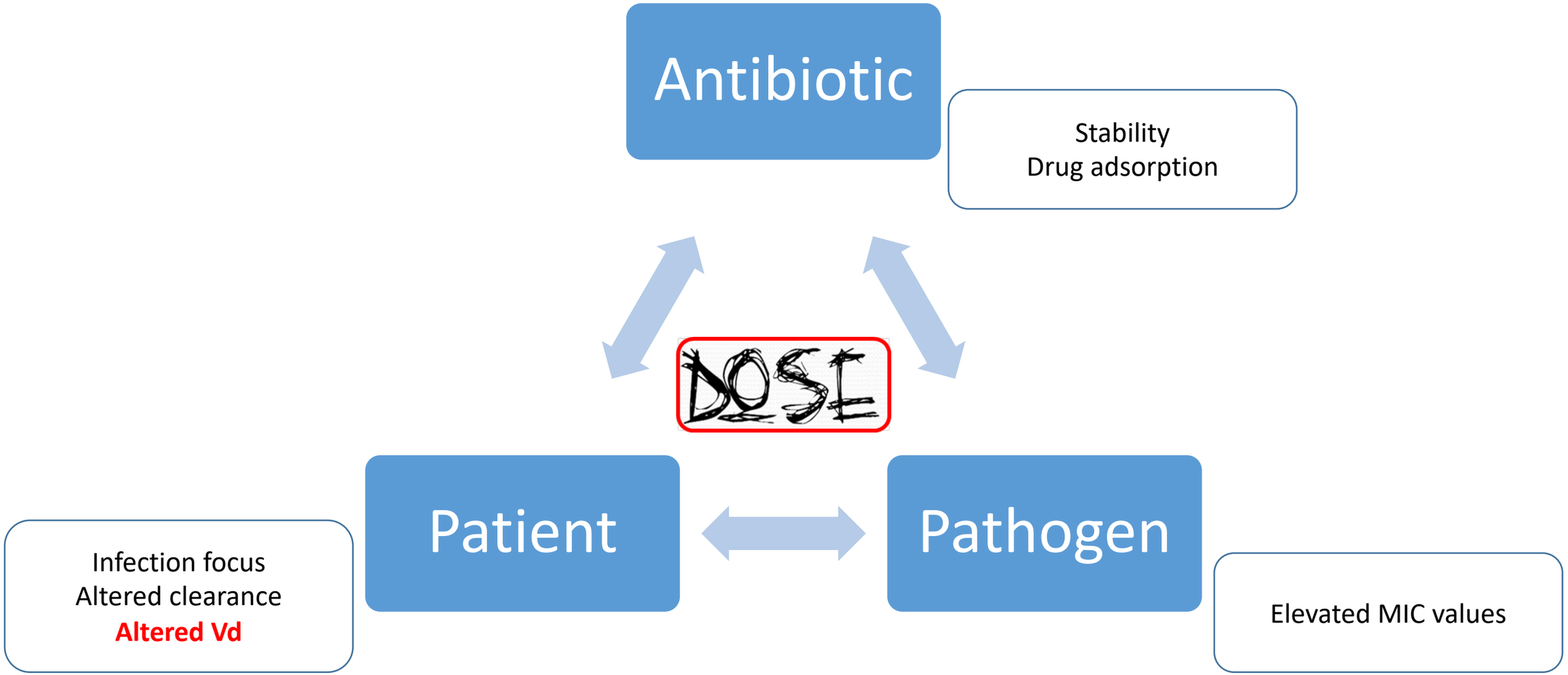
Yes. The dose of rifampicin in staphylococcal musculoskeletal infections including foreign body requires a higher dose of 450 mg q12h.

Case 2: rifampicin dosing in MI

1. No, the prescribed dose is ok

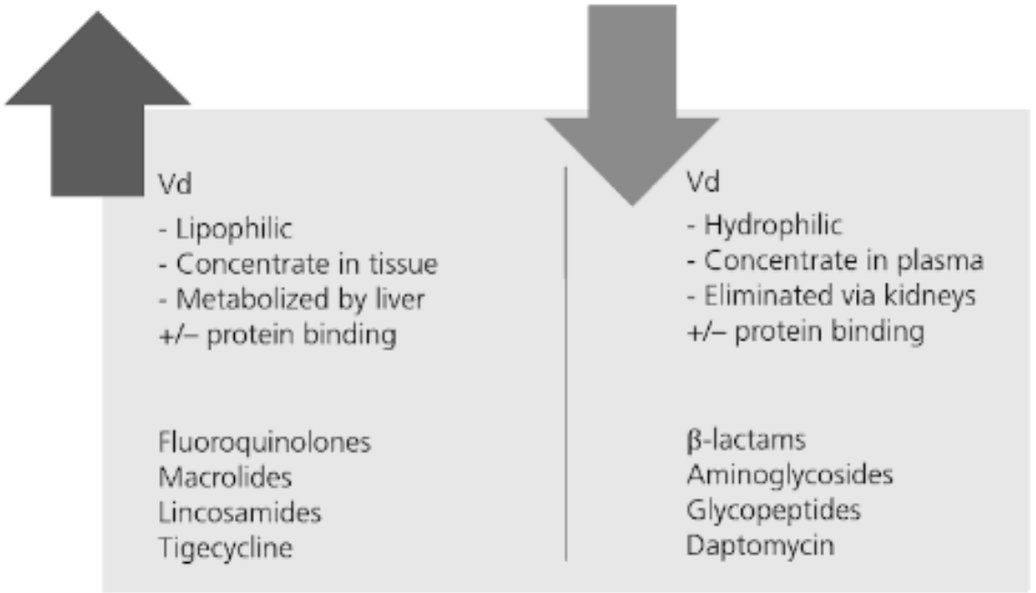
2. The dose of rifampicin in staphylococcal musculoskeletal infections including foreign body requires a higher dose of 450 mg q12h.

Case 2: AB dosing in function of an altered Vd



Case 2: AB dosing in function of an altered Vd

- Vd is determined by **physicochemical properties of the AB**:
  - molecular weight
  - degree of ionization
  - protein binding
  - lipid solubility
- Vd is determined by **patient characteristics**
  - bodyweight
  - fluid status, fluid loading
  - hypoalbuminemia



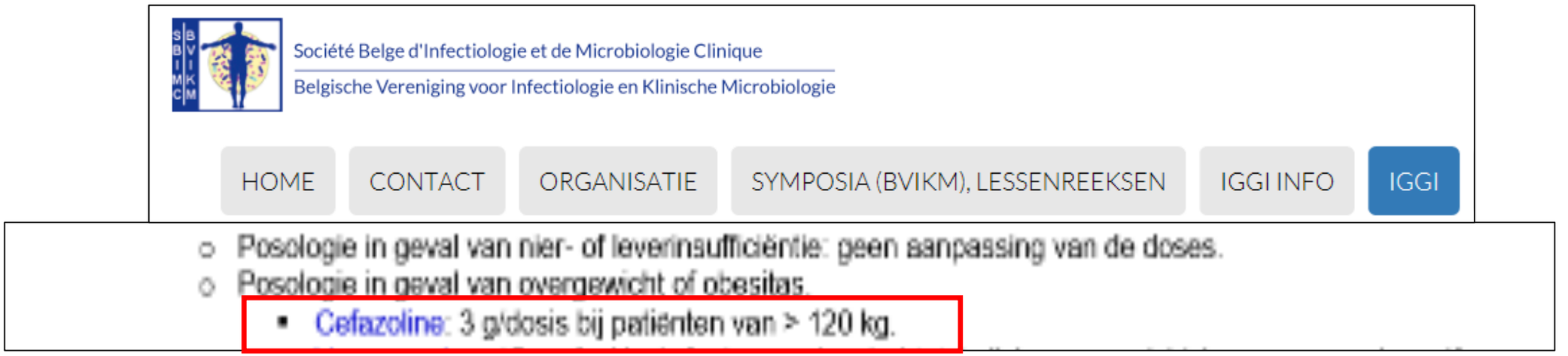
Case 2: AB dosing in function of an altered Vd

- Vd can be altered by
  - Bodyweight: Bodyweight (over- vs. underweight)

Case 2: AB dosing in function of an altered Vd

- Vd can be altered by
  - Bodyweight: **overweight**

Surgical prophylaxis: > 120 kg: cefazoline IV 2g → 3g

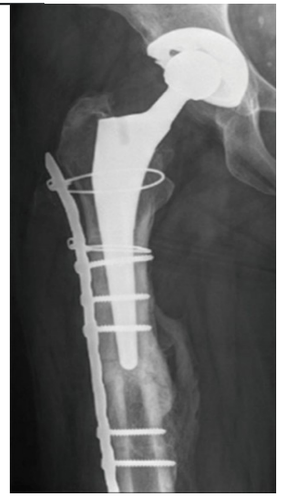


IGGI guide. www.bvikm.org

Case 2: AB dosing in function of an altered Vd

- Vd can be altered by
  - Bodyweight: **underweight**

Case 2: rifampicin dosing in function of an altered Vd



- Admission: fracture-related infection with MSSA from internal fixation material

R/ flucloxacillin IV 1g q4h + **rifampicin** PO 300 mg q12h

Musculoskeletal infection with foreign body: high dose rifampicin (450 mg q12h)

However…

In casu: **underweighted** patient (36kg!!) AND 20 mg/kg/24h → 720 mg/24h

therapy of 3 months: side effects!! (hepatotoxicity)

→ rifampicin 300 mg q12h is already a high dose

Case 3: voriconazole & neurotoxicity

- A girl, 4 yrs old, 15 kg, known with severe aplastic anemia, was admitted for HSCT and is treated with **voriconazole (2 x 120 mg IV/day)** for invasive aspergillosis.

- A trough level is sampled on day 8 and is perfectly within the therapeutic range (**3.7 mg/L**, ref 2-5,5 mg/L). However, the patient shows increasing neurotoxicity (hallucinations and confusion).

- You are the clinical pharmacist that is attending the weekly multidisciplinary case discussion at the pediatric ward.

The clinicians ask if voriconazole should be switched to liposomal amfotericine B (L-AmB) because of the clear association between voriconazole and neurotoxicity.

Case 3: Would you recommend to switch to L-AmB?

No: a VRC trough level of 3.7 mg/L will not lead to neurotoxicity. Other causes of neurotoxicity should be excluded.

No: the dose should be decreased to a trough level of 1.5 mg/L, neurotoxicity will then disappear

Yes: the patient has a low serum albumin (24 g/dL). Therefore the free VRC levels will be higher than normal, leading to neurotoxicity

No: hallucinations and confusion linked to VRC are innocent

Case 3: Would you recommend to switch to L-AmB?

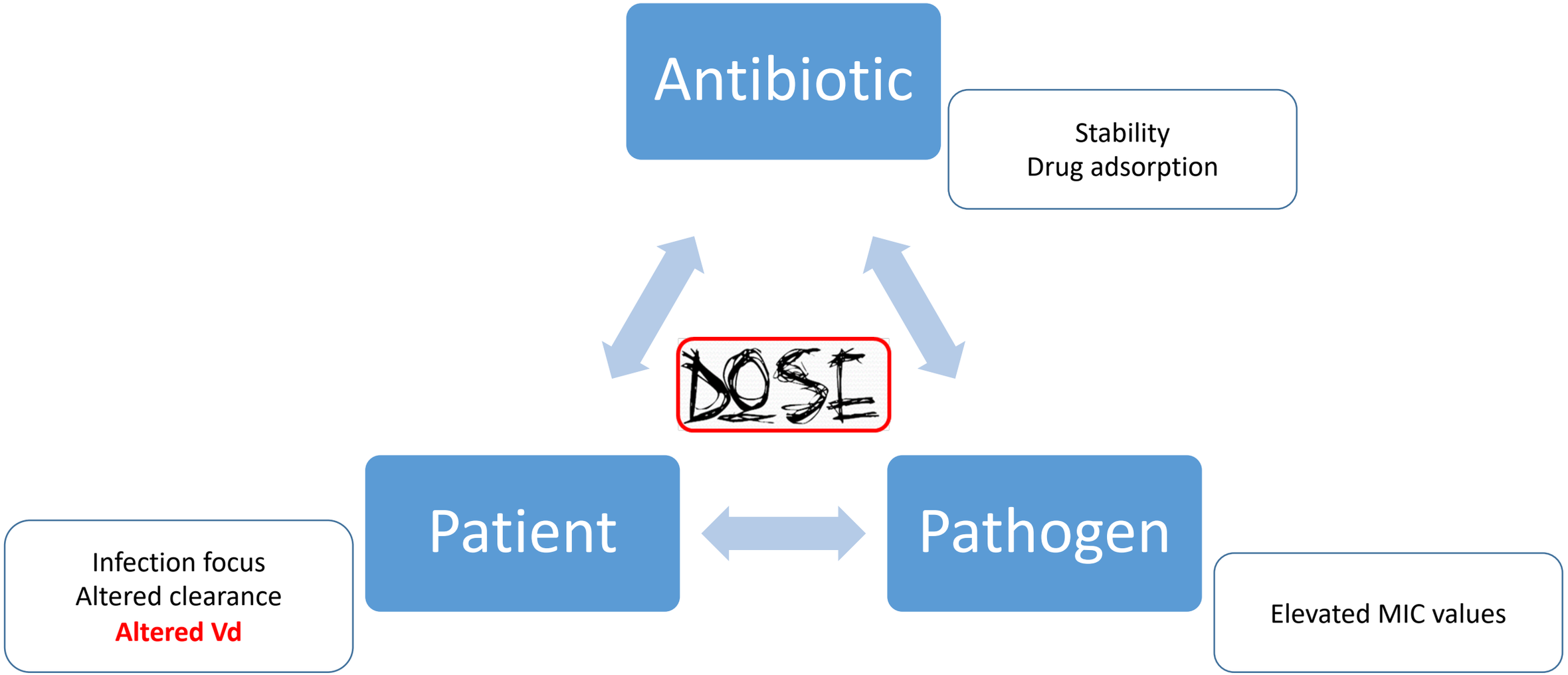
1. No: a voriconazole trough level of 3.7 mg/L will not lead to neurotoxicity. Other causes of neurotoxicity (e.g. CNS lesions, other concomitant neurotoxic medications) should be assessed.

2. No: the dose should be lowered to attainment of a trough level of about 1.5 mg/L, neurotoxicity will then probably disappear

3. Yes: the patient has a low serum albumin (24 g/dL). Therefore the free voriconazole concentrations will be higher than normal, and therefore a therapeutic (non-toxic) voriconazole level can lead to neurotoxicity

4. No: hallucinations and confusion linked to voriconazole are innocent

Case 3: AB dosing in function of an altered Vd



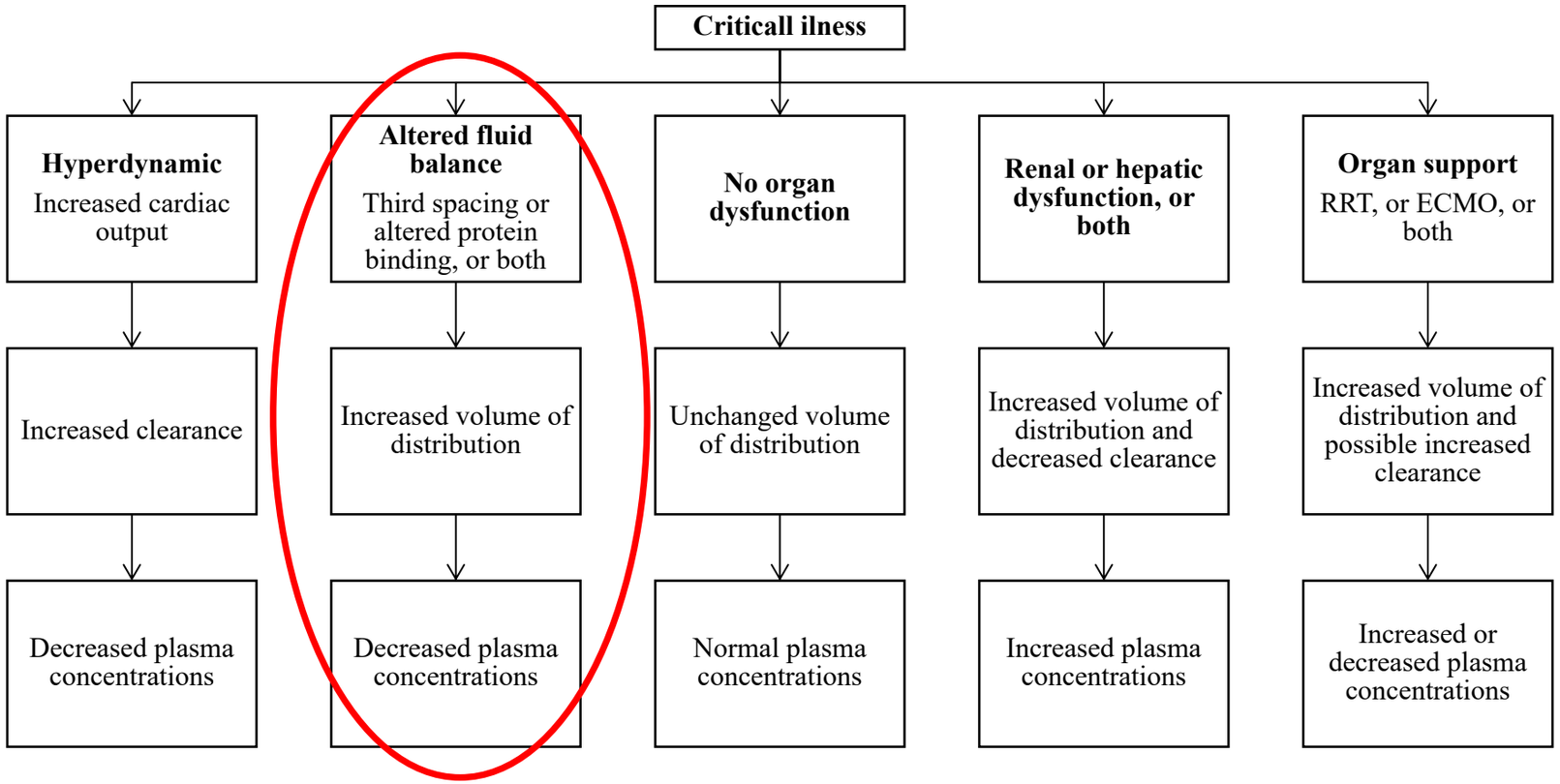
Case 3: AB dosing in function of an altered Vd

- Vd can be altered by
  - Body weight (over- vs. underweight)
  - Critical illness
  - Hypoalbuminemia

Capillary leak

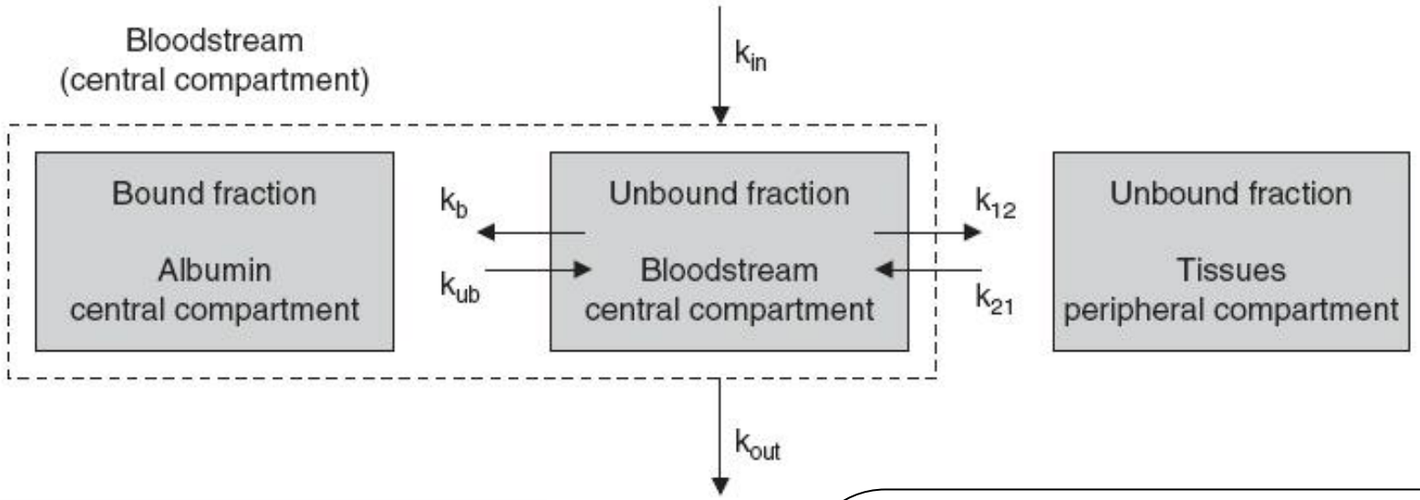
Hypoalbuminaemia

e.g. aminoglycosides, beta-lactams and vancomycin



Roberts et al. Lancet Infect Dis. 2014

Case 3: Impact of hypoalbuminemia on the PK of voriconazole



Most drugs (linear PK)

- Free concentration ↑
- Tissue distribution ↑
- Elimination and clearance ↑
- Decrease in total concentration
- Underdosing, potential therapeutic failure especially in BSI

Drugs with non-linear PK

- Free concentration ↑
- Tissue distribution ↑
- Elimination rate =
- Total concentration is unaltered, free fraction ↑
- Efficacy/toxicity ↑

Case 3: Impact of hypoalbuminemia on the PK of voriconazole

Impact of Hypoalbuminemia on Voriconazole Pharmacokinetics in Critically Ill Adult Patients

Kim Vanstraelen,[a] Joost Wauters,[b] Ine Vercammen,[a] Henriette de Loor,[c] Johan Maertens,[d] Katrien Lagrou,[e] Pieter Annaert,[f] Isabel Spriet[a]

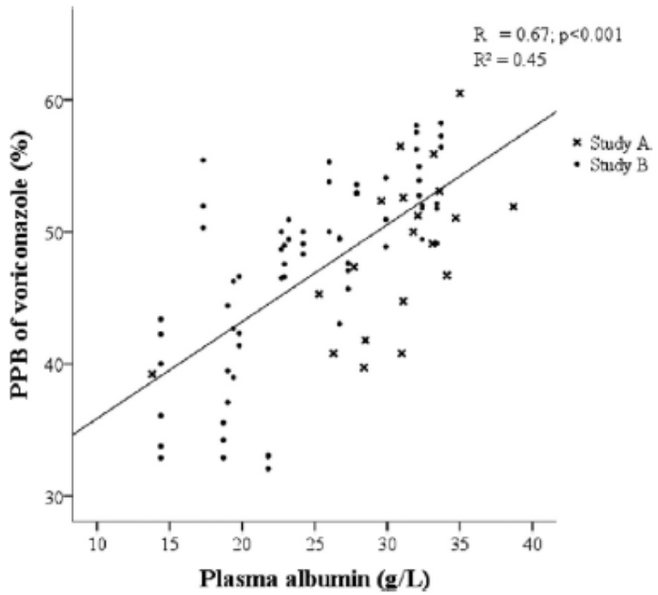


FIG 1 Positive correlation between the percentages of voriconazole plasma protein binding (PPB) and plasma albumin concentrations (in grams/liter) according to the univariate analysis of the combined set of data from study A (patients admitted to the ICU and treated with voriconazole) and study B (patients admitted to the ICU and not treated with voriconazole; plasma spiked with 1.5, 2.9, and 9 mg/liter voriconazole).

Table 2: Adjusted total voriconazole plasma concentrations[a] (mg/L) in relation to varying serum albumin concentrations (g/L) and a constant total plasma bilirubin concentrations of 1 mg/dL .

Adjusted total VRC[a] concentrations (mg/L)		Measured total voriconazole plasma concentration (mg/L)																							
		3,0	3.5	4,0	4.1	4.2	4.3	4.4*	4.5*	4.6*	4.7*	4.8*	4.9*	5,0*	5.1*	5.2*	5.3*	5.4*	5.5	5.6	5.7	5.8	5.9	6,0
Serum albumin (g/L)	10	3,8	4,4	5,0	5,2	5,3	5,4	5,5	5,7	5,8	5,9	6,0	6,2	6,3	6,4	6,6	6,7	6,8	6,9	7,1	7,2	7,3	7,4	7,6
	11	3,7	4,4	5,0	5,1	5,2	5,4	5,5	5,6	5,7	5,9	6,0	6,1	6,2	6,4	6,5	6,6	6,7	6,9	7,0	7,1	7,2	7,4	7,5
	12	3,7	4,3	4,9	5,1	5,2	5,3	5,4	5,6	5,7	5,8	5,9	6,0	6,2	6,3	6,4	6,5	6,7	6,8	6,9	7,0	7,2	7,3	7,4
	13	3,7	4,3	4,9	5,0	5,1	5,2	5,4	5,5	5,6	5,7	5,9	6,0	6,1	6,2	6,3	6,5	6,6	6,7	6,8	7,0	7,1	7,2	7,3
	14	3,6	4,2	4,8	4,9	5,1	5,2	5,3	5,4	5,6	5,7	5,8	5,9	6,0	6,2	6,3	6,4	6,5	6,6	6,8	6,9	7,0	7,1	7,2
	15	3,6	4,2	4,8	4,9	5,0	5,1	5,3	5,4	5,5	5,6	5,7	5,8	6,0	6,1	6,2	6,3	6,4	6,6	6,7	6,8	6,9	7,0	7,2
	20	3,4	3,9	4,5	4,6	4,7	4,8	5,0	5,1	5,2	5,3	5,4	5,5	5,6	5,7	5,9	6,0	6,1	6,2	6,3	6,4	6,5	6,6	6,8
	25	3,2	3,7	4,2	4,3	4,5	4,6	4,7	4,8	4,9	5,0	5,1	5,2	5,3	5,4	5,5	5,6	5,7	5,8	5,9	6,0	6,1	6,3	6,4
	30	3,0	3,5	4,0	4,1	4,2	4,3	4,4	4,5	4,6	4,7	4,8	4,9	5,0	5,1	5,2	5,3	5,4	5,5	5,6	5,7	5,8	5,9	6,0
	35	2,8	3,2	3,7	3,8	3,9	4,0	4,1	4,2	4,3	4,4	4,4	4,5	4,6	4,7	4,8	4,9	5,0	5,1	5,2	5,3	5,4	5,5	5,6
	40	2,6	3,0	3,4	3,5	3,6	3,7	3,8	3,9	4,0	4,0	4,1	4,2	4,3	4,4	4,5	4,6	4,6	4,7	4,8	4,9	5,0	5,1	5,2

- VRC=voriconazole
- [a]Adjusted total voriconazole concentrations were calculated with the formula "Adjusted total VRC conc = (100- VRC PPB) x measured total VRC conc x 2/100" where "VRC PPB = $30.5015+0.668 \times HSA-0.1867 \times Bili_{tot}$" based on the multivariate analysis on the combined dataset from study A and B.
- The dark grey cells indicate the supratherapeutic adjusted total voriconazole concentrations, assuming a total voriconazole plasma concentration of 5.5 mg/L as upper limit of the reference range and an average voriconazole PPB of 50%.
- The light grey cells indicate the additional supratherapeutic adjusted voriconazole concentrations, assuming a total voriconazole plasma concentration of 4 mg/L as upper limit of the reference range and an average voriconazole PPB of 50%.
- *Measured total voriconazole concentrations (mg/L) within the reference range (<5.5mg/L) which can result in elevated unbound voriconazole and supratherapeutic adjusted total voriconazole concentrations (mg/L) in function of the severity of hypoalbuminemia.

Antimicrobial Agents and Chemotherapy p. 6782–6789 November 2014 Volume 58 Number 11

Case 4: colistin dosing & renal function

Man, 54 yrs old, 67.3 kg, 203 cm → BMI 16.2

Medical history

- B-ALL → allogene SCTx → cGVHD
- COPD, smoker, hypercholesterolemia, aHT, STEMI (2013)
- rectumcarcinoma (2018) → total mesorectal excision

Reason for admission

- enterocutaneous fistula
- malnutrition, fever, hypotension, tachycardia

→ Initiation of broadspectrum AB based on culture results (*K. pneumoniae*) : piptazo + **colistin**

You are the clinical pharmacist on the abdominal surgery ward.
You are asked which dose of colistin should be started.
The patient's renal function is 112 mL/min.1.73m2 (CKD-EPI), 135 mL/min.1.73m2 (MDRD), 129 mL/min (CG)

Case 4: Which dose of colistin would you recommend?

A LD of 9 MIU, followed by a MD of 4 x 2 MIU

A LD of 9 MIU, followed by a MD of 6 x 2 MIU, as the patient shows augmented renal clearance.

A LD of 12 MIU, followed by a MD of 6 x 2 MIU, as the patient shows augmented renal clearance.

I am not sure about her renal function. I would like to confirm that the patient is really hyperclearing.

Case 4: Which dose of colistin would you recommend?

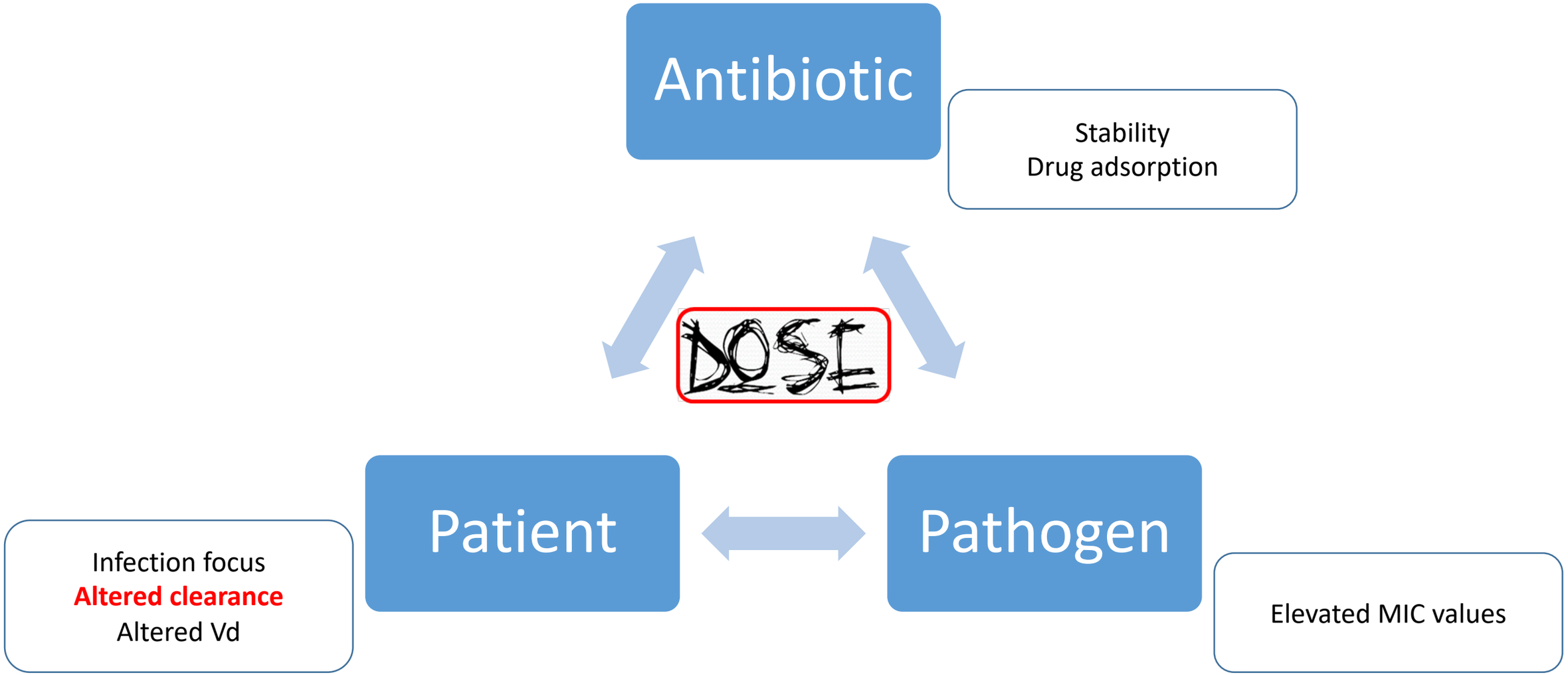
1. A loading dose of 9 MIU followed by a maintenance dose of 4 x 2 MIU.

2. A loading dose of 9 MIU followed by a maintenance dose of 6 x 2 MIU. The patient shows augmented renal clearance, as colistin is renally cleared we have to give a higher dose to make sure that the exposure is sufficient.

3. A loading dose of 12 MIU followed by a maintenance dose of 6 x 2 MIU. The patient shows augmented renal clearance, as colistin is renally cleared we have to give a higher dose to make sure that the exposure is sufficient.

4. **I am not sure about her renal function. I would like to confirm that the patient is really hyperclearing.**

Case 4: AB dosing in function of an altered renal clearance



Case 4: AB dosing in renal insufficiency: IGGI table

POSOLOGIEEN BIJ ADOLESCENTEN EN VOLWASSENEN MET NIERINSUFFICIENTIE:
ANTIBIOTICA

VOORAFGAANDELIJKE OPMERKINGEN BETREFFENDE POSOLOGIEEN BIJ PATIENTEN MET NIERINSUFFICIENTIE

- ***Aminosiden***

ANTIBIOTICUM	EERSTE DOSIS/ OPLAADDOSIS	(GESCHATTE) GLOMERULAIRE FILTRATIESNELHEID			
		89 › 60 ML/MIN	59 › 30 ML/MIN	29 › 15 ML/MIN	< 15 ML/MIN (ESRD)
Amikacine iv of im (normale dosis).	25 tot 30 mg/kg	25 tot 30 mg/kg toegediend met de kortst mogelijke intervallen (minimum 24 uur) die toelaten dalserumconcentraties te bereiken van < 3 µg/ml.			
	15 tot 30 mg/kg	15 tot 30 mg/kg q24h	15 tot 30 mg/kg q48h	15 tot 30 mg/kg q72h	15 tot 30 mg/kg q96h
	25 mg/kg	15 mg/kg q24h	15 mg/kg q48h	Geen onderhoudstherapie (enkel éénmalig 15 mg/kg).	
	15 tot 25 mg/kg	15 tot 25mg/kg q24h	15 tot 25 mg/kg q24h		15 mg/kg q48h
	15 tot 25 mg/kg	15 mg/kg q24h	15 mg/kg q24h	15 mg/kg q48h	15 mg/kg q48h	15 mg/kg q72h	15 mg/kg q96h

Current IGGI table ‘Dosing in renal insufficiency’

Set up as a consensus document

ANTIBIOTICUM	(GESCHATTE) GLOMERULAIRE FILTRATIESNELHEID				
	≥ 90 ML/MIN[1]	89 → 60 ML/MIN	59 → 30 ML/MIN	29 → 15 ML/MIN	< 15 ML/MIN (ESRD[2])
Amikacine iv (of im).	Doses van 25 tot 30 mg/kg toegediend met de kortst mogelijke intervallen (minimum 24 uur) die toelaten dalserumconcentraties te bereiken van < 3 µg/ml.				
	15 mg/kg q24h				
	25 mg/kg q24h				

IGGI guide. www.bvikm.org

Case 4: AB dosing in renal insufficiency: IGGI table

POSOLOGIEEN VAN ANTI-INFECTIEUZE GENEESMIDDELEN: ADOLESCENTEN EN VOLWASSENEN MET NIERINSUFFICIENTIE

VOORAFGAANDELIJKE OPMERKINGEN BETREFFENDE DE POSOLOGIEEN VAN ANTI-INFECTIEUZE GENEES-MIDDELEN BIJ PATIENTEN MET NIERINSUFFICIENTIE

- ***Antibiotica***
  - Aminosiden.
  - Azaliden, ketoliden, lincosamiden, (neo)macroliden.
  - Carbapenems, monobactams.
  - Cefalosporines.
  - Fluoroquinolonen.
  - Glycopeptiden.
  - Penicillines.
  - Rifamycines.
  - Tetracyclines.
  - 5-nitro-imidazolen.
  - Diverse andere antibiotica.

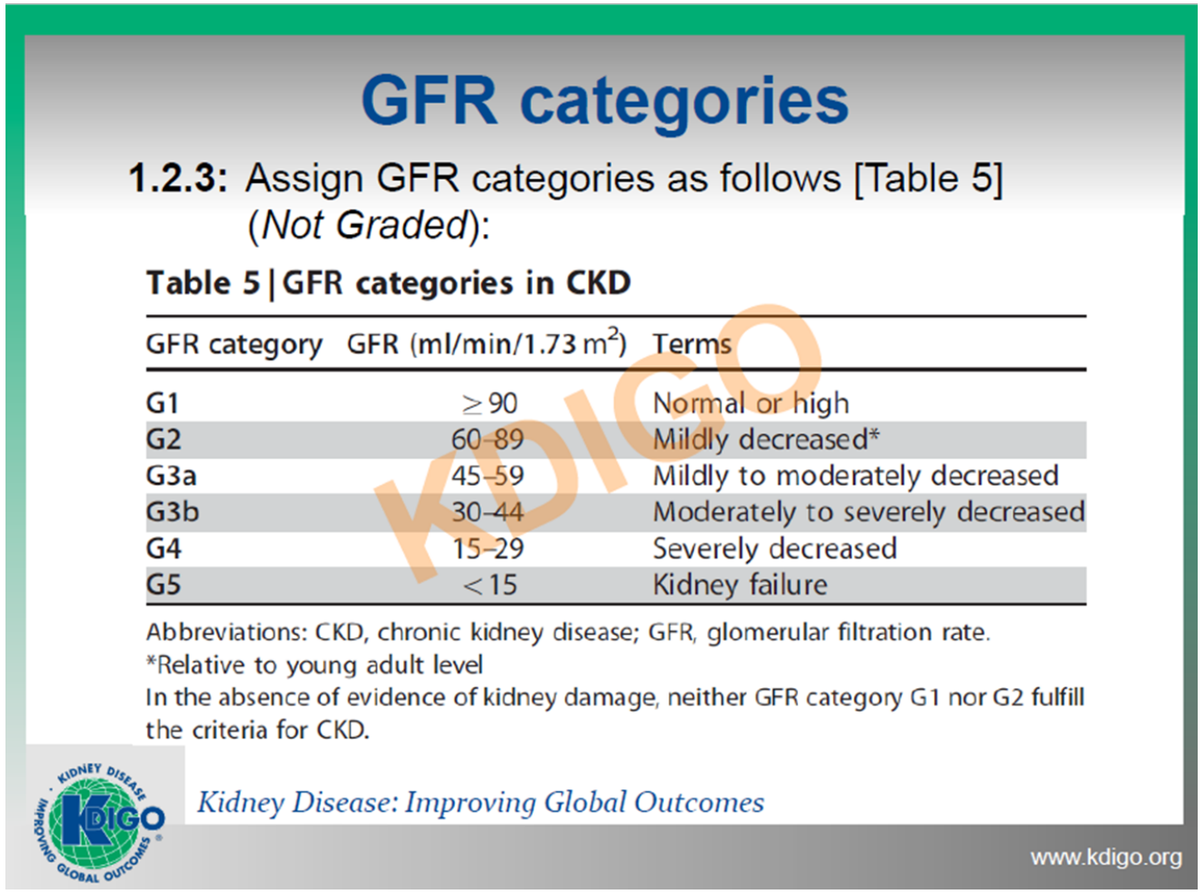
- VZA – Antibiotica werkgroep:
- Revision of the current dosing table by end of 2019

Case 4: AB dosing in renal insufficiency: IGGI table

+ in IGGI table:

- Division in **stages of renal insufficiency** (> 90, 89-60, 59-30, 29-15, < 15 mL/min)

  → corresponding to KDIGO stages for chronic kidney disease
- **Standard dosing** is provided for patients with > 90 mL/min
- **Several dosing regimens** are provided per antibiotic (e.g. for flucloxacillin: 4 x 1g; 4 x 2g and 6 x 2g/day)



GFR categories

1.2.3: Assign GFR categories as follows [Table 5] (*Not Graded*):

Table 5 | GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥ 90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	< 15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Kidney Disease: Improving Global Outcomes

www.kdigo.org

KDIGO = Kidney Disease: Improving Global Outcomes

https://kdigo.org/guidelines/

Case 4: Can CKD-EPI be used?

- The patient's BMI was only 16, with low muscle mass
- Low muscle mass → low creatinine secretion in serum (low SCr values)
- Estimators will overestimate the patient's renal function

→**24h timed urinary collection** is the only accurate way to know the patient's renal clearance

→CrCl = Ucr x Volume / SCr x 1440

Case 4: Can CKD-EPI be used?

Parameter	Case patient before AB therapy	Reference values UZ Leuven
sCr	0,62 mg/dL	0,51-0,95 mg/dL
eGFR (**CKD-EPI**)	112,5 ml/min/1,73m²	> 73 ml/min/1,73m²
eGFR (**MDRD**)	135,2 ml/min/1,73m²	> 63 ml/min/1,73m²
Cockroft&Gault	129,7 ml/min	> 100 ml/min
uCr	45,7 mg/dL	7-18 mg/dL
V_u	1850 ml/24u	-
Measured Cl_{Cr} : $Cl_{cr} = \frac{[Cr]_u \, x \, Vu}{[Cr]_p} \, x \, \frac{1{,}73m^2}{BSA}$	$\frac{45{,}7\frac{mg}{dL} \, x \, 1850 \, mL}{0{,}62\frac{mg}{dL} \, x \, 1440 \, min} \, x \, \frac{1{,}73m^2}{2{,}02m^2}$ **= 81 ml/min/1,73m²**	-

Should we always reduce the dose?

- Renal dose adjustments are based on AUC measurements in phase I studies including a small number of healthy patients **with CKD**
- In many acutely infected patients, renal impairment will be acute and transient, rather than chronic, especially in hospitalized patients
- Renal dosing protocols , based on data gathered in not acutely ill patients with CKD
  - Are usefull for adjusting chronic medication (NOAC, metformin, …) in patients with CKD
  - ! But might lead to inappropriate antibiotic dose reduction in acutely infected patients potentially explaining the lower efficacy in moderate renal impairment

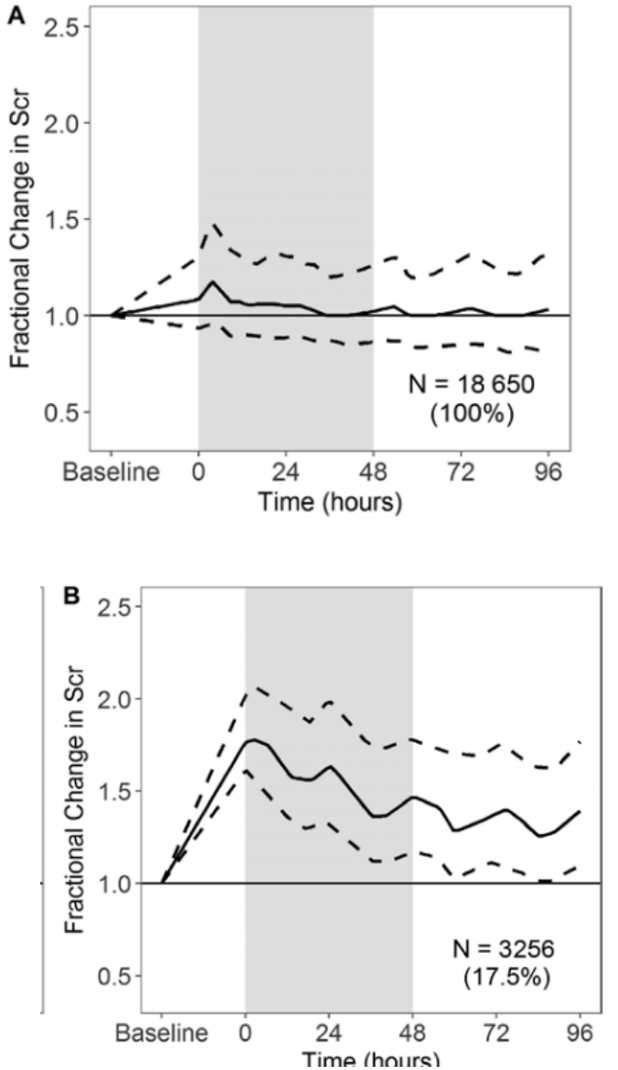
Crass RL. CID 2018

Renal Dosing of Antibiotics: Are We Jumping the Gun?

Ryan L. Crass,[1] Keith A. Rodvold,[2] Bruce A. Mueller,[1] Manjunath P. Pai[1]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor; [2]Departments of Pharmacy Practice and Medicine, Colleges of Pharmacy and Medicine, University of Illinois at Chicago

- Illustration of the dynamic nature of renal impairment in acutely infected patients
  - Retrospective study
  - 18500 patients included with cUTI (41%) or acute bacterial pneumonia (11%) or SSI (32%) or cIAI (16%)
  - Rate of AKI on admission: 17.5%
  - Kidney injury resolved in 57% of patients after 48h



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- Conclusion
  - Adequate antibiotic exposure is very important in the first 48h - the authors call this 'THE CRITICAL PERIOD'
  - For antibiotics with a wide safety margin (e.g. betalactams) dose adjustments should be deferred until 48h after initiation when the trajectory of the patient's renal function is better known
  - If renal impairment persists: dose adjustment should be carried out on day 3 to minimize toxicity

Should we always reduce the dose?

The following recommendations should be added in the IGGI table:

- For betalactams: dose reductions should be postponed to 48h
- For vancomycin, aminoglycosides, colistin: dose reductions should not be deferred as this carries a risk for toxicity

Relevant for back-office clinical validation/CMA!

Case 5: Vancomycin dosing

- Man 18 yrs, 1.87m, 91 kg
- Gastric adenocarcinoma → distal gastrectomy and Roux-en-Y anastomosis

- Postoperative complication:

intra-abdominal sepsis with *E. faecium* → re-laparatomy and ICU transfer

- eGFR CKD-EPI > 90 ml/min/1,73m²; CrCl8h= 156 ml/min
- R/ vancomycin 1g, followed by continuous infusion 2g/24h
- **TDM after 24h: 15 mg/L (target: 20 – 25 mg/L)**

Do you agree with the initiated vancomycin dosing regimen?

Case 5: Do you agree with the vancomycin dosing?

Yes. Adapt future doses in function of serum vancomycin levels

No. A LD of 25 mg/kg was needed, followed by a CI of 2g/24h, irrespective of renal function. Adapt future doses in function of TDM results.

No. A LD of 25 mg/kg was needed, followed by a CI of 2,5g/24h, taking renal function into account. Adapt future doses in function of TDM results.

Case 5: Vancomycin dosing

1. Yes.

   Adapt future doses in function of serum vancomycin levels

2. No.

   A loading dose of 25 mg/kg was needed (LD 2,275 g)

   Followed by a CI of 2g/24h, irrespective of renal function

   Adapt future doses in function of serum vancomycin levels

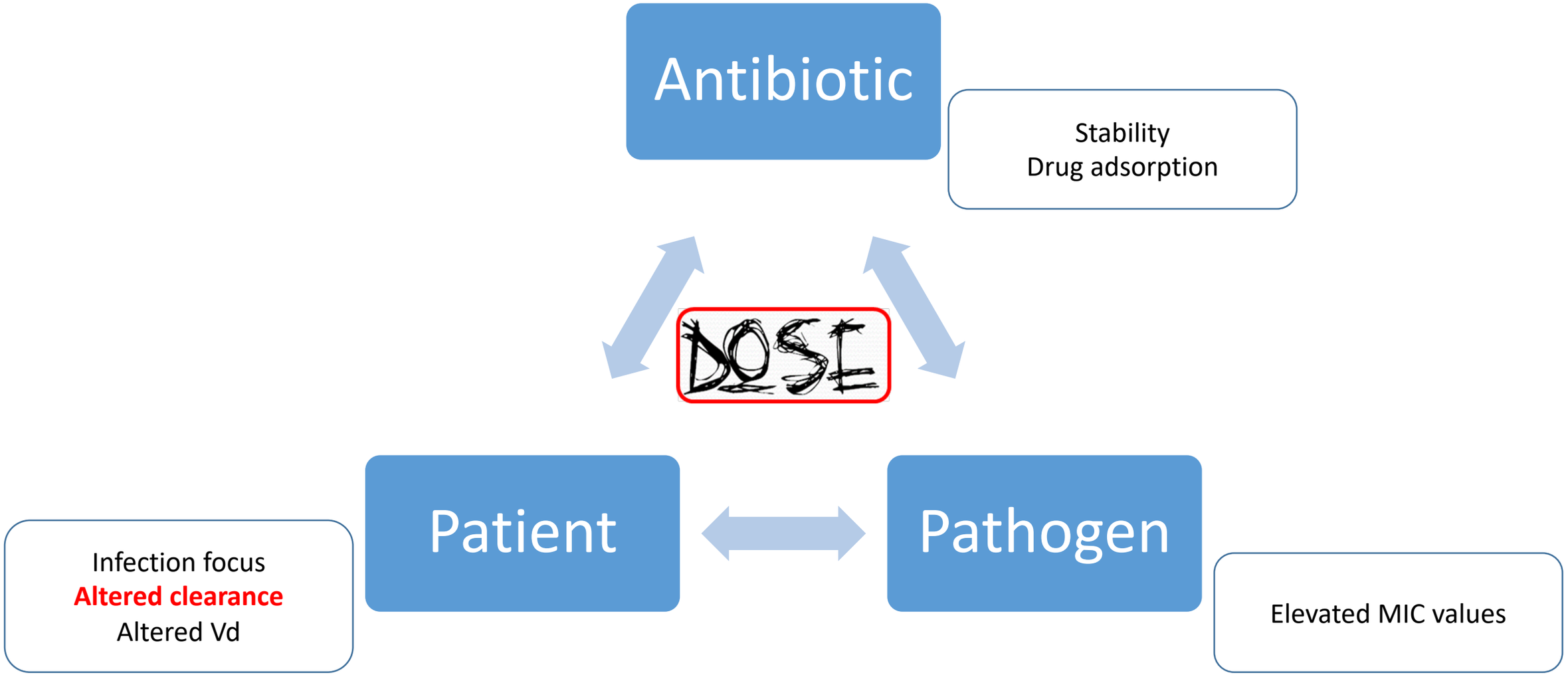
3. No.

A loading dose of 25 mg/kg was needed (LD 2,275 g)

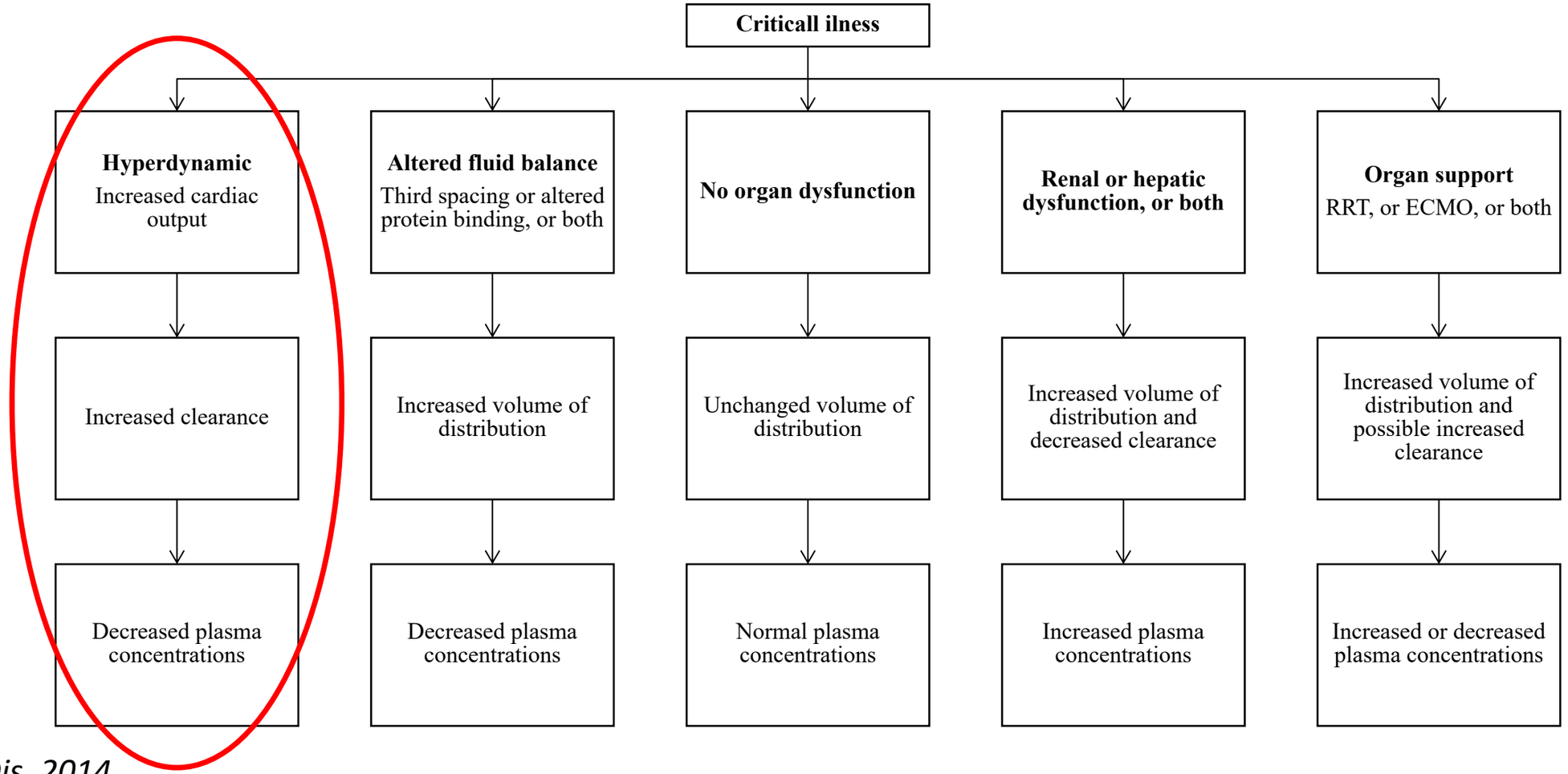
Followed by a CI of 2,5g/24h, taking renal function into account

Adapt future doses in function of serum vancomycin levels

Case 5: AB dosing in function of an altered renal clearance



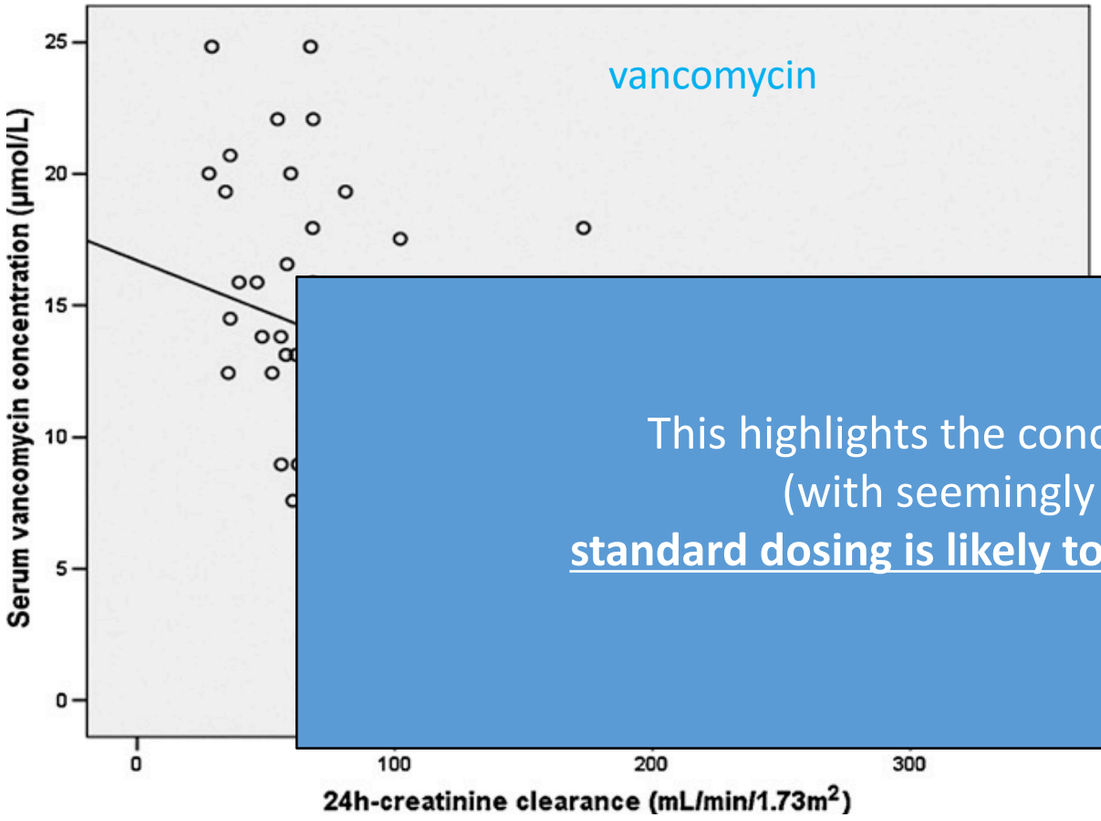
Case 5: AB dosing in function of an altered renal clearance



e.g. hydrophylic antimicrobials with predominant renal elimination aminoglycosides, beta-lactams and vancomycin

Roberts et al. Lancet Infect Dis. 2014

Case 5: AB dosing in function of an altered renal clearance



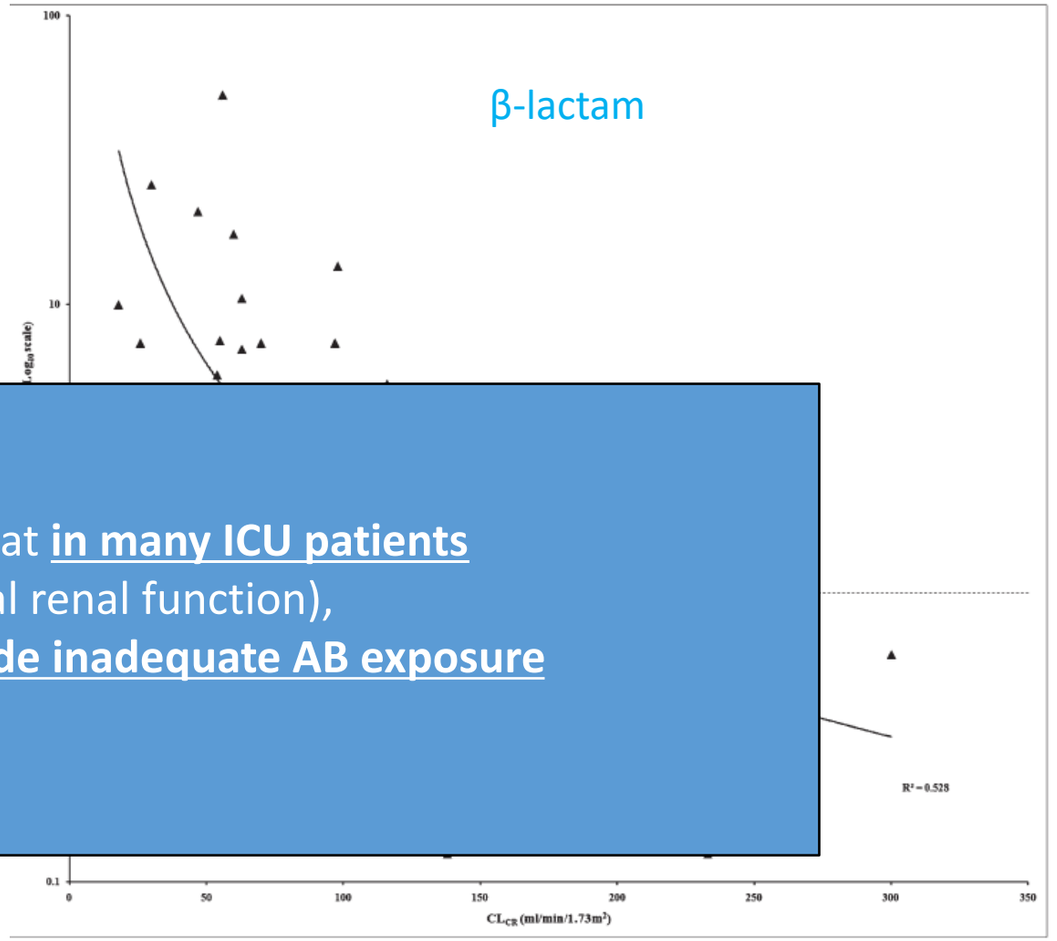


FIGURE 1. Trough drug concentration/MIC ratio (log_{10} scale) as a function of CL_{CR}. Plot of trough drug concentration to MIC ratio as a function of CL_{CR}. A value > 1 indicates a trough concentration greater than MIC of the known or suspected pathogen. A trend line has been fitted with an R^2 value of 0.53. CL_{CR} = creatinine clearance; MIC = minimum inhibitory concentration.

This highlights the concern that **in many ICU patients**
(with seemingly normal renal function),
standard dosing is likely to provide inadequate AB exposure

References:

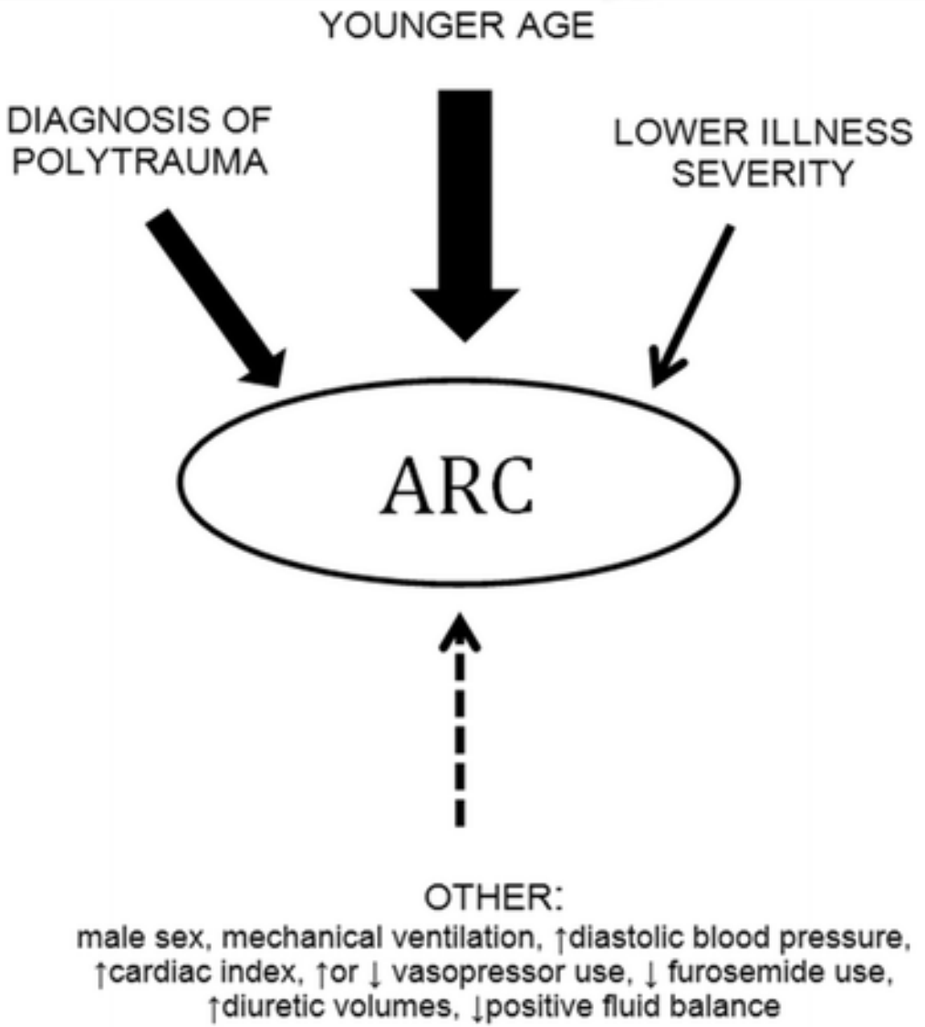
1. *Baptista et al. International Journal of Antimicrobial Agents 39 (2012) 420-423.*
2. *Udy et al. CHEST 142 (2012) 31-39*
3. *Baptista et al. Critical Care 18 (2014) 1-9*

Case 5: AB dosing in function of an altered renal clearance

Kidney function

Normal:
CrCl = 90 - 125 ml/min/1,73m²

Augmented renal clearance (ARC):
CrCl > 130ml/min/1,73m²



Bilbao-Meseguer et al. Clin Pharmacokinet 2018. Sep;57(9):1107-1121.

Case 5: AB dosing in function of an altered renal clearance

ARC: impact on drug PK?

- impact on drugs with predominant **renal clearance**
- especially important for drugs with **no clinically assessable effect**

➡ **hydrophilic antibiotics**

(beta-lactams, vancomycin, aminoglycosides…)

Case 5: AB dosing in function of an altered renal clearance

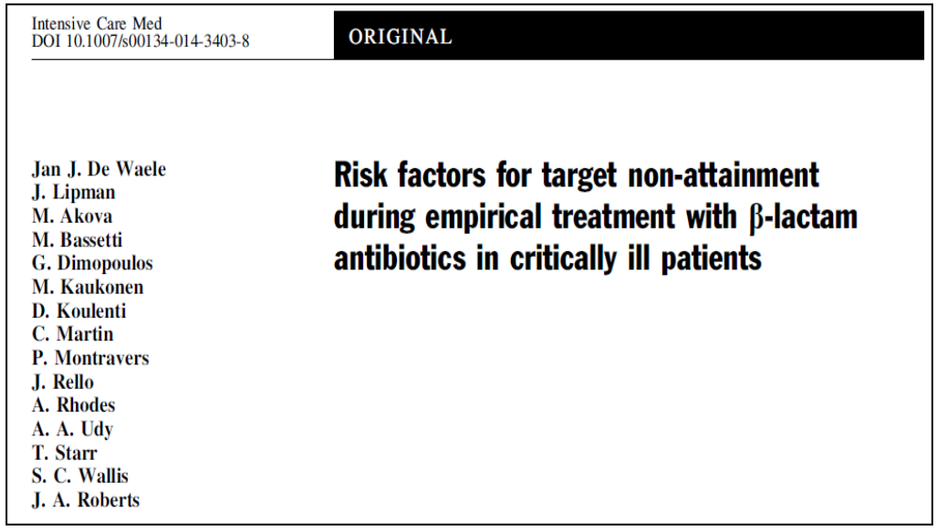
Multivariate Regression Results of Clinical Outcome for Patients Who Did Not Receive Renal Replacement Therapy

Model Parameters	50% $fT_{>MIC}$			100% $fT_{>MIC}$		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
APACHE II score	0.94	.92–.96	<.001	0.94	.92–.96	.97
SOFA score	0.97	.94–1.00	.053	0.97	.94–1.01	.13
50% $fT_{>MIC}$	1.03	1.01 –1.04	.001	…		
100% $fT_{>MIC}$	…			1.02	1.01 –1.05	.040
AIC	1758.60					
BIC	1785.07					

Roberts et al. 2014. *Clin Infect Dis*

Case 5: AB dosing in function of an altered renal clearance

ICU: large point prevalence survey



Intensive Care Med
DOI 10.1007/s00134-014-3403-8

ORIGINAL

Jan J. De Waele
J. Lipman
M. Akova
M. Bassetti
G. Dimopoulos
M. Kaukonen
D. Koulenti
C. Martin
P. Montravers
J. Rello
A. Rhodes
A. A. Udy
T. Starr
S. C. Wallis
J. A. Roberts

Risk factors for target non-attainment during empirical treatment with β-lactam antibiotics in critically ill patients

Clinical outome (clinical cure) ~ target attainment

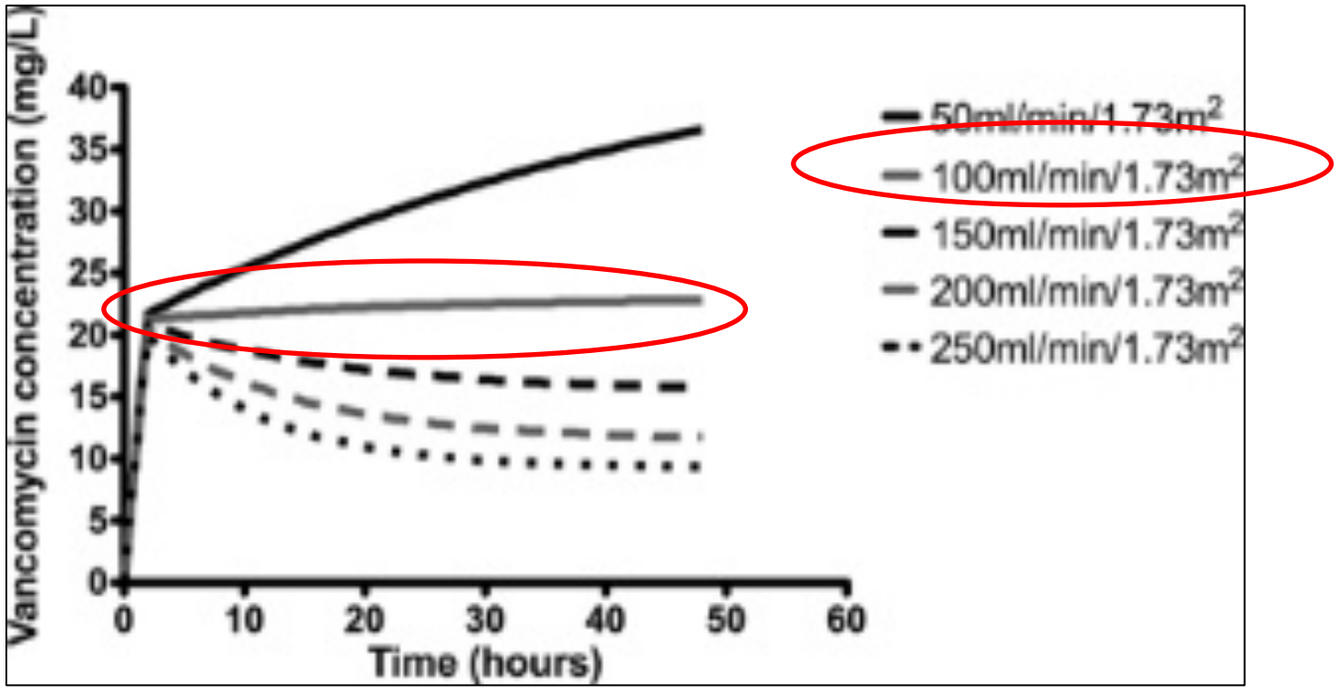
~ 1/renal clearance (ARC, CrCl>130ml/min/1,73m²)

~ extended / continuous infusion

De Waele JJ et al. 2014. *Intensive Care Med*

Case 5: AB dosing in function of an altered renal clearance

The effect of renal clearance on vancomycin concentrations administered by continuous infusion (after loading dose).



CONTINUE TOEDIENING (3 lumina)

AANDACHTSPUNTEN BIJ VOORSCHRIJVEN

Zie SCHEMA'S EMV. Kies obv: continu infuus, eGFR en gewicht.

LADINGSDOSIS
- **25 mg/kg** (max 2,5 g), over minimaal 2 uur

ONDERHOUDSDOSIS
- start **onmiddellijk** na leeglopen ladingsdosis
- afh van nierfunctie (**eGFR** volgens CKD-EPI):

eGFR (mL/min/1,73m²)	Onderhouds-dosis	Debiet	Oplos-middel
> 100	2,5g/24 uur	250 mL /24u	250 mL NaCl 0,9%
50-100	2g/24 uur		
10-50	1g/24 uur		

Roberts et al. Antimicrob Agents Chemother. 2011
Vancoprotocol UZ Leuven 2019.

Case 6: Therapeutic dose monitoring (TDM) of vancomycin

Women, 46 years old, known with short-bowel syndrome

Treated for many years with home TPN during the night via the PAC

Admission via the ED for high fever

- CR-BSI with MR-CNS : R/ vancomycine, started at 2 x 1g, intermittent infusion
- CKD-EPI: 88 mL/min.1,73m^2, weight: 71 kg

Trough level monitoring on day 3: **33 mg/L**

- No changes in renal function
- Still high fever, positive hemocultures
- No thrombi, no foreign material…

Is 33 mg/L a correct vanco trough level?

Case 6: Is 33 mg/L a correct level?

The level is falsely elevated: the blood sample was taken when the next dose was already infused.

The level is falsely elevated: the blood sample was taken 4hr before the next administration

The level is falsely elevated: the blood sample was taken via the PAC

The level is falsely elevated: the commercial immuno-assay used by the lab was not correctly calibrated

Case 6: Is 33 mg/L a correct level?

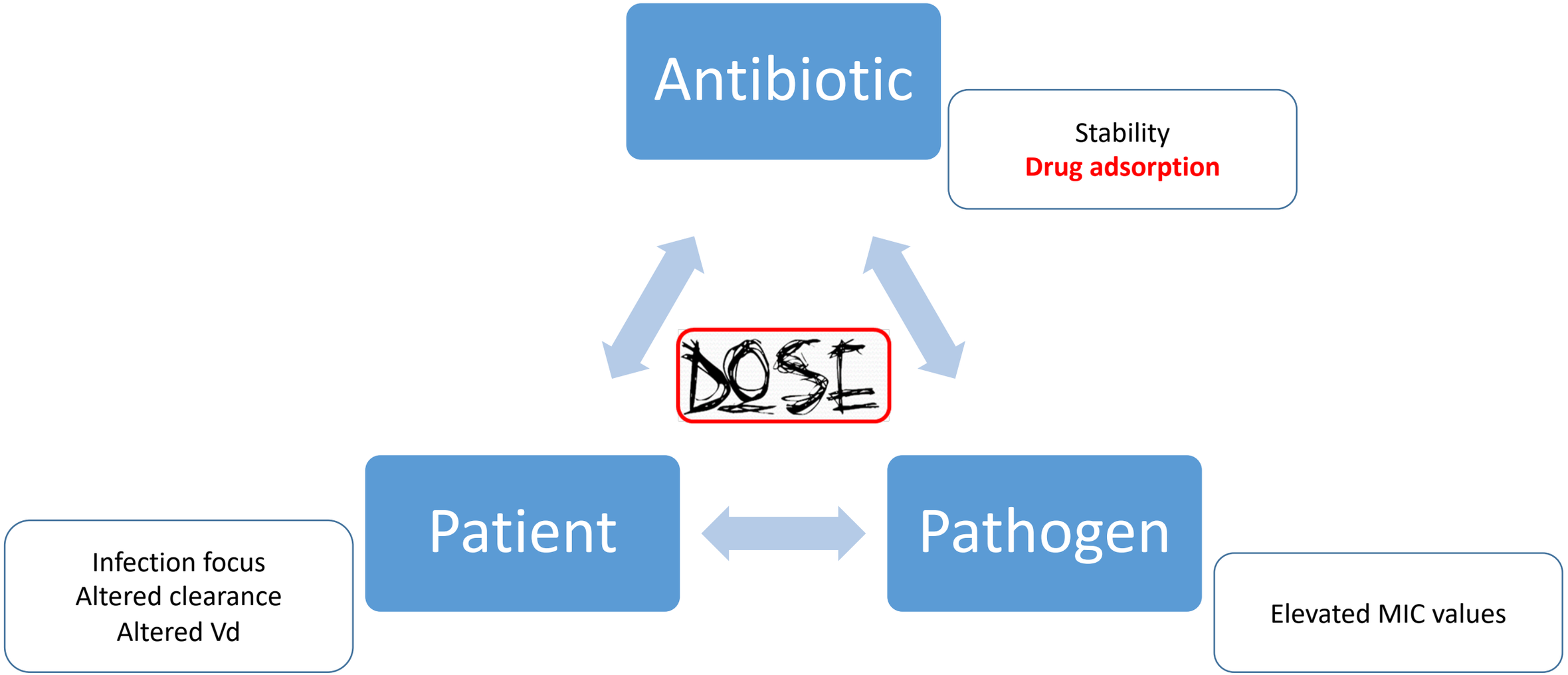
1. The level is falsely elevated: the blood sample was taken when the next dose was already infused.

2. The level is falsely elevated: the blood sample was taken 4hr before the next administration

3. **The level is falsely elevated: the blood sample was taken via the PAC**

4. The level is falsely elevated: the commercial immuno-assay used by the lab was not correctly calibrated

Case 6: AB dosing & drug adsorption



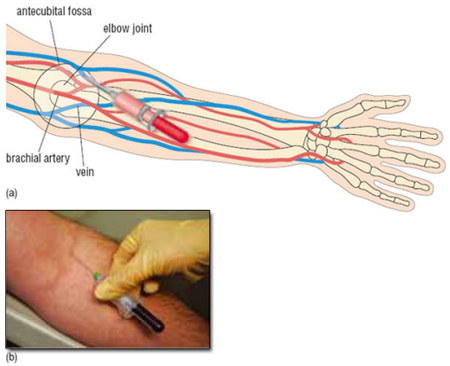
Case 6: TDM based dosing = ultimate personalised dosing

CRITERIA	AMINO GLYCOSIDES	VANCO	TEICO	VORICO	POSACO
PLASMA-EFFECT CORRELATION	++	++	+	+	-?
ESTABLISHED PKPD TARGET	+	+	+/-	+	+
NARROW THERAPEUTIC MARGIN	++	+	-	+	+/-
HIGH INTERPATIENT VARIABILITY	+	+	+	+	+
DIFFICULT INTERPRETATION OF CLINICAL EFFECT	+	+	+	+	+
BIOASSAY AVAILABLE	+	+	+	+	+

Case 6: Requirements TDM based dosing

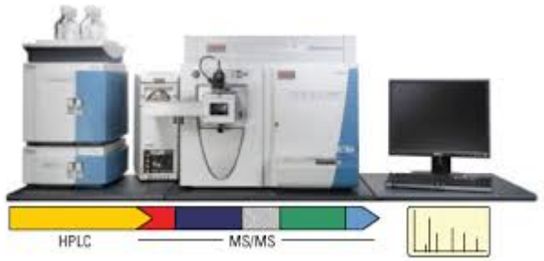
From the PATIENT

1. Prescription for TDM
2. Venipuncture
3. Correct tubes
4. Correct storage on ward
5. Sending sample to lab



to the LAB

1. Correct storage in lab
2. Sample preparation
3. Analysis
    1. Commercial IA
    2. LC-MSMS



and back to the PATIENT

1. Validation of result
2. Advice for dose adaptation based on reference values
3. Actual dose adjustment

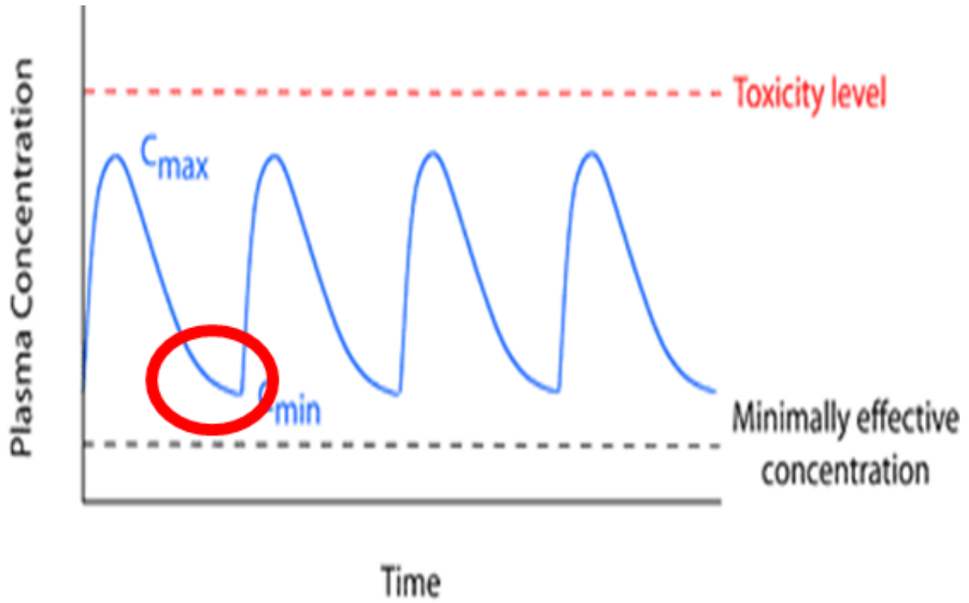
Drug	Reference
Voriconazole	1-6 mg/L
Posaconazole	> 0,7 mg/L
Itraconazole	0,5-4 mg/L

TDM is a multidisciplinary process, quality should be assured in the pre-analytical, analytical and post-analytical phase

Case 6: AB dosing based on TDM: importance of the right sampling time

- **Trough** level: just before the next dose

AB dosing based on TDM: importance of right sampling time



- ✓ Not at 4 am or 6 am when all other blood samples are taken…
- ✓ Not when AB is already infused….

Case 6: Falsely elevated vancomycin concentrations due to sampling via the catheter

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03749.x

Letter to the Editors

Falsely elevated vancomycin plasma concentrations sampled from central venous implantable catheters (portacaths)

Daniel F. B. Wright,[1] Hesham S. Al-Sallami,[1] Pamela M. Jackson[2] & David M. Reith[2]

[1]School of Pharmacy, University of Otago and [2]Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Boy, treated at home with continuous infusion of vancomycin via central venous port catheter
Target level: 20-25 mg/L

Level taken via peripheral venipuncture: 22.4 mg/L
Level PAC 1 (before extensive flushing): **44.2 mg/L**
Level PAC 2 (after extensive flushing) : 26.9 mg/L

Blood sampling should be carried out via peripheral sampling!!

Case 7: Continuous vs. intermittent infusion vs. oral therapy?

- You are the hospital pharmacist responsible for the organisation of OPAT.

- A patient admitted for osteomyelitis caused by MSSA and treated for 10 days with 6 x 2g flucloxacillin IV is clinically stable, CRP and wbc is decreased/normalized, the patient does not have fever and is ready to be discharged.

- You are discussing with the trauma surgeon and ID specialist what the best AB treatment option would be after discharge.

You are discussing the pro's and cons of oral clindamycin vs. IV flucloxacillin in OPAT

Case 7: Continuous vs. intermittent infusion vs. oral therapy?

1. **You are in favor of OPAT with IV flucloxacillin**

   - Flucloxacillin is a bactericidal antibiotic with very good anti-staphylococcal activity
   - Flucloxacillin is a timedependent antibiotic, so continuous infusion will optimize PKPD target attainment
   - Stability is sufficient to allow a daily administration in two times
   - Using elastomeric devices will allow patients to be mobile, go outside, etc.

2. **You are in favor of oral clindamycin**

   - Clindamycin is a bio-equivalent antibiotic and therefore oral treatment is possible
   - Clindamycin acts bacteriostatic however after 10 days of IV treatment with a bactericidal antibiotic clindamycin can reliably be started
   - Flucloxacillin is not stable enough to allow reliable OPAT treatment
   - Oral treatment is more elegant than IV OPAT

Case 7: continuous vs. intermittent vs. oral treatment?

You are in favor of OPAT with IV flucloxacillin. **A**

You are in favor of oral clindamycin. **B**

Case 7: Continuous vs. intermittent infusion vs. oral therapy?

1. **You are in favor of OPAT with IV flucloxacillin**

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   - **Flucloxacillin is a timedependent antibiotic, so continuous infusion will optimize PKPD target attainment**
   - **Stability is sufficient to allow a daily administration in two times**
   - **Using elastomeric devices will allow patients to be mobile, go outside, etc**.

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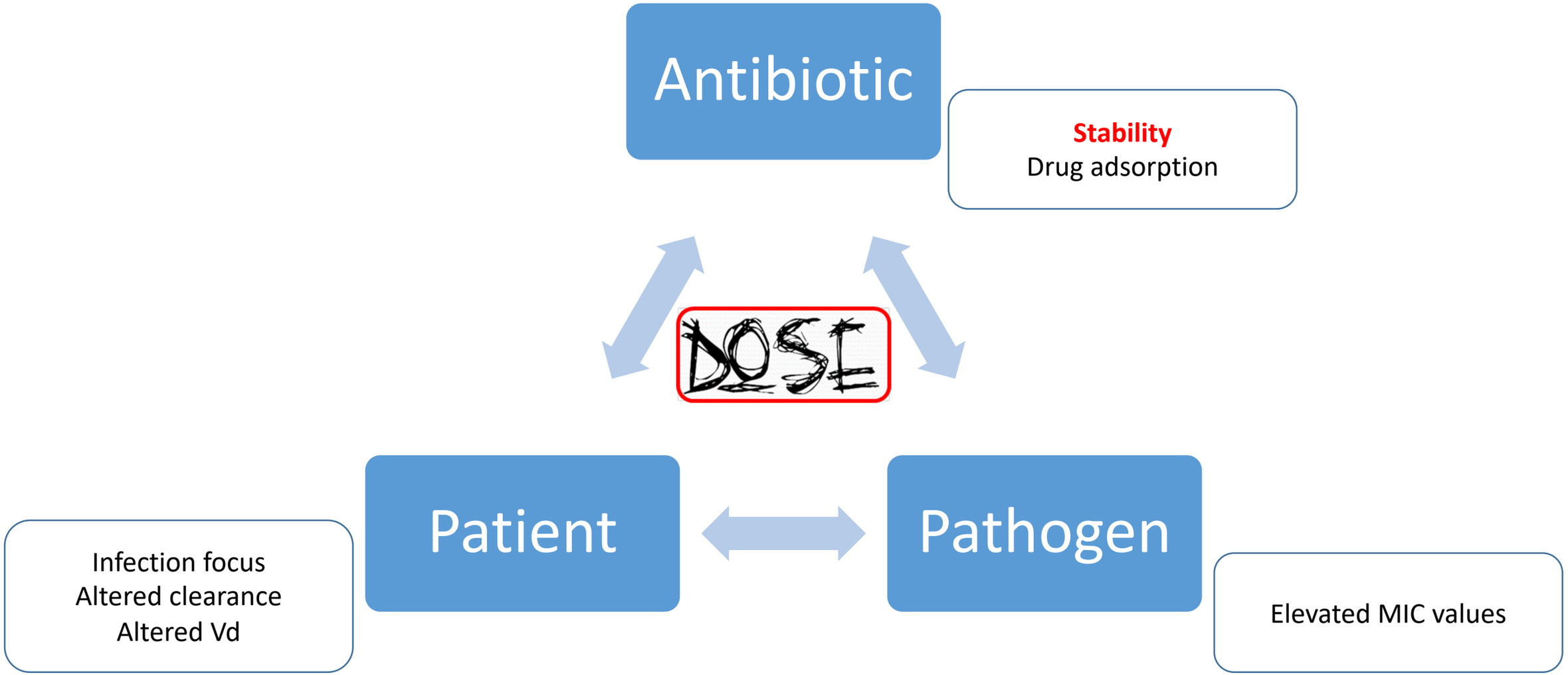
   - **Flucloxacillin is not stable enough to allow reliable OPAT treatment**
   - Oral treatment is more elegant than IV OPAT

Case 7: Prolonged/Continuous AB dosing & stability



Case 7: Prolonged/Continuous AB dosing & stability

- Concept of PL/CON infusion
  - Avoidance of peak concentrations → less toxicity for vancomycin

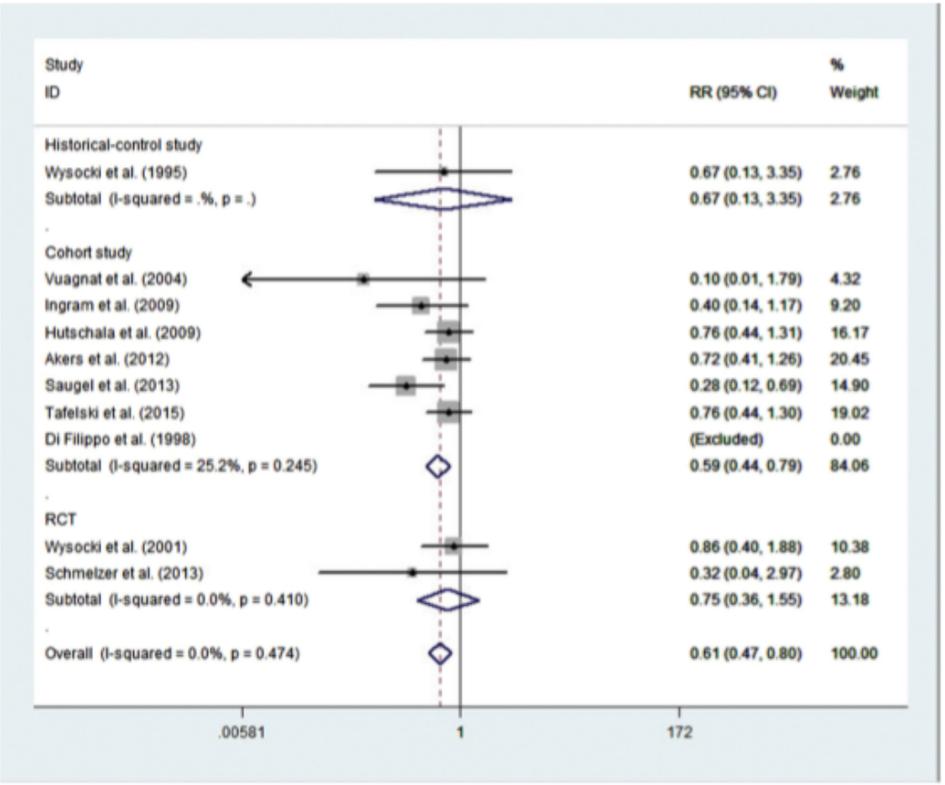


Fig. 2. Forest plot of nephrotoxicity. Forest plot summary of the unadjusted risk ratio (RR) of the studies included in the meta-analysis comparing the incidence of nephrotoxicity in patients treated with continuous infusion of vancomycin (CIV) versus intermittent infusion of vancomycin (IIV). RCT, randomised controlled trial.

Hao JJ et al. IJAA 2016; 47: 28-35.

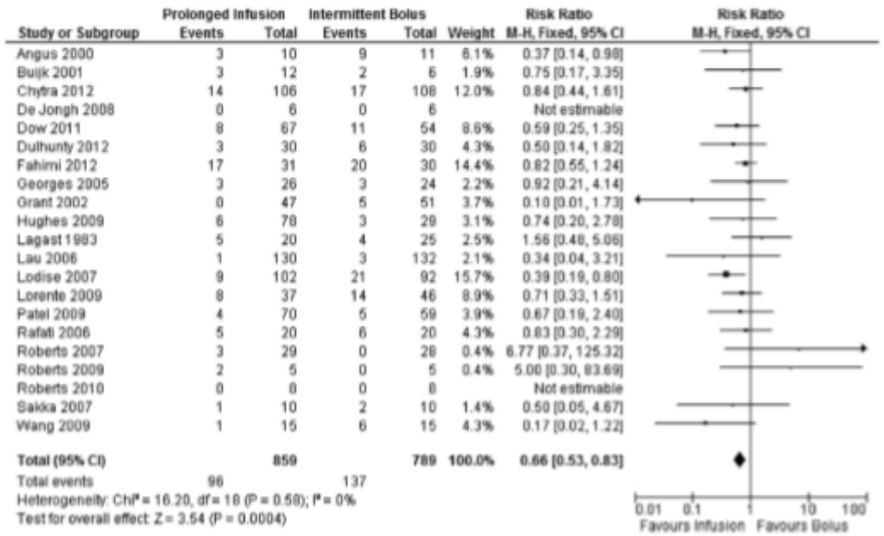
Case 7: Prolonged/Continuous AB dosing & stability

- Concept of PL/CON infusion
  - Better PKPD target attainment for betalactams → better efficacy (clinical cure, mortality)

But!

No statistically significant difference when

- Only looking to RCTs
- Only looking to studies in which equivalent doses were used in both groups



Study or Subgroup	Prolonged Infusion Events	Total	Intermittent Bolus Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Angus 2000	3	10	9	11	6.1%	0.37 [0.14, 0.98]
Buijk 2001	3	12	2	6	1.9%	0.75 [0.17, 3.35]
Chytra 2012	14	106	17	108	12.0%	0.84 [0.44, 1.61]
De Jongh 2008	0	6	0	6		Not estimable
Dow 2011	8	67	11	54	8.6%	0.59 [0.25, 1.35]
Dulhunty 2012	3	30	6	30	4.3%	0.50 [0.14, 1.82]
Fahimi 2012	17	31	20	30	14.4%	0.82 [0.55, 1.24]
Georges 2005	3	26	3	24	2.2%	0.92 [0.21, 4.14]
Grant 2002	0	47	5	51	3.7%	0.10 [0.01, 1.73]
Hughes 2009	6	78	3	29	3.1%	0.74 [0.20, 2.78]
Lagast 1983	5	20	4	25	2.5%	1.56 [0.48, 5.06]
Lau 2006	1	130	3	132	2.1%	0.34 [0.04, 3.21]
Lodise 2007	9	102	21	92	15.7%	0.39 [0.19, 0.80]
Lorente 2009	8	37	14	46	8.9%	0.71 [0.33, 1.51]
Patel 2009	4	70	5	59	3.9%	0.67 [0.19, 2.40]
Rafati 2006	5	20	6	20	4.3%	0.83 [0.30, 2.29]
Roberts 2007	3	29	0	28	0.4%	6.77 [0.37, 125.32]
Roberts 2009	2	5	0	5	0.4%	5.00 [0.30, 83.69]
Roberts 2010	0	8	0	8		Not estimable
Sakka 2007	1	10	2	10	1.4%	0.50 [0.05, 4.67]
Wang 2009	1	15	6	15	4.3%	0.17 [0.02, 1.22]
Total (95% CI)		**859**		**789**	**100.0%**	**0.66 [0.53, 0.83]**
Total events	96		137			

Heterogeneity: Chi² = 16.20, df = 18 (P = 0.58); I² = 0%
Test for overall effect: Z = 3.54 (P = 0.0004)

Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100
Favours Infusion Favours Bolus

Fig. 2. Forest plot summary of the pooled relative risks (RRs) of the studies comparing mortality rates in patients receiving prolonged infusion and intermittent boluses. CI, confidence interval.

Teo J et al. IJAA 2014: 43: 403-11.

Case 7: Requirements for prolonged/continuous infusion

- Dedicated line to avoid incompatibilities
  - Easy in OPAT
  - Not alway feasible in hospitalized patients
- Loading dose (electronic prescribing)
- Stability (in OPAT in specific device)
  - Flucloxacillin: 2 x 6g/12h
- Mobility of patient?
  - Decreasing with infusion pump in hospitalized patients
  - Feasible (in OPAT) with elastomeric devices
- Cost of (electronic) infusion pumps/syringe drivers?

Case 7: Requirements for prolonged/continuous infusion

Eur J Clin Microbiol Infect Dis (2013) 32:763–768
DOI 10.1007/s10096-012-1803-7

ARTICLE

A survey of beta-lactam antibiotics and vancomycin dosing strategies in intensive care units and general wards in Belgian hospitals

F. M. Buyle · J. Decruyenaere · J. De Waele · P. M. Tulkens · T. Van Audenrode · P. Depuydt · G. Claeys · H. Robays · D. Vogelaers

Table 1 Recommendations for the administration of the four beta-lactam antibiotics and vancomycin: intensive care unit (ICU) versus non-ICU

	n	Non ICU				ICU		
		Intermittent infusions	Prolonged infusions		Combination	Intermittent	Prolonged	Combination
		II (%)	EC (%)	CI (%)	II/CI (%)			
Ceftazidime	32	19 (59)	0 (0)	13 (41)	0 (0)			
Cefepime	20	18 (90)	1 (5)	1 (5)	0 (0)			
Piperacillin–tazobactam	34	30 (88)	4 (12)	0 (0)	0 (0)			
Meropenem	34	22 (65)	11 (32)	1 (3)	0 (0)			
Vancomycin	34	19 (56)	0 (0)	12 (35)	3 (9)			

Administration of BL and vancomyin in BE: heterogeneity in daily clinical practice

Possibility for standardization?

Conclusion

Personalized dosing

Keep the patient in mind!!

Thank you

Questions?