Workshop TDM and dose optimisation of antibiotics and antifungals

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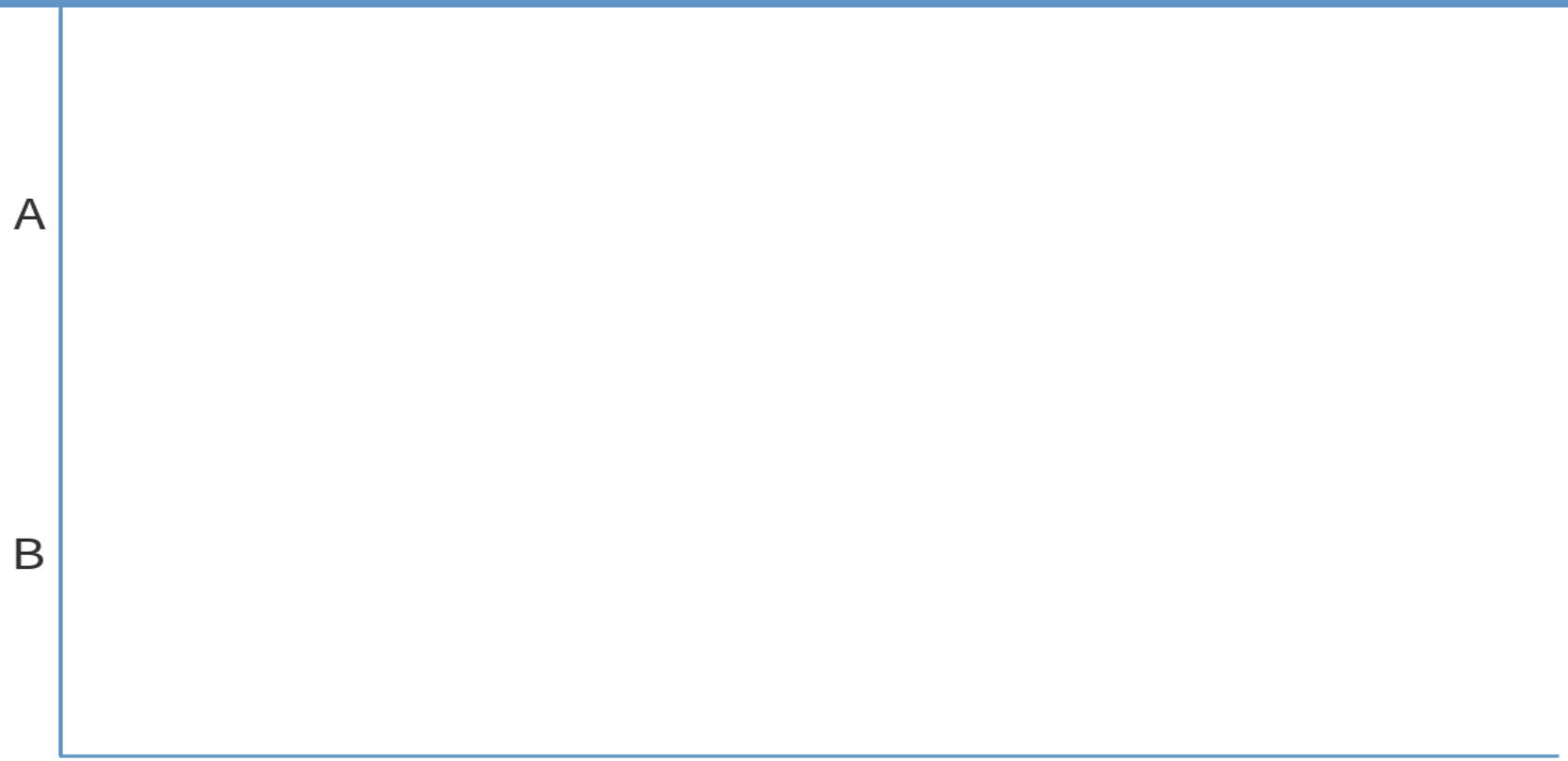
Are you a registered hospital pharmacist (A) or a resident (B)?



Questions:

What is the most important PK parameter for the first dose of an antibiotic? Clearance or Volume of distribution?

How long is the Post Antibiotic Effect or Post MIC Effect of an aminoglycoside? 2 hours or 7 hours?

A flucloxacillin serum concentration of 40 mg/L is enough to treat an infection with a micro-organism that has a MIC value of 2 mg/L Yes or No?

What is the most important PK parameter for the first dose of an antibiotic? Clearance (A) or Volume of distribution (B)?

CL **A**

Vd **B**

How long is the Post Antibiotic Effect or Post MIC Effect of an aminoglycoside? 2 hours (A) or 7 hours (B)?

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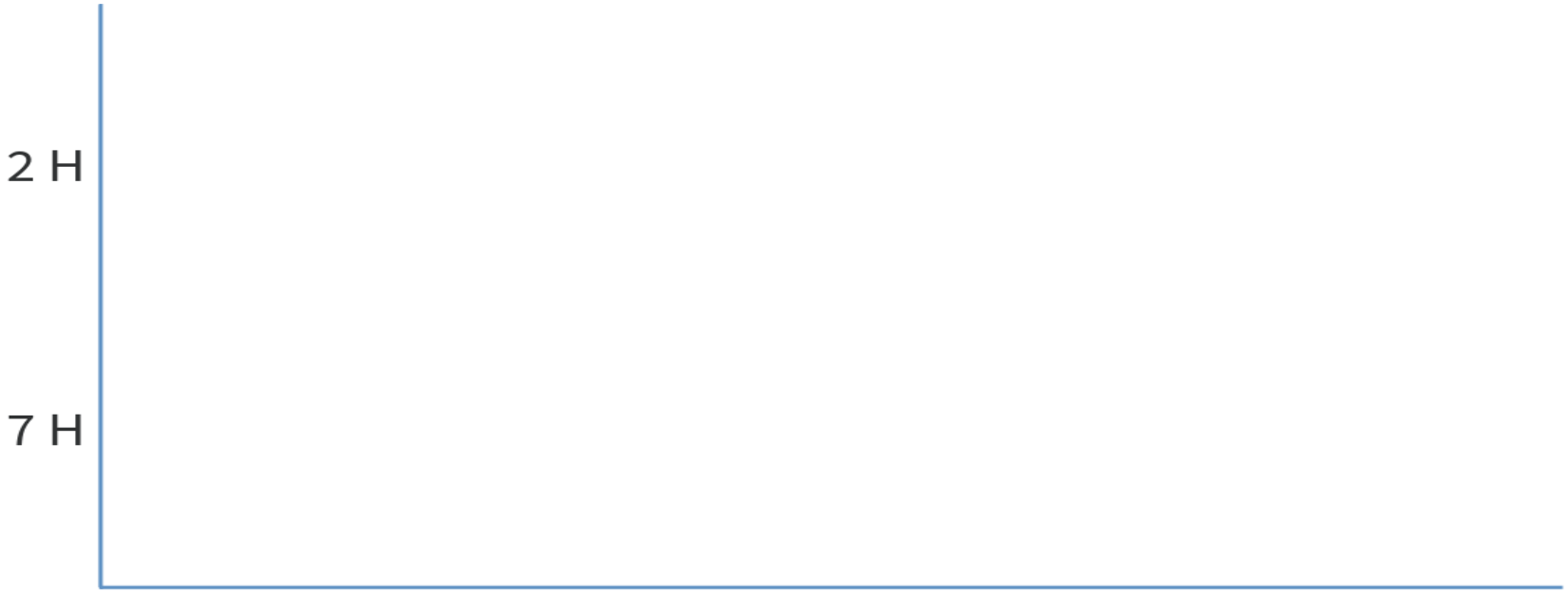
Text **DAANTOUW592** to **+31 970 0449 8375** once to join



A flucloxacillin serum concentration of 40 mg/L is enough to treat an infection with a micro-organism that has a MIC value of 2 mg/L Yes (A) or No (B)?

Yes **A**

No **B**

Case tobramycin

Male, born 8th june 1978

1,86m, 75 kg

serum creat 91 micromol/L.

Urinary infection, started with beta-lactam + tobramycine

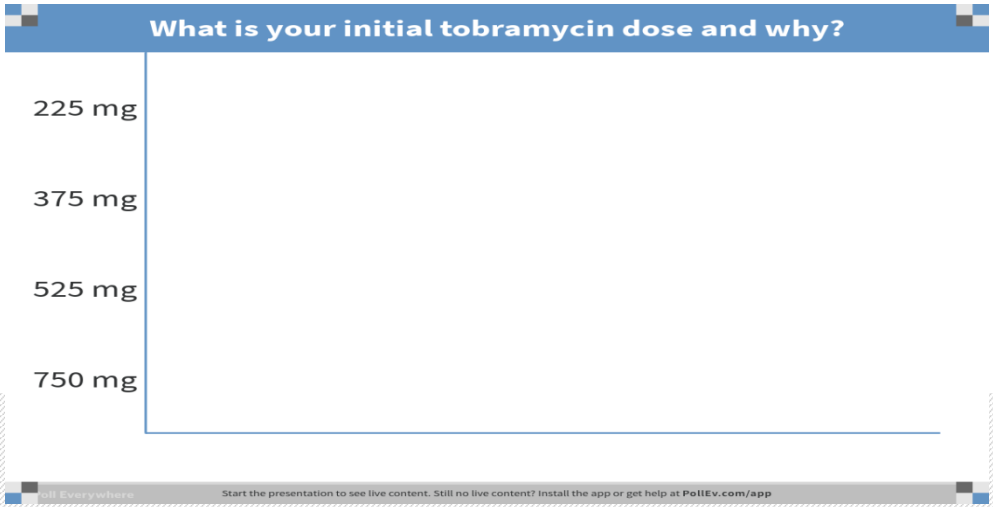
What is your initial tobramycin dose and why?

A) 225 mg

B) 375 mg

C) 525 mg

D) 750 mg



Case tobramycin

Male, born 8th june 1978

1,86m, 75 kg

serum creat 91 micromol/L.

Urinary infection, started with beta-lactam + tobramycine

PD parameter tobramycin: Cmax/MIC = 10, assume MIC of 2 mg/L

Cmax = Dos/V = 20 mg/L

Vd = 0.2-0.3 L/kg, take 0.25 L/kg * 75 kg = 18.75 L

Dos = 20 * 18.75 = 375 mg (= 5 mg/kg)

Case tobramycin

Male, born 8th june 1978

- 1,86m, 75 kg
- serum creat 91 micromol/L.
- Pulmonary infection with sepsis, started with beta-lactam + tobramycine

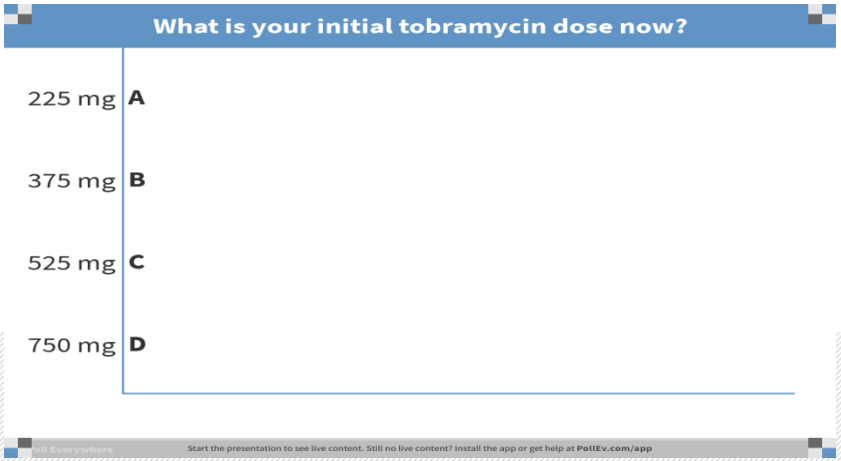
What is your initial tobramycin dose now?

A) 225 mg

B) 375 mg

C) 525 mg

D) 750 mg



Case tobramycin

Male, born 8th june 1978

- 1,86m, 75 kg
- serum creat 91 micromol/L.
- Pulmonary infection with sepsis, started with beta-lactam + tobramycine

PD parameter tobramycin: Cmax/MIC = 10, assume MIC of 2 mg/L

Cmax = Dos/V = 20 mg/L

Vd = 0.3-0.4 L/kg, take 0.35 L/kg * 75 kg = 26.25 L

Dos = 20 * 26.25 = 525 mg (= 7 mg/kg)

Case tobramycin

Male, born 8th june 1978

1,86m, 75 kg

serum creat 91 micromol/L.

Exacerbation of his cystic fibrosis, started with beta-lactam + tobramycine

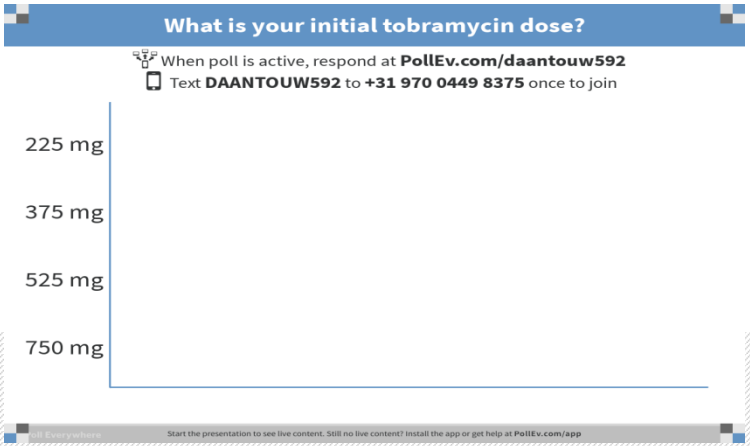
What is your initial tobramycin dose?

A) 225 mg

B) 375 mg

C) 525 mg

D) 750 mg



Case tobramycin

Male, born 8th june 1978

1,86m, 75 kg

serum creat 91 micromol/L.

Exacerbation of his cystic fibrosis, started with beta-lactam + tobramycine

European Consensus Cystic Fibrosis

Cmax = Dos/V = 25-30 mg/L (due to limited penetration into sputum)

Vd = 0.28-0.38 L/kg, take 0.33 L/kg * 75 kg = 25 L

Dos = 30 * 25 = 750 mg (= 10 mg/kg)

Summary Tobramycin

Efficacy determined by Cmax/MIC

Often poor penetration into pulmonary tissue

Cmax mainly determined by Volume of distribution, target 20 mg/L

- Vd normally: 0.2 – 0.3 L/kg
- Vd in sepsis: 0.3 – 0.4 L/kg

Standard dose (based on Vd):

- Non-sepsis: 5 mg/kg
- Sepsis: 7 mg/kg
- CF: 10 mg/kg

Note: in obese patients, take the ideal bodyweight

Case tobramycin

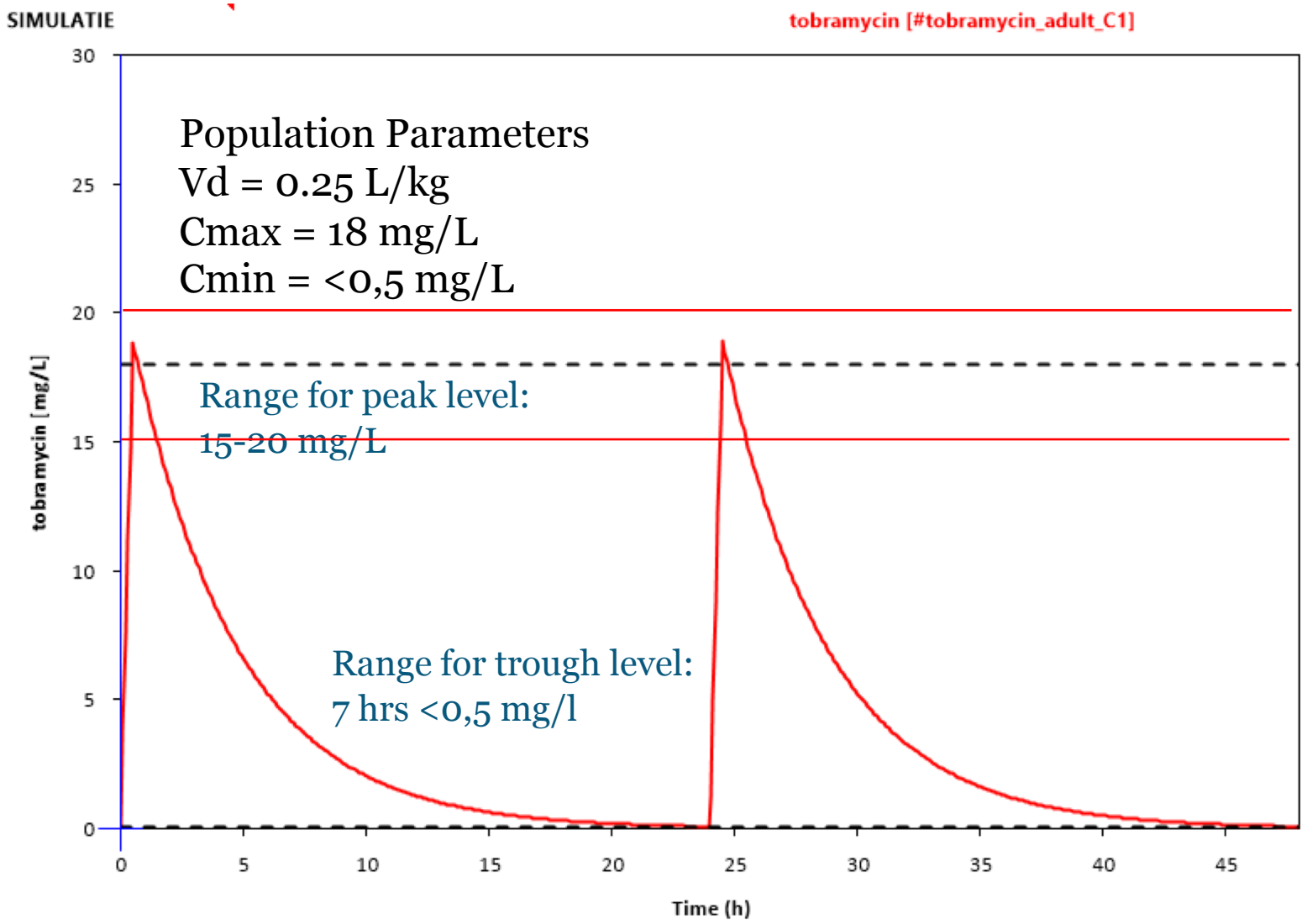
Male, born 8th june 1978

1,86m, 75 kg

serum creat 91 micromol/L.

Pulmonary infection, started with beta-lactam + tobramycine

Initial dose (5 mg/kg) 375 mg o.d. (Standard practice based on epidemiological susceptibility values and population Vd value: 5 mg/kg o.d. with a moderate renal function)


SIMULATIE
tobramycin [#tobramycin_adult_C1]
Population Parameters
Vd = 0.25 L/kg
Cmax = 18 mg/L
Cmin = <0,5 mg/L
Range for peak level:
15-20 mg/L
Range for trough level:
7 hrs <0,5 mg/l
tobramycin [mg/L]
Time (h)
0
5
10
15
20
25
30
35
40
45

Case tobramycin

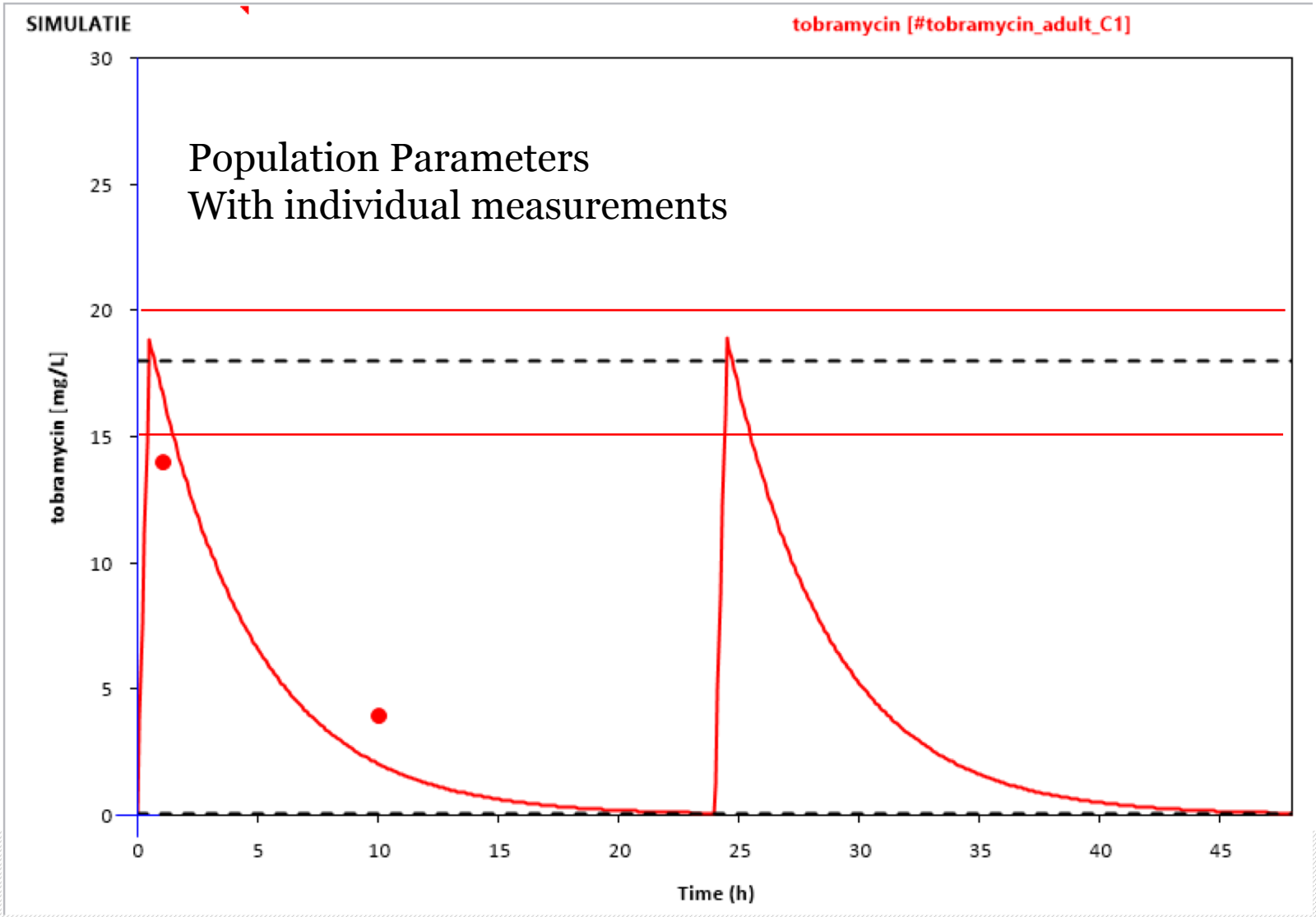
Male, born 8th june 1958

- 1,86m, 75 kg
- serum creat 91 micromol/L.
- Pulmonary infection, started with beta-lactam + tobramycine

Initial dose 375 mg o.d. (Standard practice 5 mg/kg o.d. with a moderate renal function)

Blood samples

- **1 h after start (peak level): 14 mg/L**
- **after 10 h: 4 mg/L.**


SIMULATIE
tobramycin [#tobramycin_adult_C1]
Population Parameters
With individual measurements
tobramycin [mg/L]
30
25
20
15
10
5
0
0
5
10
15
20
25
30
35
40
45
Time (h)

Case tobramycin

Male, born 8th june 1958

1,86m, 75 kg, serum creat 91 micromol/L.

Pulmonary infection, started with beta-lactam + tobramycine

Initial dose: 375 mg o.d. (Standard practice 5 mg/kg o.d. with a moderate renal function)

Blood samples: 1 h after start (peak level): 14 mg/L; after 10 h: 4 mg/L.

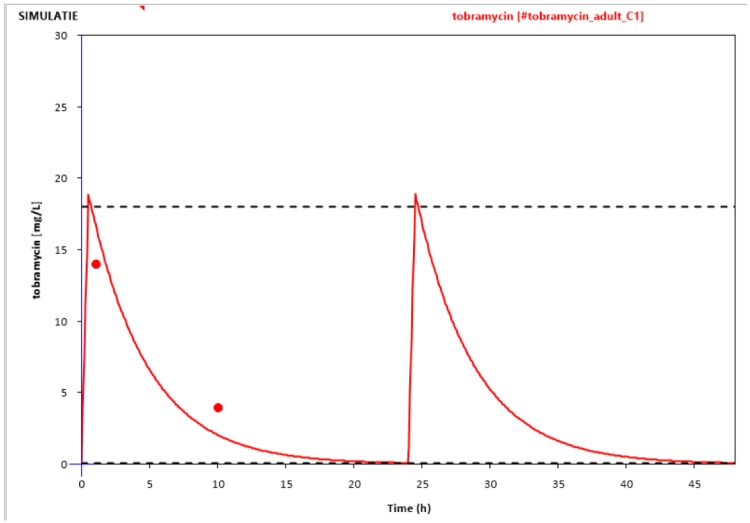
Your advice:

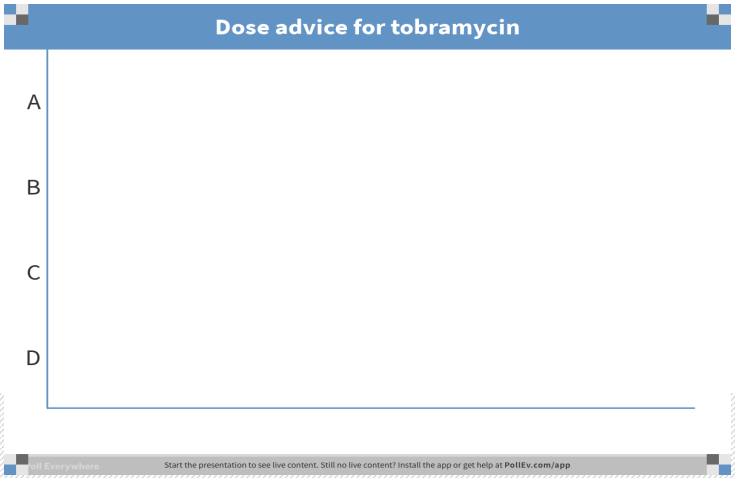
A) Maintain dose and interval

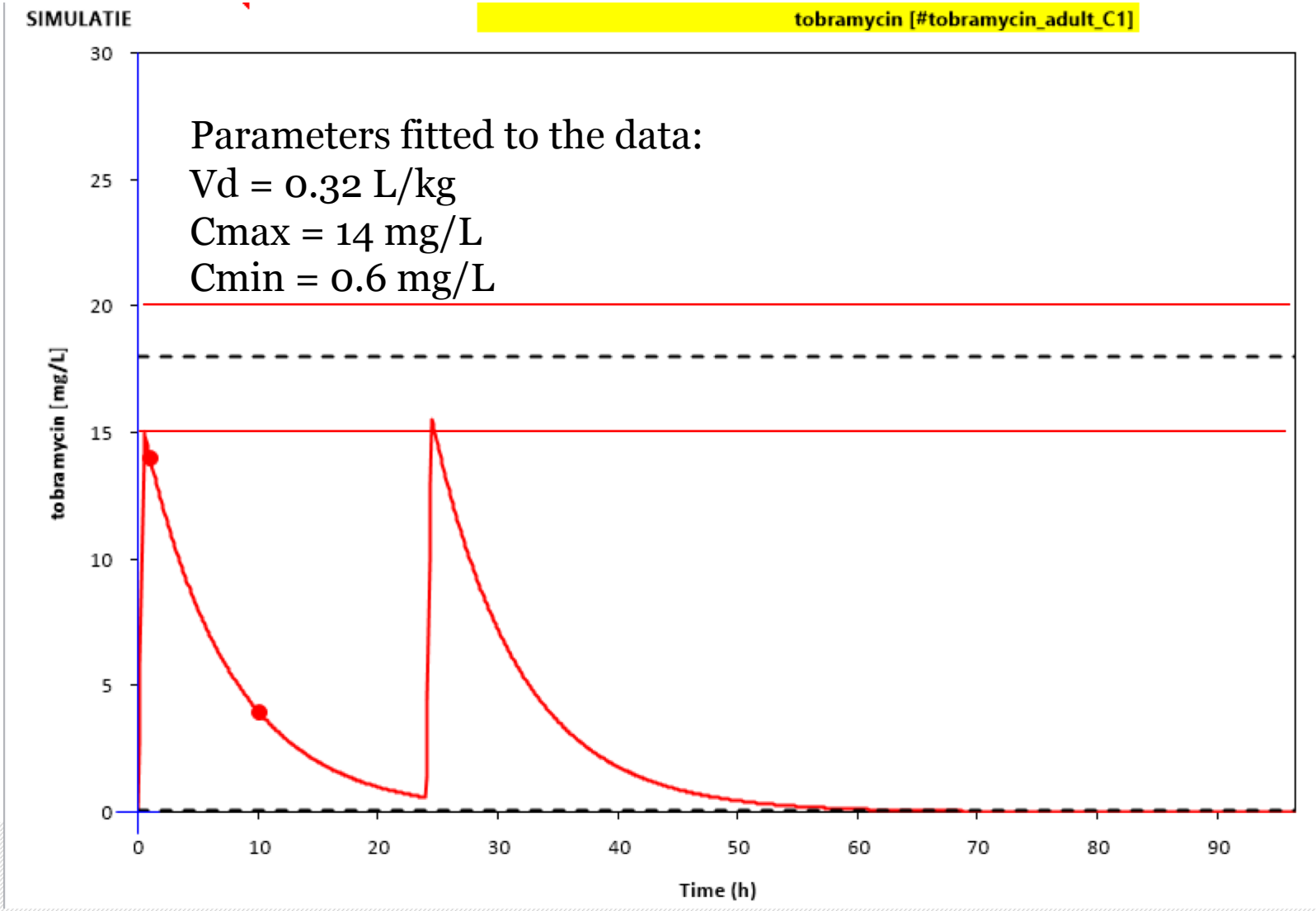
B) Decrease dose and maintain interval

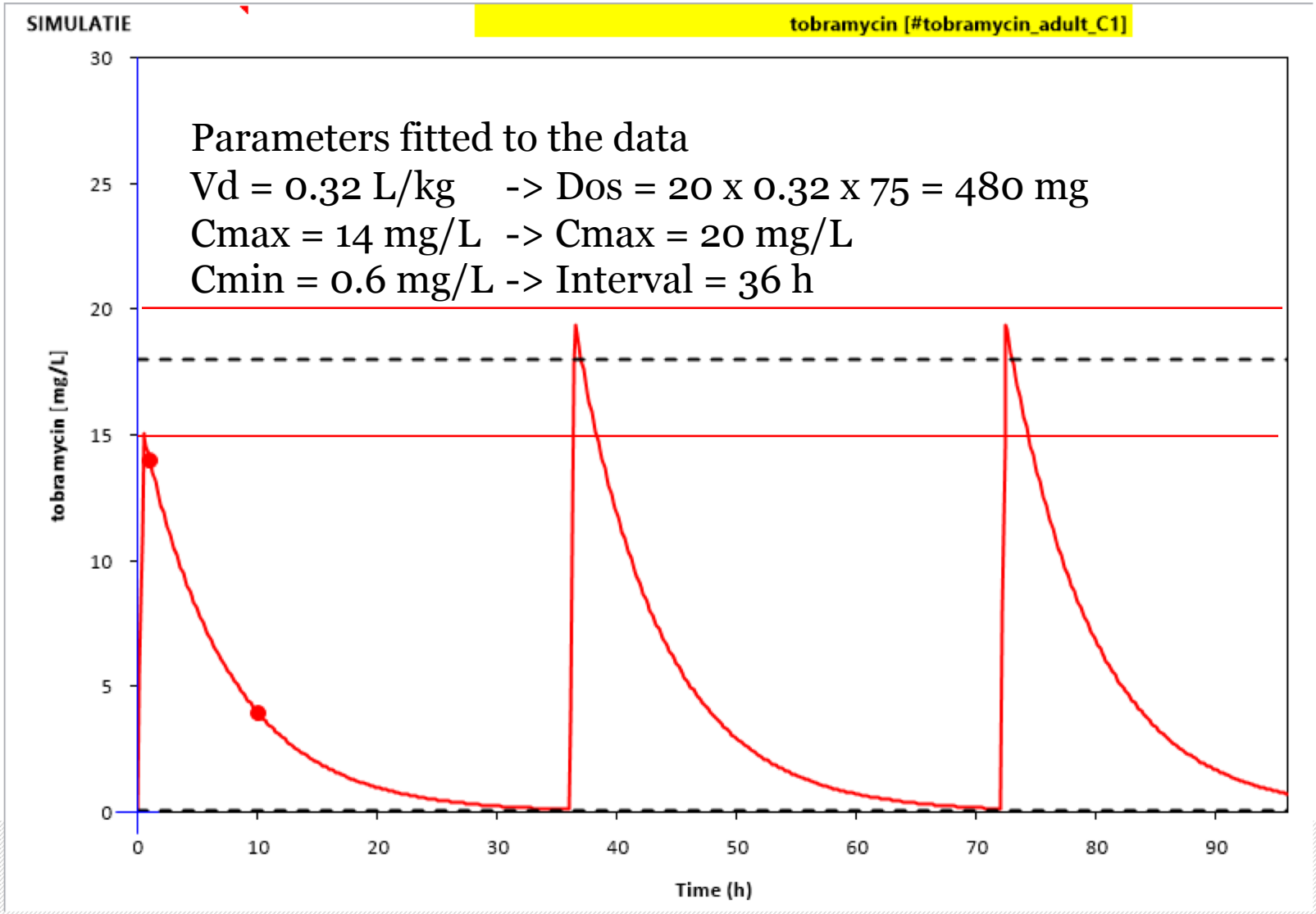
C) Increase dose and increase interval

D) Decrease dose and increase interval






SIMULATIE
tobramycin [#tobramycin_adult_C1]
Parameters fitted to the data:
Vd = 0.32 L/kg
Cmax = 14 mg/L
Cmin = 0.6 mg/L
tobramycin [mg/L]
Time (h)
0
5
10
15
20
25
30
0
10
20
30
40
50
60
70
80
90


SIMULATIE
tobramycin [#tobramycin_adult_C1]
Parameters fitted to the data
Vd = 0.32 L/kg -> Dos = 20 x 0.32 x 75 = 480 mg
Cmax = 14 mg/L -> Cmax = 20 mg/L
Cmin = 0.6 mg/L -> Interval = 36 h
tobramycin [mg/L]
Time (h)
0
5
10
15
20
25
30
0
10
20
30
40
50
60
70
80
90

Case gentamicin

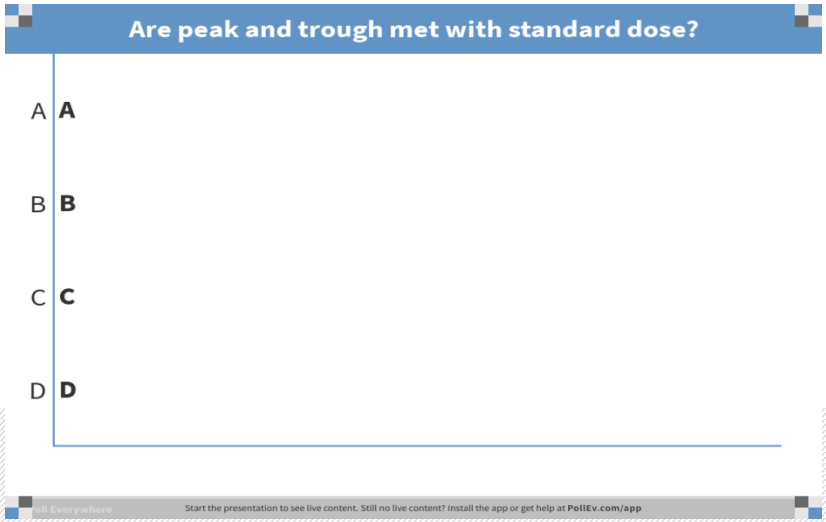
Neonate, prematurely born, birth weight 1.6 kg, open ductus botalli, treated with indomethacin i.v., signs of infection.

- Indication for antibiotics (amoxicillin/gentamicin)
- gentamicin started with 5 mg/kg once every 36 hours according to local protocol for neonates with infection

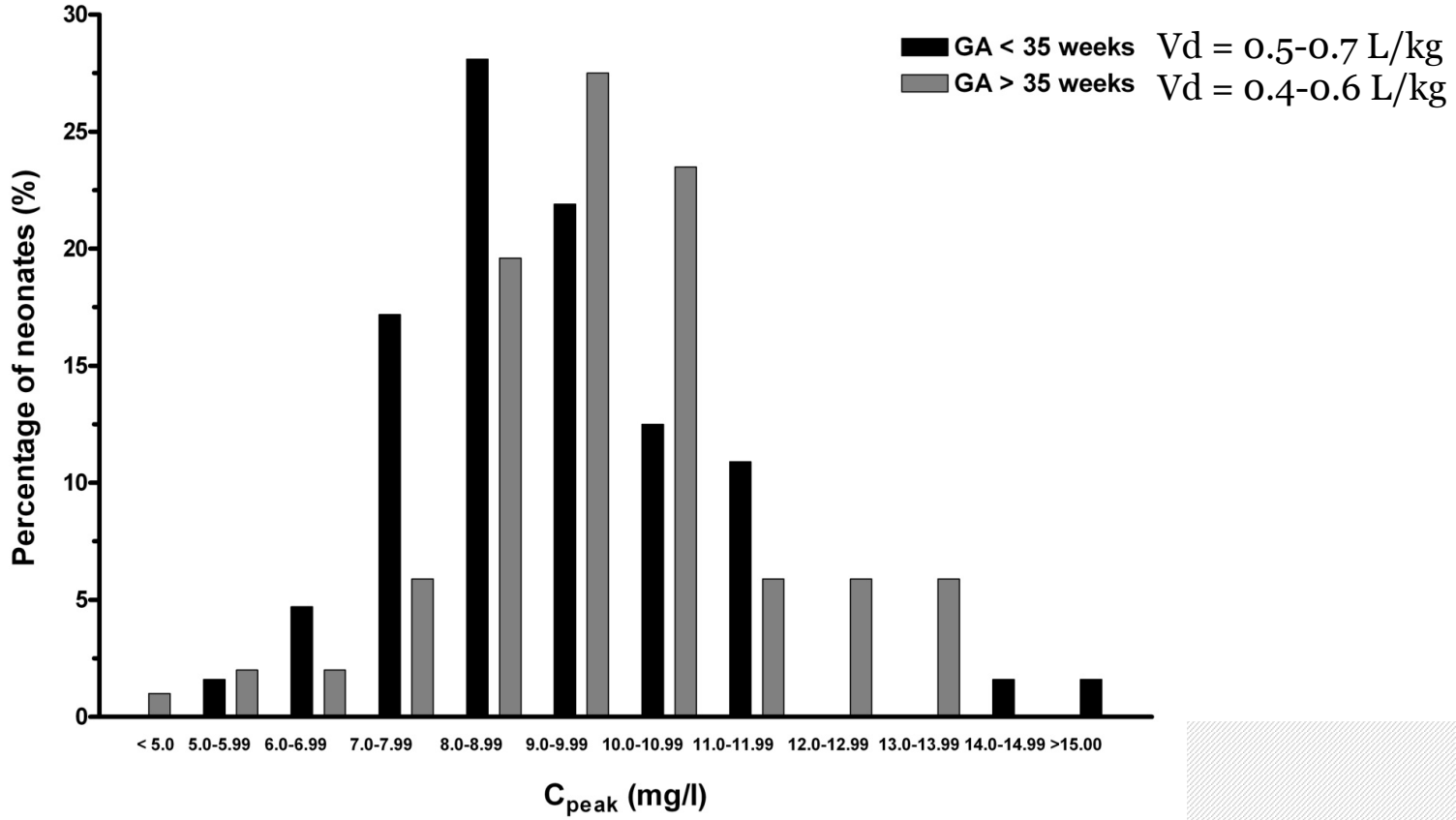
Target drug levels are 9-11 (peak) and ≤1 (trough) mg/L

Do you expect levels are met?

A) Peak Yes, trough higher
B) Peak higher, trough higher
C) Peak lower, trough Yes
D) Peak lower, trough higher



Distribution of the peak level in 115 neonates treated with 5 mg/kg



Premature neonates

Volume of distribution (in L/kg) increase with decreasing gestation

Term:	0.4-0.6 L/kg
Preterm:	0.5-0.7 L/kg
Extremely premature:	0.6-0.8 L/kg

Open ductus Botalli

Blood vessel connecting the main pulmonary artery to the proximal descending aorta to bypass the fetus's fluid-filled non-functioning lungs

Closure is normally spontaneous at birth, but can be done by NSAID treatment

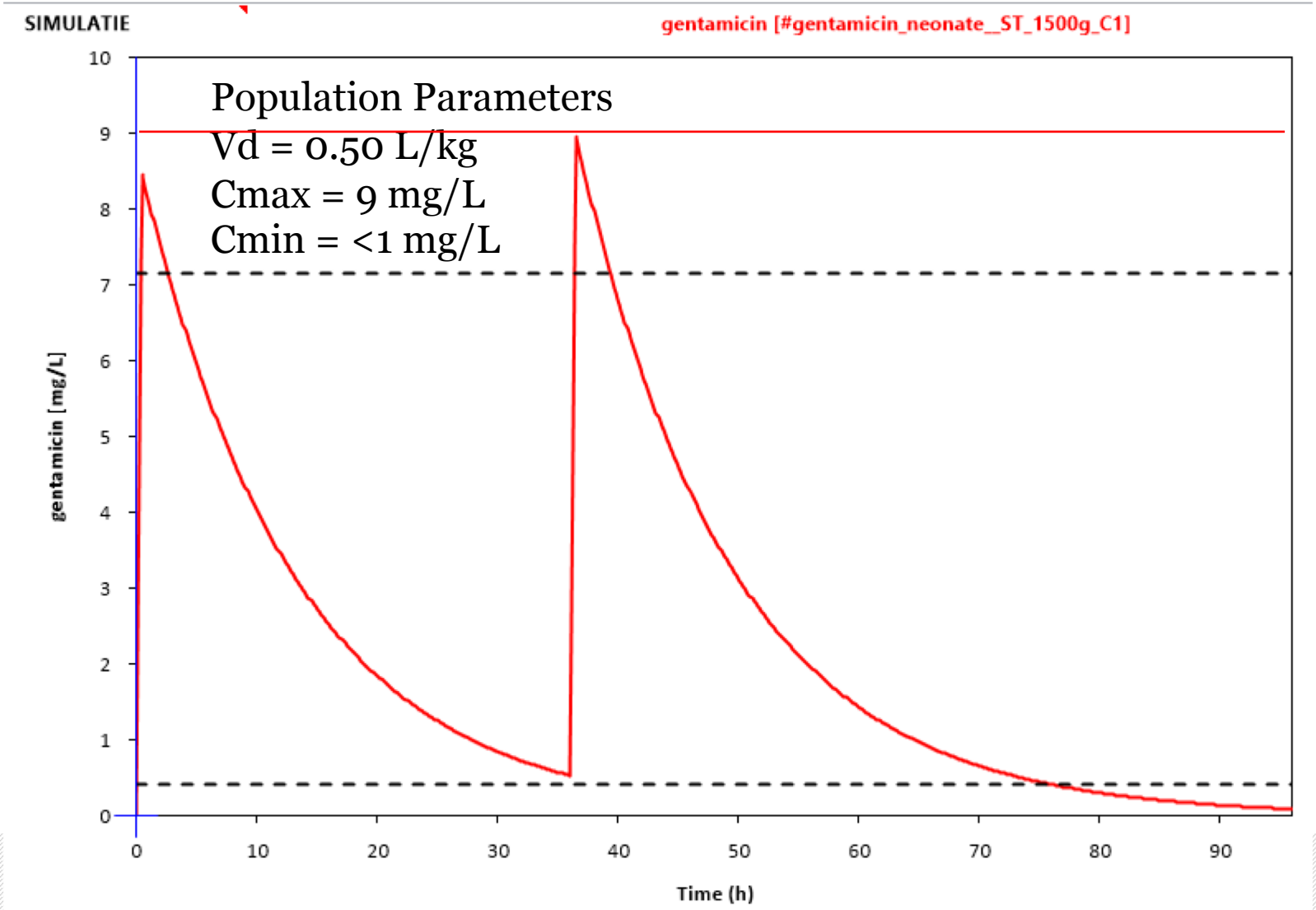
NSAID’s reduce renal blood flow and renal drug clearance

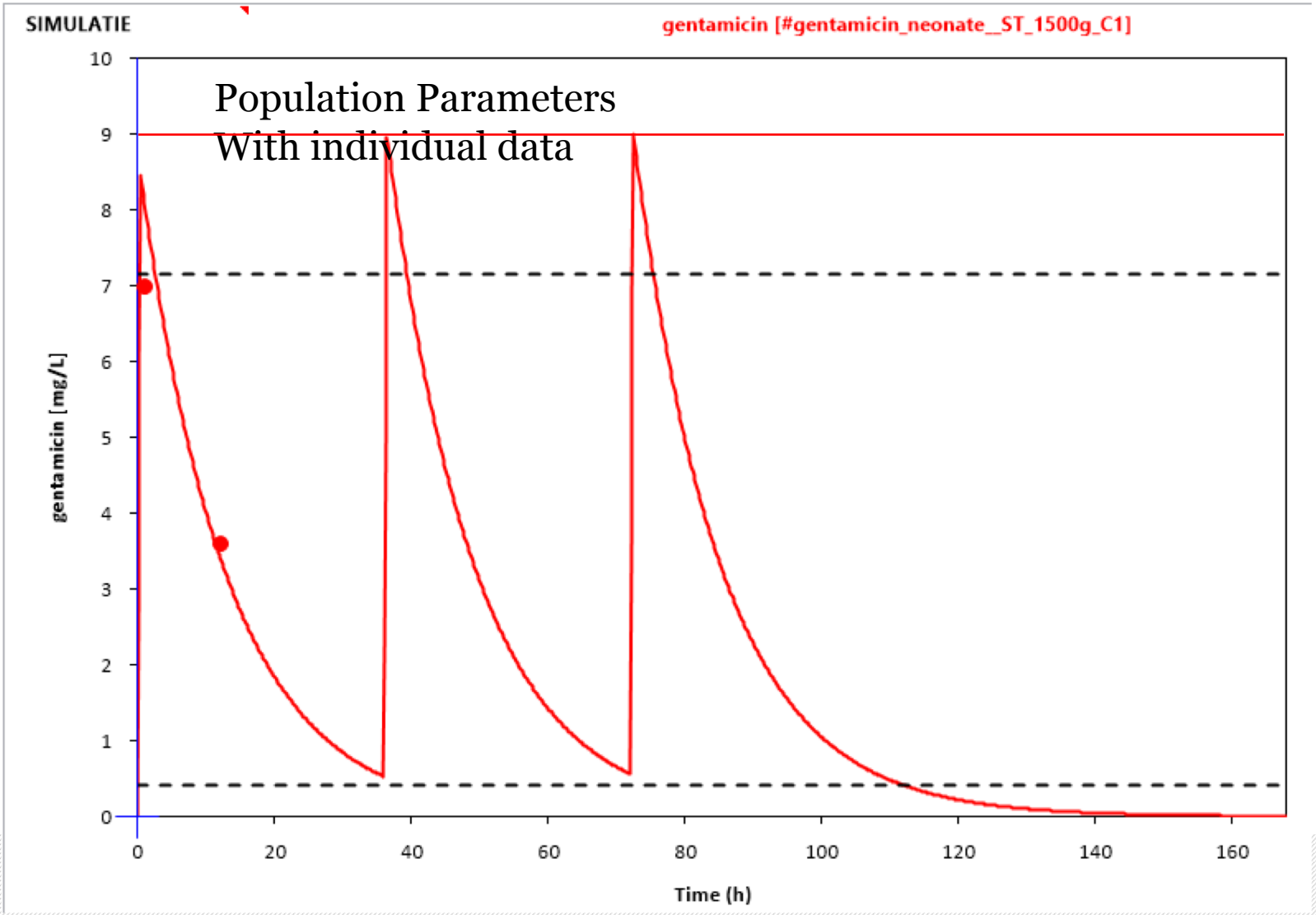
Case gentamicin in premature neonate

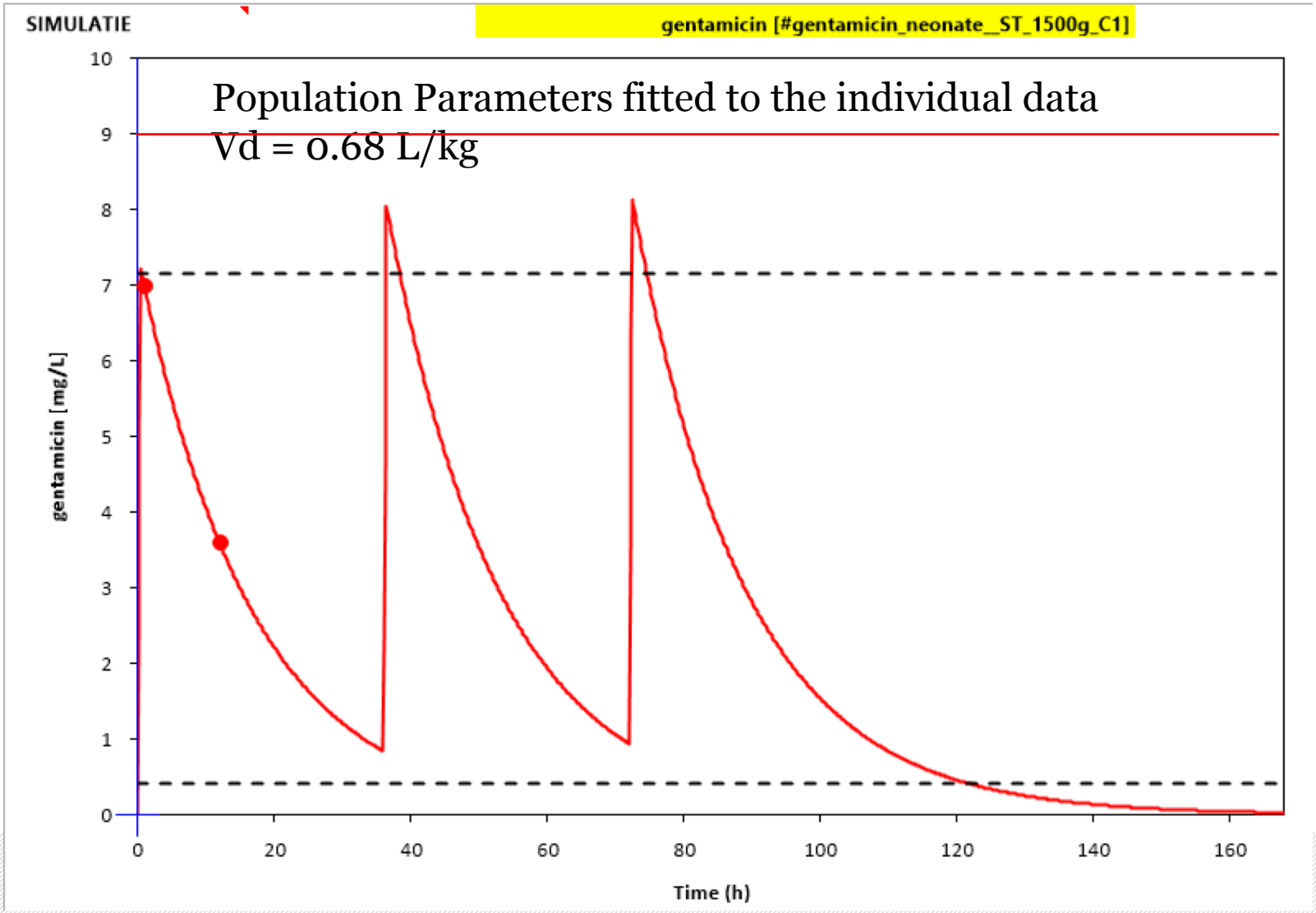
Expected higher Vd and lower clearance

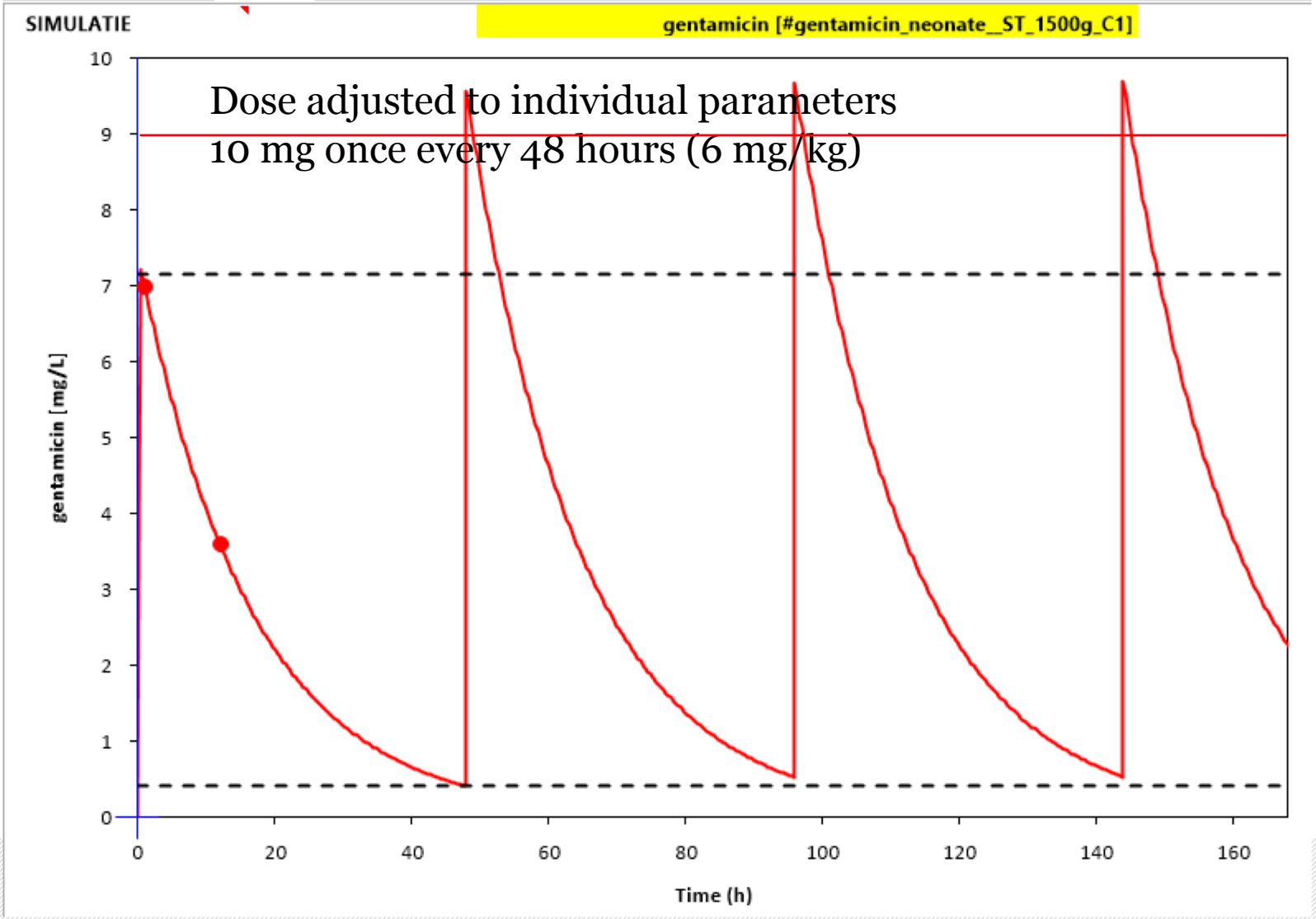
Expected lower peak and higher trough levels

Take samples immediately after dose and about 12 hours after dosing for dose optimisation


SIMULATIE
gentamicin [#gentamicin_neonate_ST_1500g_C1]
Population Parameters
Vd = 0.50 L/kg
Cmax = 9 mg/L
Cmin = <1 mg/L
gentamicin [mg/L]
Time (h)
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60
70
80
90


SIMULATIE
gentamicin [#gentamicin_neonate_ST_1500g_C1]
Population Parameters
With individual data
gentamicin [mg/L]
Time (h)
0
1
2
3
4
5
6
7
8
9
10
0
20
40
60
80
100
120
140
160


SIMULATIE
gentamicin [#gentamicin_neonate_ST_1500g_C1]
Population Parameters fitted to the individual data
Vd = 0.68 L/kg
gentamicin [mg/L]
Time (h)
0
1
2
3
4
5
6
7
8
9
10
0
20
40
60
80
100
120
140
160


SIMULATIE
gentamicin [#gentamicin_neonate__ST_1500g_C1]
Dose adjusted to individual parameters
10 mg once every 48 hours (6 mg/kg)
gentamicin [mg/L]
Time (h)
0
1
2
3
4
5
6
7
8
9
10
0
20
40
60
80
100
120
140
160

Case vancomycin

ICU patient (female, 63 y/o, 80 kg, 1.75 m, creatinine 180 micromol/L), catheter related infection, treated with vancomycin, 2000 mg/day continuous infusion, start 13.00.

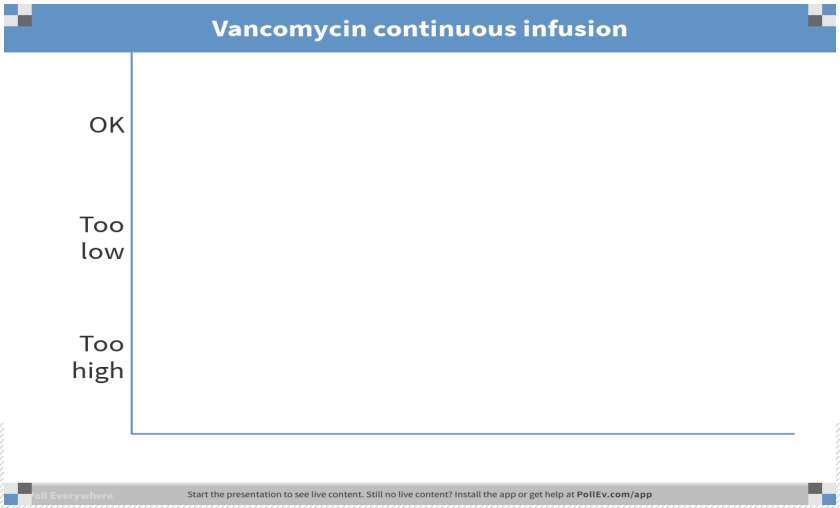
Next day, a sample is drawn at 06.00 and the vancomycin concentration is 22 mg/L (based on AUC>400 mg*h/L target is 18-25 mg/L)

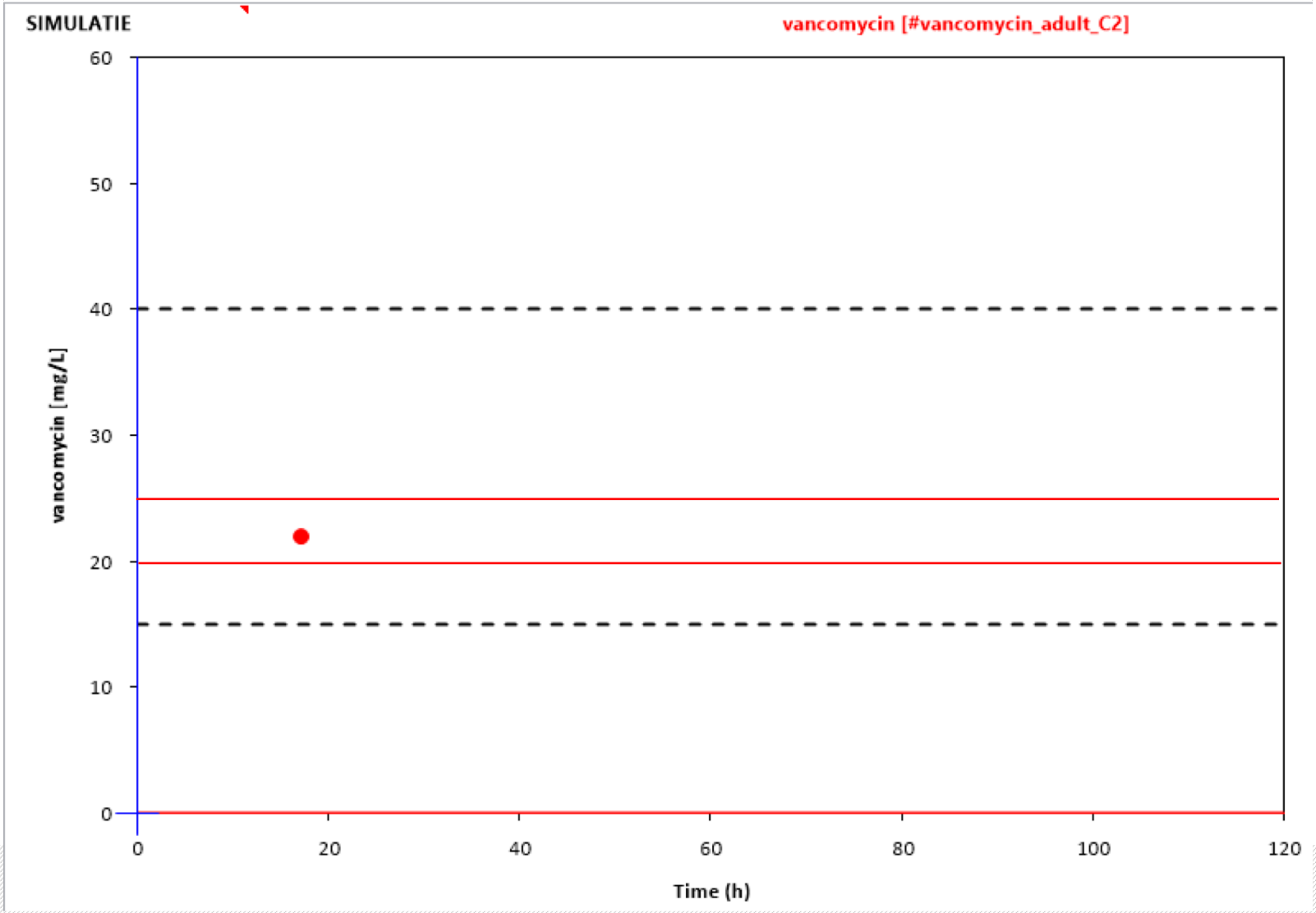
What is your opinion:

A) Dose is fine

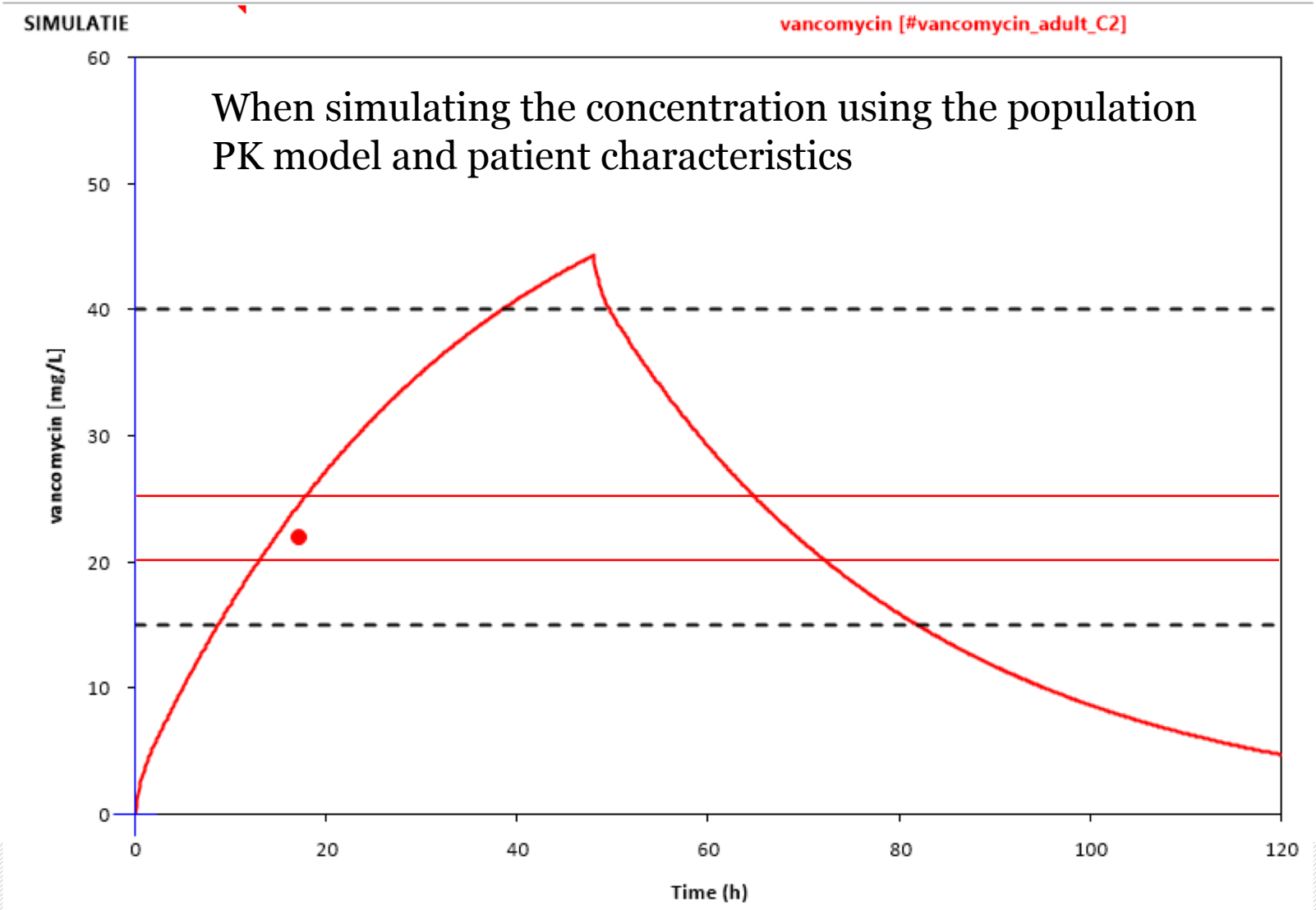
B) Dose is too low

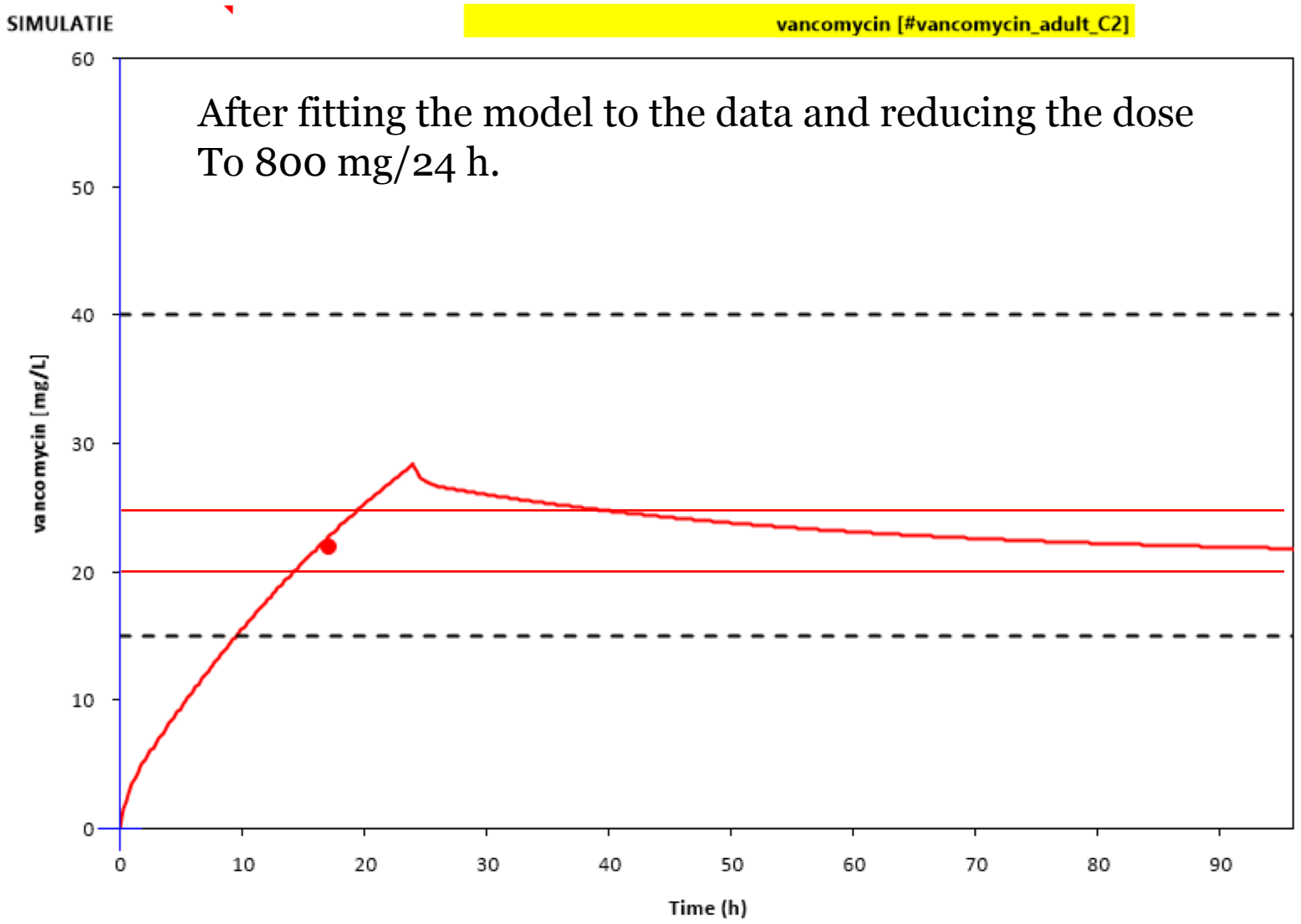
C) Dose is too high




SIMULATIE
vancomycin [#vancomycin_adult_C2]
vancomycin [mg/L]
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Time (h)

When simulating the concentration using the population PK model and patient characteristics




SIMULATIE
vancomycin [#vancomycin_adult_C2]
After fitting the model to the data and reducing the dose
To 800 mg/24 h.
vancomycin [mg/L]
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
Time (h)

Case flucloxacillin

ICU patient (male, 63 y/o, 80 kg, 1.80 m, creatinine 89 micromol/L, albumin 40 g/L) is treated with flucloxacillin because of an infectious endocarditis

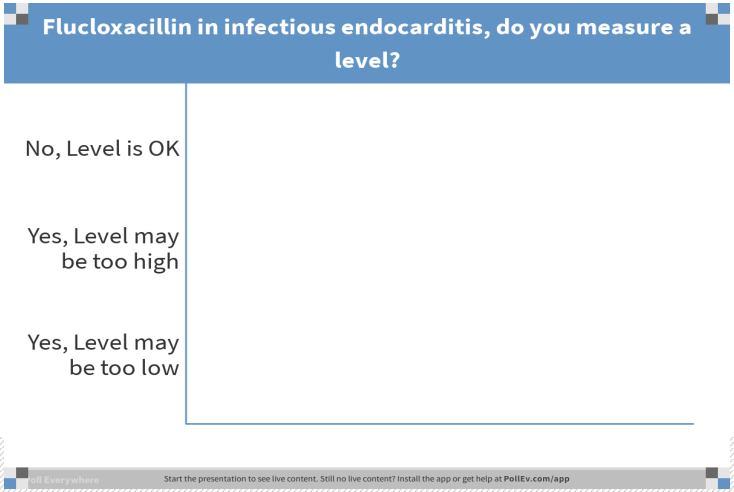
Initial dose is 12000 mg/day as continuous infusion

Do you measure a level?

A) No, level is OK

B) Yes, level may be too high

C) Yes, level may be too low



Case flucloxacillin

Flucloxacillin

Vd = 0.25v L/kg

Half life = 1 h

Cstst = (F*D/T) * 1,44 * $T_{1/2}$/Vd

Cstst = 12000/24 * 1.44 * 1/(0.25 * 80)

Cstst = 500 * 1.44 * 1/20 = 36 mg/L

Seems OK

Case flucloxacillin

ICU patient (male, 63 y/o, 80 kg, 1.80 m, creatinine 89 micromol/L, albumin 40 g/L) is treated with flucloxacillin because of an infectious endocarditis, **MIC of the infecting micro-organism is 2 mg/L**

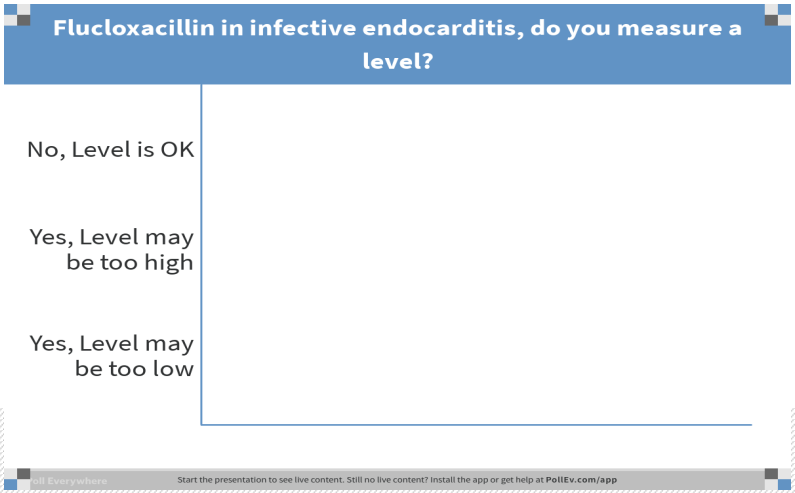
Initial dose is 12000 mg/day as continuous infusion

Do you measure a level?

A) No, level is OK

B) Yes, level may be too high

C) Yes, level may be too low



Case flucloxacillin

Flucloxacillin

- **Vd = 0.25 L/kg, half life = 1 h**
- **Cstst = (F*D/T) * 1,44 * $T_{1/2}$/Vd = 36 mg/L**
- **Protein binding is 95%**
- **Free concentration is 0.05 * 36 = 1.8 mg/L**

So yes, because level may be too low.

Case flucloxacillin

ICU patient (male, 63 y/o, 80 kg, 1.80 m, creatinine 89 micromol/L, **albumin 20 g/L**) is treated with flucloxacillin because of an infectious endocarditis, MIC of the infecting micro-organism is 2 mg/L **and the patient shows twitches**

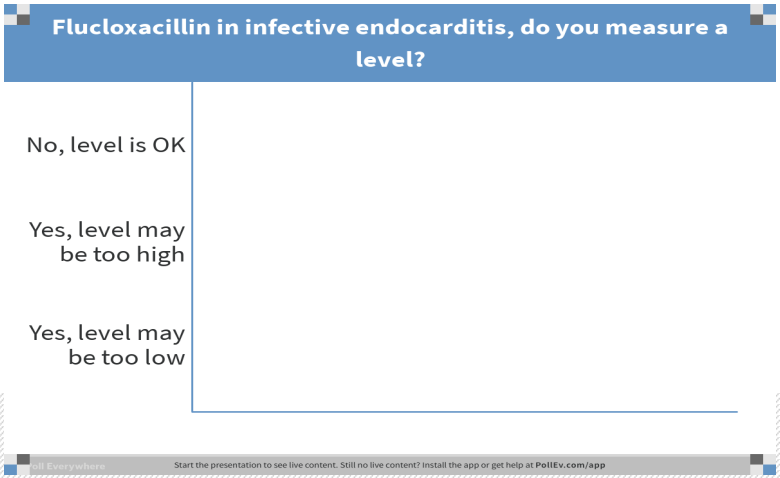
Initial dose is 12000 mg/day as continuous infusion

Do you measure a level?

A) No, level is OK

B) Yes, level may be too high

C) Yes, level may be too low



Case flucloxacillin

Flucloxacillin

- **Vd = 0.25 L/kg, half life = 1 h**
- **Cstst = (F*D/T) * 1,44 * $T_{1/2}$/Vd = 36 mg/L**
- **Patient suffers from hypoalbuminemia**
- **Free concentration is increased**
- **Patient may develop neurological side effects**

So yes, because level may be too high

Case voriconazole

Patient (70 kg) with an invasive fungal infection and inflammation starts with a loading dose of twice daily 400 mg i.v. followed by a maintenance dose of twice daily 300 mg i.v.

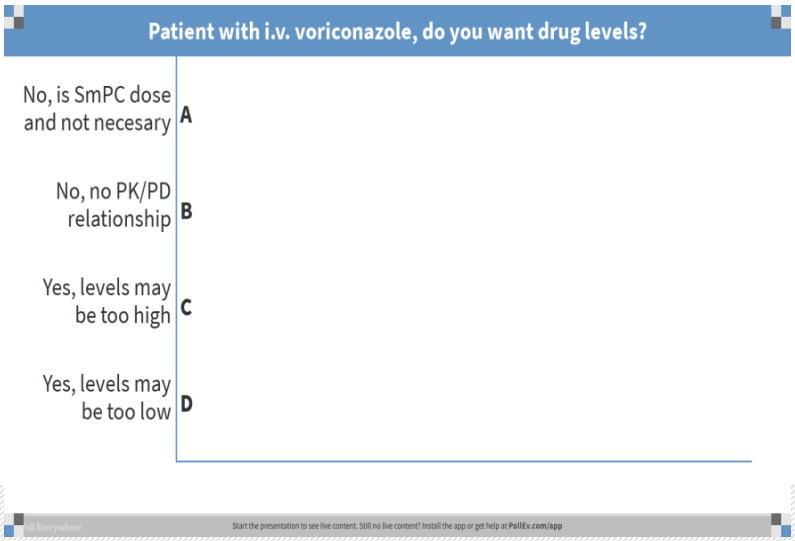
Do you measure blood levels?

A. No, is SmPC dose

B. No, no PK/PD relationship

C. Yes, levels may be too high

D. Yes, levels may be too low



Case voriconazole: PK/PD relationship

Retrospective (n=201)

- IFI: possible, probable, proven
- Outcome: partial, complete, failure

Incident	No. of patients with incident/ total no. with indicated concn (%)		*P* value[a]
Treatment failure	<1.7 mg/liter	≥1.7 mg/liter	
All treatment patients ($n = 163$)[b]	19/74 (26)	6/89 (7)	<0.01
Proven or probable IFI ($n = 67$)	12/34 (35)	2/33 (6)	<0.01
Visual/auditory hallucinations	≤5 mg/liter	>5 mg/liter	
All patients ($n = 201$)	2/170 (1.2)	10/31 (32)	<0.01

Dolton AAC 2012

TABLE 3 Factors associated with a significant change in voriconazole concentration identified from multiple linear regression analysis[a]

Model term	Coefficient	95% Confidence interval		*P* value
		Lower	Upper	
Oral administration[b]	−1.348	−1.741	−0.955	<0.01
Age (yr)[c]	0.026	0.017	0.036	<0.01
Weight (kg)	−0.028	−0.038	−0.018	<0.01
Daily dose (mg)	0.005	0.003	0.006	<0.01
Concomitant medication				
CYP2C19 inducer[d]	−2.367	−3.181	−1.553	<0.01
Prednisone/prednisolone	−1.012	−1.346	−0.678	<0.01
Methylprednisolone	−1.833	−2.445	−1.221	<0.01
Dexamethasone	−1.245	−1.991	−0.500	<0.01
Omeprazole	1.141	0.575	1.706	<0.01
Pantoprazole	0.685	0.330	1.041	<0.01
Esomeprazole	1.009	0.192	1.826	<0.05
Rabeprazole	1.414	0.800	2.028	<0.01

Dolton AAC 2012

CYP450 enzymes:

2C19*17 => ultra rapid

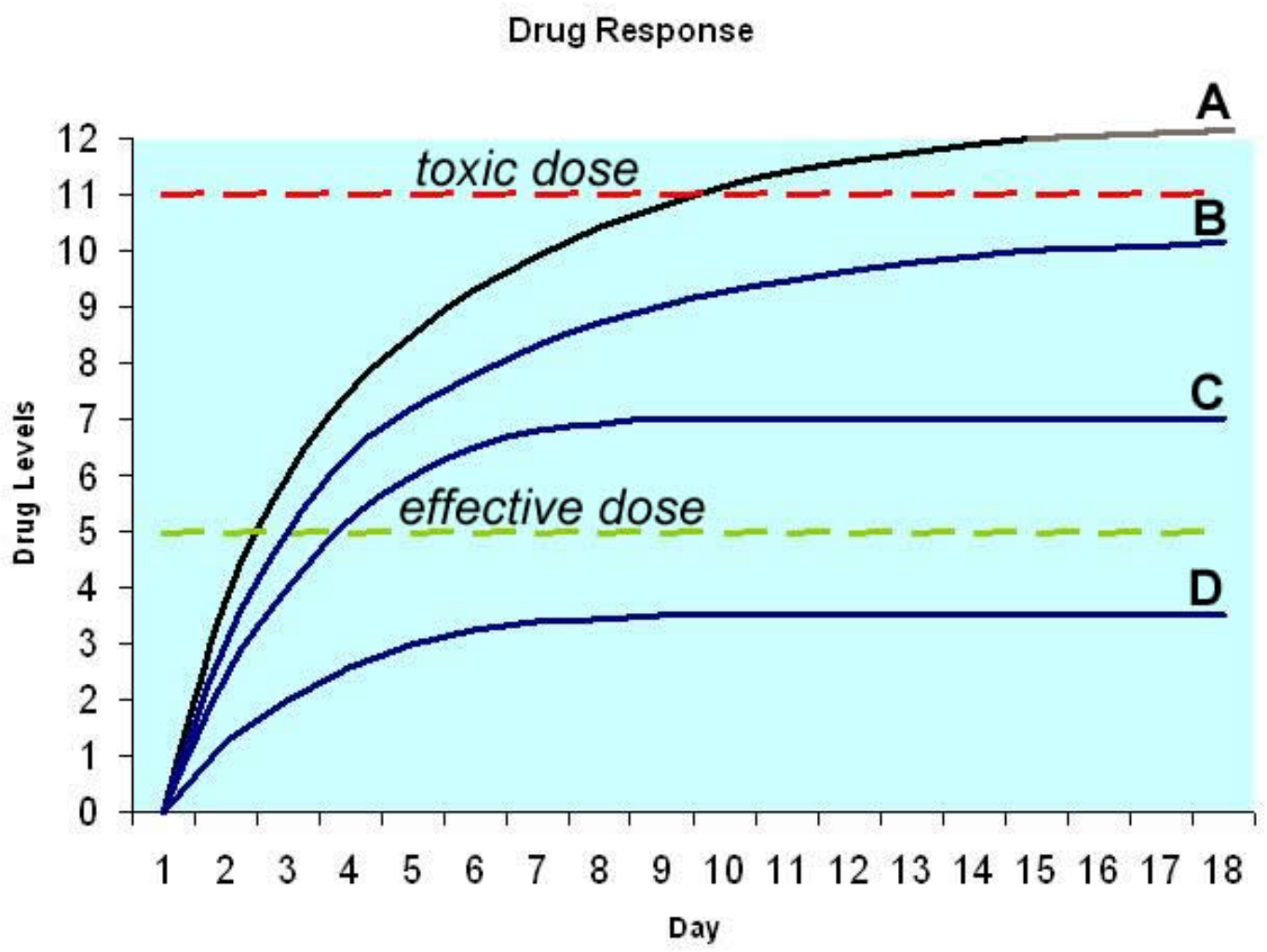
2C19*1 => extensive metabolizer

2C19*2/*3 => poor metabolizer

VORICONAZOLE

	UR[1]	EM	HEM	PM
T_{max}, h		1.3 (0.5-3.0)	1.0 (0.5-1.5)	1.5 (0.5-3.1)
C_{trough}, µg/L		968 ± 772	2636 ± 1471	4139 ± 1010
C_{max}, µg/L		3212 ± 1307	5780 ± 2094	7210 ± 1510
AUC_{τ}, µg·h/L	10 000	19 305 ± 9594	42 369 ± 19 090	58 697± 11 113
$T_{1/2}$, h		9.6 ± 5.1	16.9 ± 7.2	32.3 ± 9.4
CL_{ss}/F, L/h		12.6 ± 6.5	5.9 ± 3.5	3.5 ± 0.9

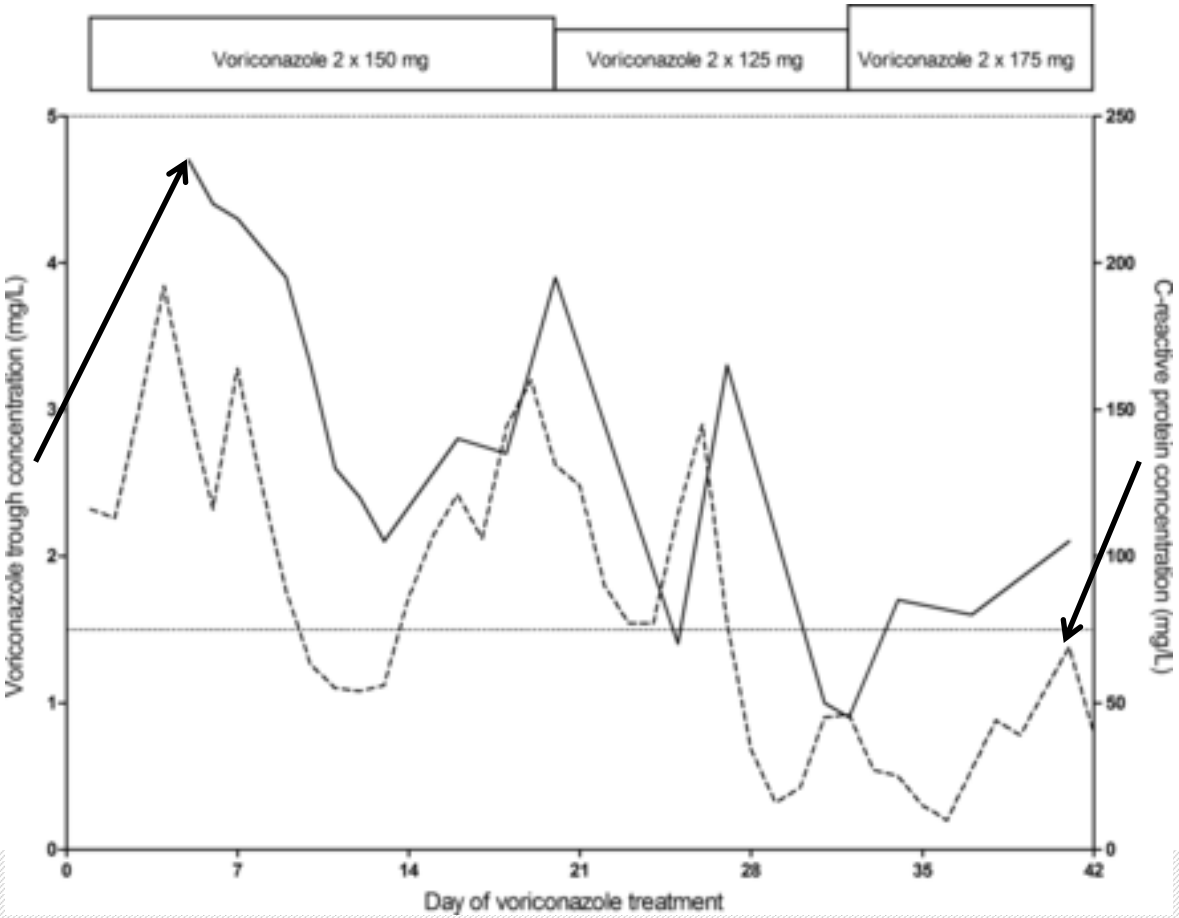
[1]**Wang** Eur J Clin Pharmacol 2009, **Lee** J Clin Pharmacol 2011


Drug Response
A
B
C
D
toxic dose
effective dose
Drug Levels
0
1
2
3
4
5
6
7
8
9
10
11
12
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Day

"SLOW"

"FAST"

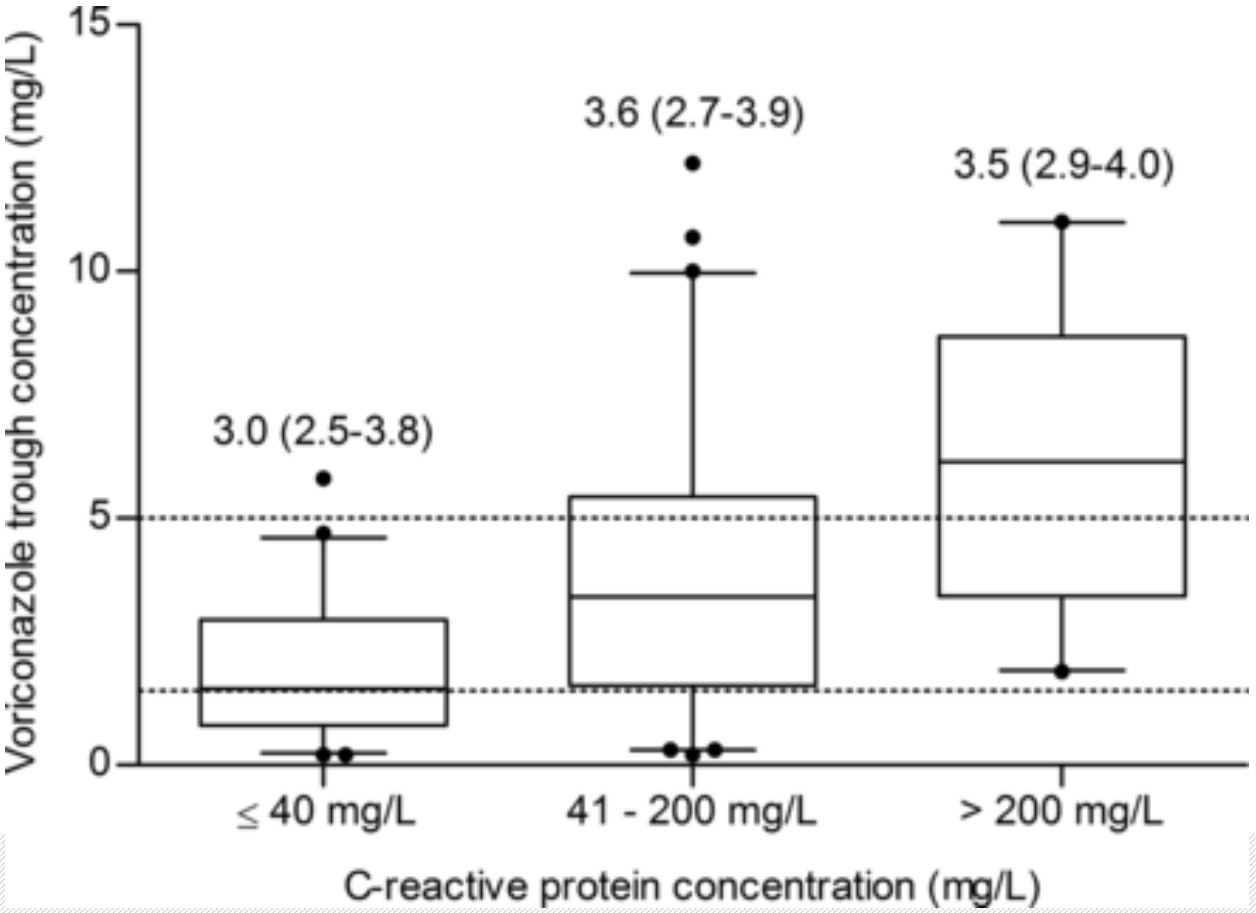
Case voriconazole: PK/CRP relationship



Van Wanrooy AAC 2014

Case voriconazole: PK/CRP relationship

Interleukin-2 modulates CYP2C19 activity



Van Wanrooy AAC 2014

Voriconazole

Saturable metabolism

Modulated by:

- drug-drug interactions (through CYP 2C19 and 3A4)
- Pharmacogenetics
- State of inflammation

Close monitoring is warranted

Summary

Aminoglycosides are dosed on peak and trough levels, do not wait for steady state, first dose kinetics

Beta-lactam are preferably given as continuous infusion and dosed on free drug concentration

Azoles are dosed on trough levels, voriconazole is very sensitive for interactions and endogenous effects on pharmacokinetics

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