Good Evening Pharmacists!

Case No. 3

Andreas von Ameln-Mayerhofer
Sindelfingen-Boeblingen General Hospital
Pharmacy Dept & Antimicrobial Stewardship Team
Germany

Day 1 (Admission)

65 year old woman (170cm, 71kg)

- with known oncology history (vulvectomy + radiotherapy 9 months ago)

- now subfebrile temperatures, wound pain, swollen (right) leg

- RR 113/61; heart rate 62/min; Temp. 37.3°C; SpO2 96%; respir. freq 13/min

- blood-analysis:

WBC	12.7 G/L	[4.4-12.5]
CRP	28 mg/dl	[0.0-0.6]
Na+	123 mmol/L	[133-145]
K+	4.4 mmol/L	[3.6-5.2]
eGFR	>90	(ckd-epi)
GPT/ALT	24 U/L	[0-35]

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Day 1

- further examination: deep vein thrombosis in the right leg + relapse of primary tumor

    => Start of anticoagulation therapy

Medication	
Enoxaparin 80mg s.c.	1-0-1
Pregabalin 25mg p.o.	1-0-2
Metamizole 1000mg p.o.	1-1-1-1
Fentanyl 37µg/h patch	every 3rd day
Movicol	1-1-0

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  Fentanyl 37µg/h patch every 3rd day
  Movicol   1-1-0

- plus infection (putative SSTI / wound infection)?
 => Start of (empiric) antibiotic therapy
  Ampicillin-Sulbactam 2/1g i.v. 1-1-1

Day 4

- deep vein thrombosis being treated

- but still CRP & WBC high, temperature > 35°C

WBC	12.4 G/L	[4.4-12.5]
CRP	26 mg/dl	[0.0-0.6]
Na+	133 mmol/L	[133-145]
K+	3.8 mmol/L	[3.6-5.2]
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Microbiology (wound swabs) material sent to mibi dept.

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on ward round there was some peculiar *scent of*….

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www.salzburgerland.com

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*plus **green-coloured** wound dressing…*

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WBC

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- but still CRP

    WBC

    CRP

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    eGFR

QUESTION 1:

What does this typical scent mean?

a) occurence of *Staphylococci*

b) occurence of *Candida*

c) occurence of **Pseudomonas !!!**

d) occurence of *anaerobic bacteria*

e) occurence of *clostridium difficile*

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=> PSEUDOMONAS AERUGINOSA!

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- but still CRP

    WBC

    CRP

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    K+

    eGFR

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QUESTION 2:

Now if it is Pseudomonas infection => what to do now?

a) Ampicillin-Sulbactam is OK => continue with therapy

b) change therapy to Linezolid i.v.

c) change therapy to Tigecyclin i.v.

d) change therapy to **Piperacillin-Tazobactam i.v.**

e) change therapy to **Meropenem i.v.**

f) change therapy to Ceftolozan-Tazobactam i.v.

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Decision is dependent on local resistance status!

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- deep vein thrombosis being treated

- but still CRP & WBC high, temperature > 35°C   => suspected infection site!
- suspected Pseudomonas – infection

  => Switch of antibiotic therapy to **Meropenem**

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 => Switch of antibiotic therapy to Meropenem 3 x 2g i.v.   t.i.d.   (= 6g/d)

Day 6

THERAPEUTIC DRUG MONITORING („TDM")   of meropenem

- Day 2 of meropenem-therapy

Two blood probes measured by means of HPLC-DAD   (gradient Tris pH 8 / MeOH, λ = 300nm)

=> 34 and 13.9 mg/L

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www.prisma.de

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=> we perform a plasma-conc.-simulation!

TDM-simulation No.1:   (day 6)
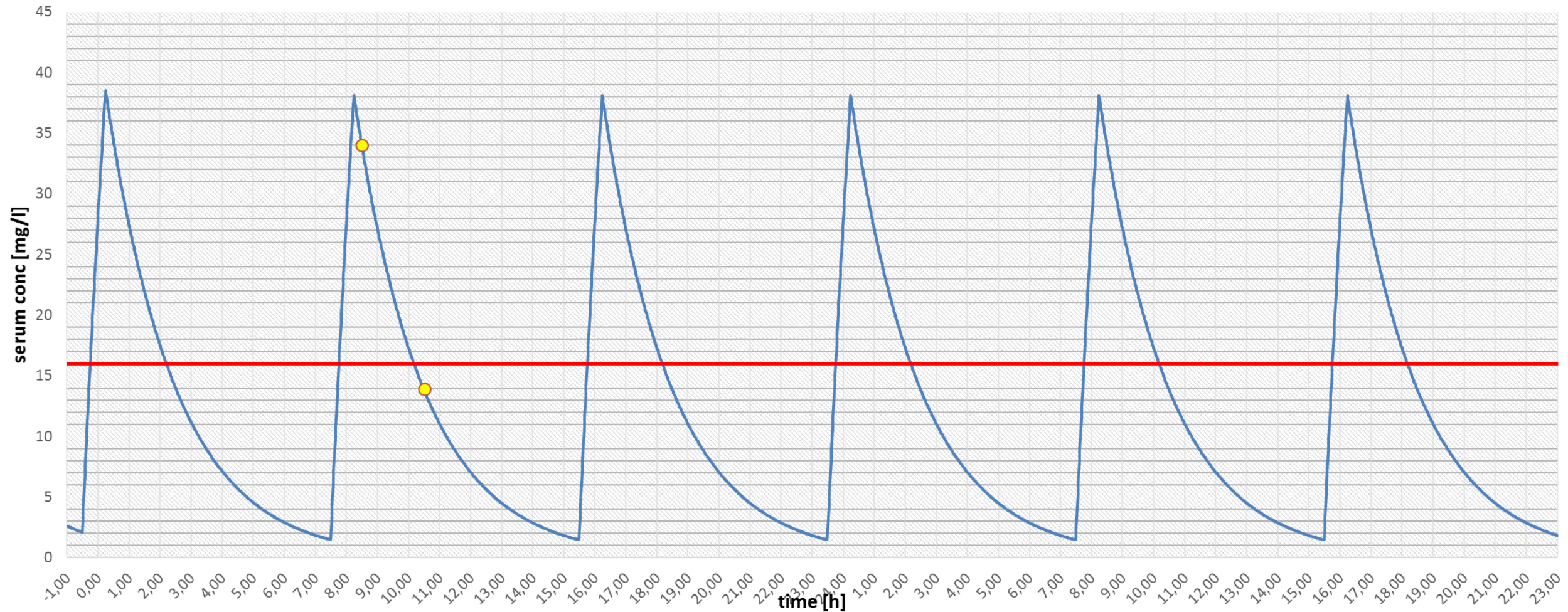
Measured concentrations embedded within the plasma curve simulation
=> target set at 50% of time above 4 x MIC („ƒt>4MIC")

TDM-simulation No.1:   (day 6)

30% > MIC

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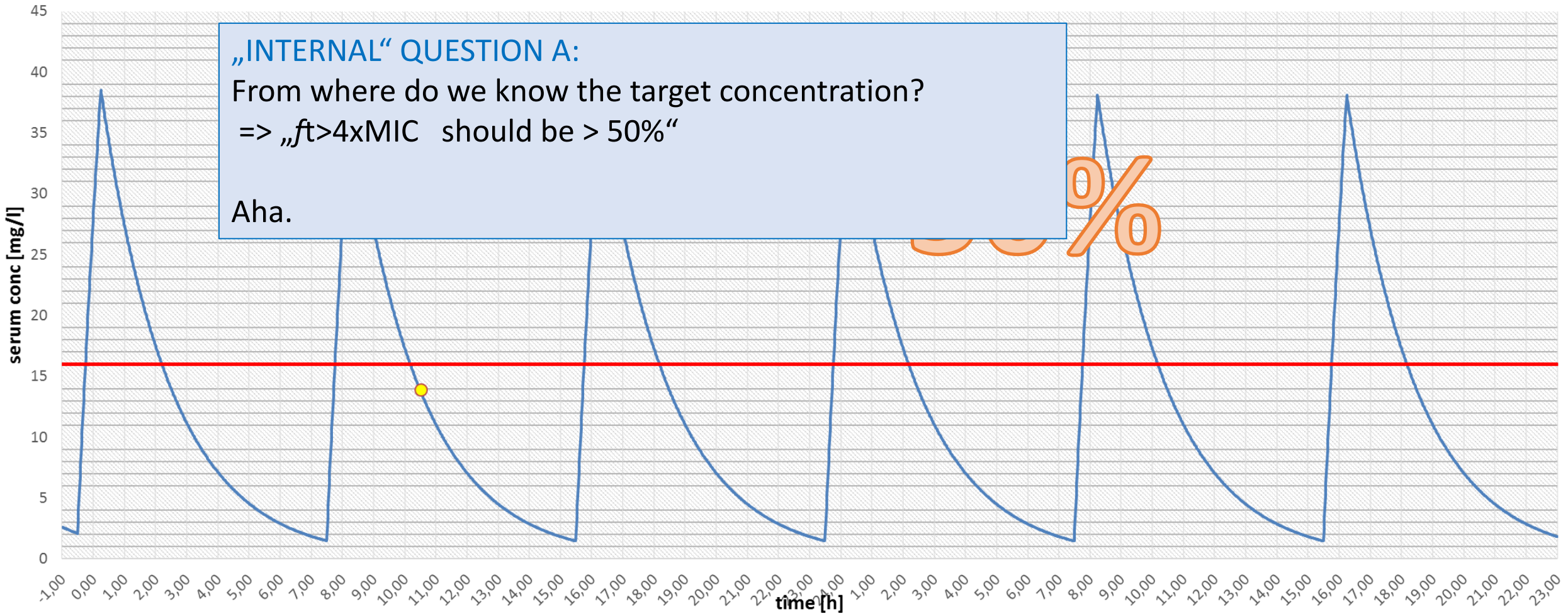=> check your national / european MIC-distribution

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Google   mic eucast distribution

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Home   Contact   Site

EUCAST EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

MIC and zone distributions and ECOFFs

Organization

Consultations

EUCAST News

New definitions of S, I and R

Clinical breakpoints and dosing

Rapid AST in blood cultures

Expert rules and intrinsic resistance

Resistance mechanisms

SOPs and Guidance documents

Ciprofloxacin/Escherichia coli
Antimicrobial wild type distributions
of microorganisms – references
database EUCAST

MIC and zone diameter distributions and ECOFFs

1. Distributions and ECOFFs

2. MIC and zone diameter correlations

Google   mic euca

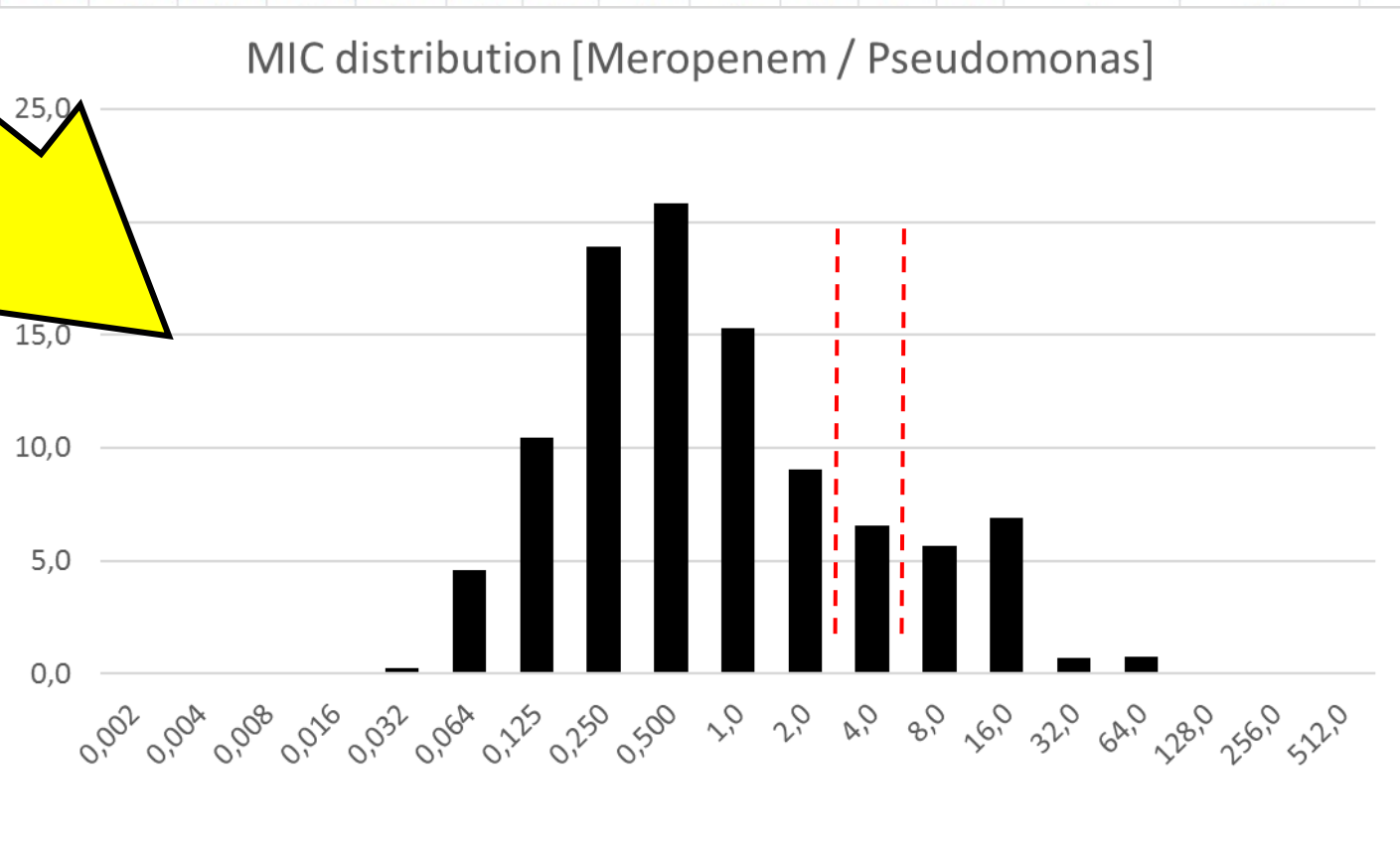# TDM-simulation No.1:   (day 6)

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	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	ECOFF
Amikacin	0	0	0	0	0	0	0	93	374	975	5478	6313	2979	998	104	152	19	5	0	14	17490	16
Ampicillin-sulbactam (ratio)	0	0	0	0	0	0	1	21	3	5	7	16	24	80	3468	0	0	1		1	3625	-
Aztreonam	0	0	0	0	1	2	6	8	62	90	524	1295	537	434	230	62	41	1	0	11	3293	16
Cefepime	0	0	0	1	1	1	99	152	793	3787	10519	7295	6110	4438	3779	113	38	12	0	12	37138	8
Cefotaxime	0	0	0	0	2	3	2	2	10	13	21	93	412	419	274	155	79	14	0	6	1499	32
Cefpirome	0	0	0	0	0	0	1	9	135	262	154	77	38	16	6	6	0	0		4	704	-
Cefpodoxime	0	0	0	0	0	8	0	3	1	0	0	1	2	2	7	414	0	0		1	438	-
Ceftazidime	0	0	0	1	4	8	31	292	966	5975	12322	6271	2738	1712	815	751	167	117	106	84	32276	8
Ceftazidime-avibactam	0	0	0	0	0	0	1	20	96	82	42	20	22	17	16	8	0	0		3	324	-
Ceftobiprole	0	0	0	1	4	11	11	67	446	2209	2134	1437	1373	1435	98	168	0	0		21	9394	8
Ceftolozane	0	0	0	0	0	1	39	848	940	454	461	198	45	49	673	0	0			8	3708	4
Ceftolozane-tazobactam	0	0	0	0	0	8	150	1738	1528	737	533	225	68	82	645	2	8	0		17	5724	4
Ceftriaxone	0	0	0	0	0	79	135	239	374	868	2008	2961	4489	21738	9	11	0			6	32911	-
Ciprofloxacin	0	0	19	42	535	3046	9357	4590	3291	1930	1510	887	939	526	519	729	140	28	105	83	28193	0.5
Clinafloxacin	0	0	0	0	12	36	147	336	165	104	51	36	27	0	0	0	0	0	104	2	1018	-
Colistin	0	0	0	0	0	4	17	103	1538	9273	8012	411	43	58	14	5	13	0	6	22	19497	4
Doripenem	0	0	0	9	80	587	1667	2194	2196	1439	795	878	662	596	45	7	0	0	0	17	11155	1
Eravacycline	0	0	0	2	1	1	2	4	13	39	62	464	677	215	45	0	1	0	0	5	1526	32
Ertapenem	0	0	0	1	1	1	4	4	20	38	102	131	131	99	37	44	0	0	0	2	613	-
Fosfomycin	0	0	0	0	0	0	0	0	8	2	30	55	56	97	236	468	239	19	40	5	1250	-
Gatifloxacin	0	0	0	0	4	85	116	493	2289	1179	831	443	489	357	66	16	2	6	106	8	6482	-
Gemifloxacin	0	0	0	0	44	54	405	678	279	179	86	58	95	14	8	10	0	0	0	5	1910	-
Gentamicin	0	0	0	1	5	6	73	449	1411	4741	9173	4729	1613	862	302	511	88	153	169	53	24286	8
Imipenem	0	0	1	4	8	85	294	1197	8391	24813	12841	4363	4221	6906	651	388	22	39	108	90	64332	4
Kanamycin	0	0	0	0	0	0	1	0	0	2	4	2	2	16	48	150	115	98	0	1	438	-
Levofloxacin	0	0	0	0	19	98	387	2884	4692	2464	1745	1203	470	289	237	296	87	0	0	11	14871	2
Meropenem	0	0	7	41	147	2632	6017	10882	11987	8805	5197	3791	3265	3959	392	443	33	14	0	74	57612	2
Moxifloxacin	0	0	0	1	17	19	86	236	758	1924	976	620	671	208	180	182	443	8	0	9	6329	4
Netilmicin	0	0	0	0	2	4	8	53	175	235	192	74	36	9	1	7	42	25		5	863	4
Norfloxacin	0	0	0	0	0	6	49	139	38	17	8	0	0	0	1	0	0	0		2	258	-

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Kanamycin	0	0	0	0	0	0	1															
Levofloxacin	0	0	0	0	19	98	387															
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Norfloxacin	0	0	0	0	0	6	49	139	38	17	8	0	0	0	1	0	0	0	2	258	-	

MIC distribution [Meropenem / Pseudomonas]

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MIC distribution [Meropenem / Pseudomonas]

4 mg/L x 4 = 16 mg/L
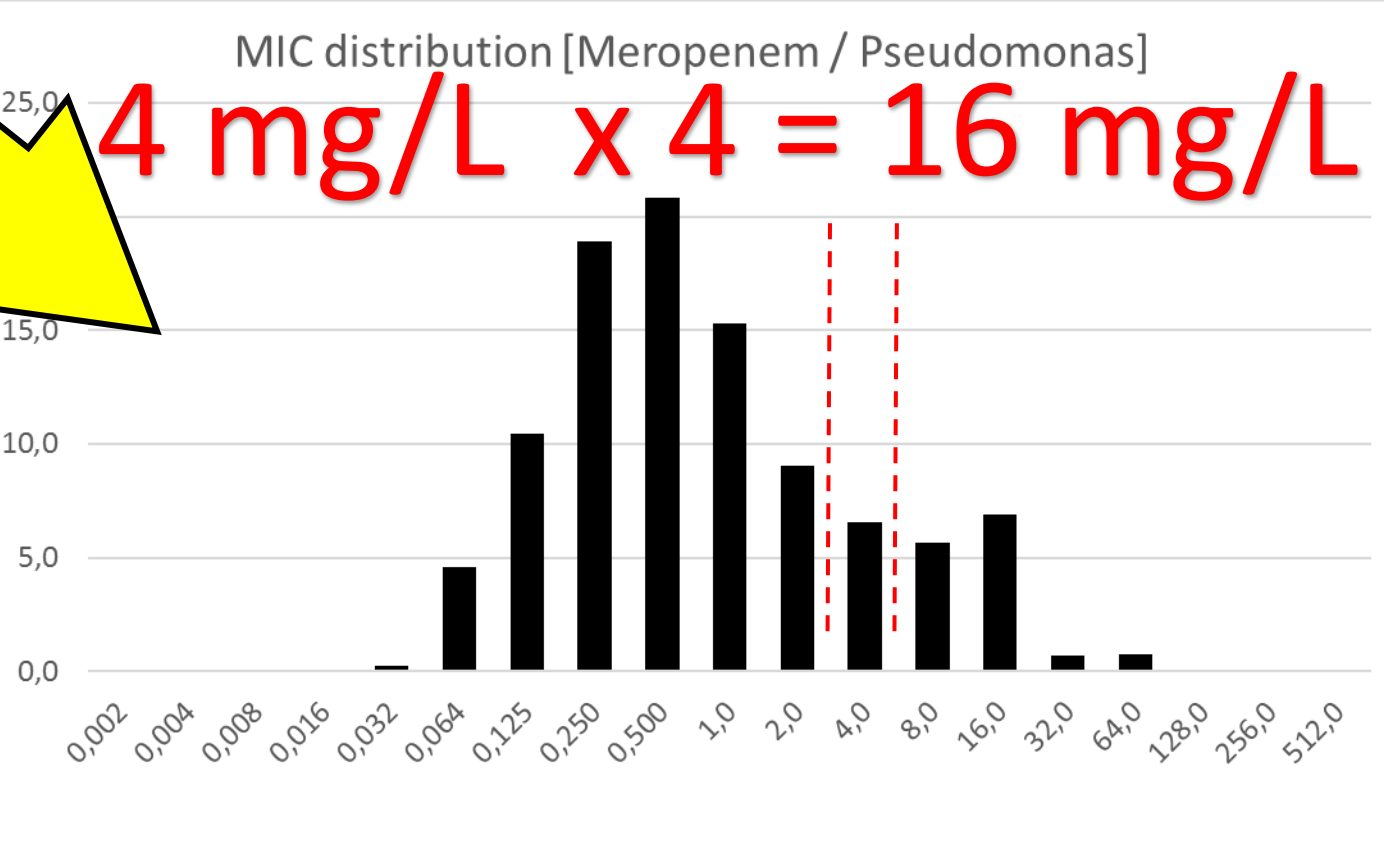
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=> check your own microbiology lab (if possible)

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MiBi-results:

Erregernachweise

K1	zahlreich	Streptococcus dysgalactiae (C/G-Strep.)
K2	zahlreich	Pseudomonas aeruginosa
K3	zahlreich	Fusobacterium nucleatum

- Fusobacterium nucleatum ist ein strikter Anaerobier und ist an infektiösen Prozessen im orofazialen Bereich und bei pleuropulmonalen Infektionen (nekrotisierende Pneumonie, Lungenabszess) beteiligt. Gegen Fusobakterien sind ß-Laktame + BLI, Carbapeneme und Metronidazol wirksam. Infektionen mit Anaerobiern sind häufig Mischinfektionen. Eine antibiotische Therapie sollte immer je nach Lokalistation erfolgen und die Begleitflora abdecken (ggf. Kombinationstherapie).

Kein Nachweis von Pilzen (Sprosspilze, Schimmelpilze).

MiBi-results:

Antibiogramm	K1	MHK	K2	MHK
3MRGN			R	
Penicillin G	S	<=0.06		
Ampicillin	S		R	
Piperacillin	S		R	32.0
Amoxic./Clav.sre.	S		R	
Ampicillin/Sulbactam	S		R	
Piperac.-Tazobactam			S	16.0
Cefazolin	S			
Cefuroxim	S		R	
Cefpodoxim	S		R	
Cefotaxim	S		R	
Ceftriaxon	S		R	
Ceftazidim			R	8.0
Meropenem	S		I	4.0
Gentamicin	R	<=64.0	S	4.0
Amikacin			S	4.0
Tobramycin			S	<=1.0

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A:
w the target concentration?
e > 50%"

get the MIC

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Erregernachweise

K1 zahlreich — **Streptococcus dysgalactiae (C/G-Strep.)**

K2 zahlreich — **Pseudomonas aeruginosa**
K3 zahlreich — **Fusobacterium nucleatum**

- Fusobacterium nucleatum ist ein strikter Anaerobier und ist an infektiösen Prozessen im orofazialen Bereich und bei pleuropulmonalen Infektionen (nekrotisierende Pneumonie, Lungenabszess) beteiligt. Gegen Fusobakterien sind ß-Laktame + BLI, Carbapeneme und Metronidazol wirksam. Infektionen mit Anaerobiern sind häufig Mischinfektionen. Eine antibiotische Therapie sollte immer je nach Lokalistation erfolgen und die Begleitflora abdecken (ggf. Kombinationstherapie).

Kein Nachweis von Pilzen (Sprosspilze, Schimmelpilze).

o.1:   (day 6)

Antibiogramm	K1	MHK	K2	MHK
3MRGN			R	
Penicillin G	S	<=0.06		
Ampicillin	S		R	
Piperacillin	S		R	32.0
Amoxic./Clav.sre.	S		R	
Ampicillin/Sulbactam	S		R	
Piperac.-Tazobactam			S	16.0
Cefazolin	S			
Cefuroxim	S		R	
Cefpodoxim	S		R	
Cefotaxim	S		R	
Ceftriaxon	S		R	
Ceftazidim			R	8.0
Meropenem	S		I	4.0
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QUESTION 3:
Pseudomonas (et al) **confirmed** (Meropenem started)
                          and MIC = 4 mg/L

 => **TARGET** of mero- concentration is **4 x MIC = 16 mg/L**

...

But we are at calculated 30% fT>4xMIC !

Antibiogramm	K1	MHK	K2	MHK
3MRGN			R	
Penicillin G	S	<=0.06		
Ampicillin	S		R	
Piperacillin	S		R	32.0
Amoxic./Clav.sre.	S		R	
Ampicillin/Sulbactam	S		R	
Piperac.-Tazobactam			S	16.0
Cefazolin	S			
Cefuroxim	S		R	
Cefpodoxim	S		R	
Cefotaxim	S		R	
Ceftriaxon	S		R	
Ceftazidim			R	8.0
Meropenem	S		I	4.0
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Pseudomonas (et al) **confirmed** (Meropenem started)
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=> TARGET of mero- concentration is **4 x MIC = 16 mg/L**
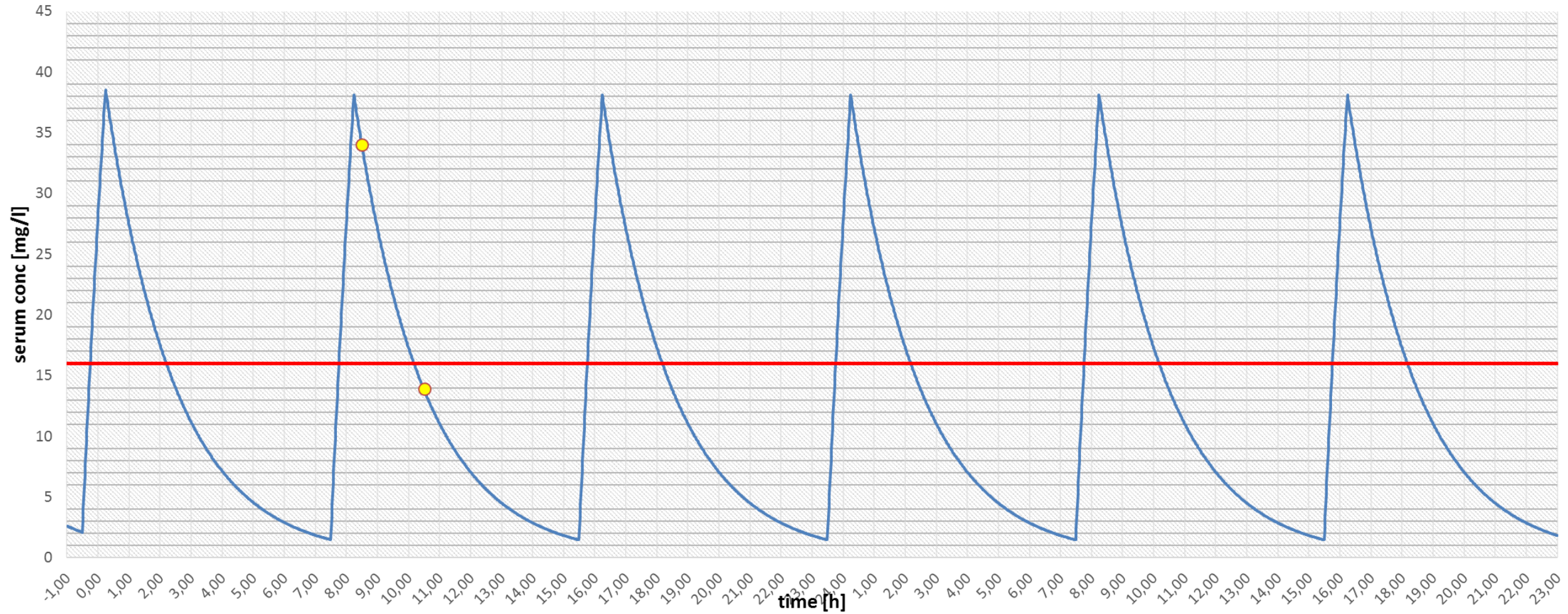
...

But we are at calculated 30% fT>4xMIC !

What shall we do now???

a) increase dose

b) decrease dose

c) switch antibiotic (e.g. to ciprofloxacin)

o.1: (day 6)

Antibiogramm	K1	MHK	K2	MHK
3MRGN			R	
Penicillin G	S	<=0.06		
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Cefazolin	S			
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QUESTION 3:
Pseudomonas (et al) **confirmed** (Meropenem started)
and MIC = 4 mg/L

=> **TARGET** of mero- concentration is **4 x MIC = 16 mg/L**

...

But we are at calculated 30% fT>4xMIC !

What shall we do now???

a) increase dose => new dose: **3 x 3g i.v. meropenem**

b) decrease dose **plus prolongation!**

c) switch antibiotic (e.g. to ciprofloxacin)

Antibiogramm	K1	MHK	K2	MHK
3MRGN			R	

Gentamicin	R	<=64.0	S	4.0
Amikacin			S	4.0
Tobramycin			S	<=1.0

c) switch antibiotic (e.g. to ciprofloxacin)

Antibiogramm	K1	MHK	K2	MHK
3MRGN			R	

o.1:   (day 6)
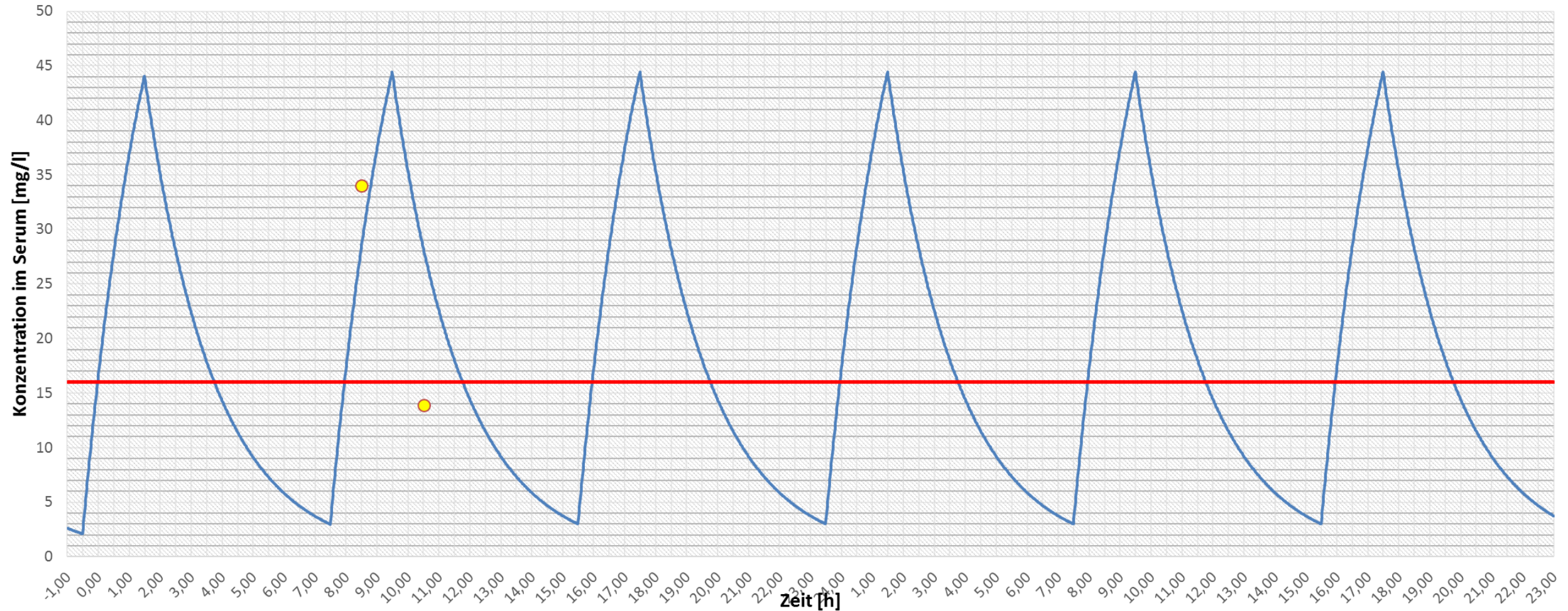
Gentamicin	R	<=64.0	S	4.0
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Tobramycin			S	<=1.0

c) switch antibiotic (e.g. to ciprofloxacin)

Day 6

THERAPEUTIC DRUG MONITORING   („TDM")   of meropenem

- Day 2 of meropenem-therapy => result: recommendation: *„increase dosage"*

      increase to 3 gramm t.i.d.! (9 gramm per day) !

Day 6

THERAPEUTIC DRUG MONITORING ("TDM") of meropenem

- Day 2 of meropenem-therapy => result: recommendation: *"increase dosage"*

        increase to 3 gramm t.i.d.! (9 gramm per day) !

- Recommendation was accepted.

 ….

Day 10

SURGERY: wound revision (excision of diff. tissues plus cystectomia (with ileum conduit) …)

=> Drop in eGFR!

=> concommitant increase in meropenem-concentration!
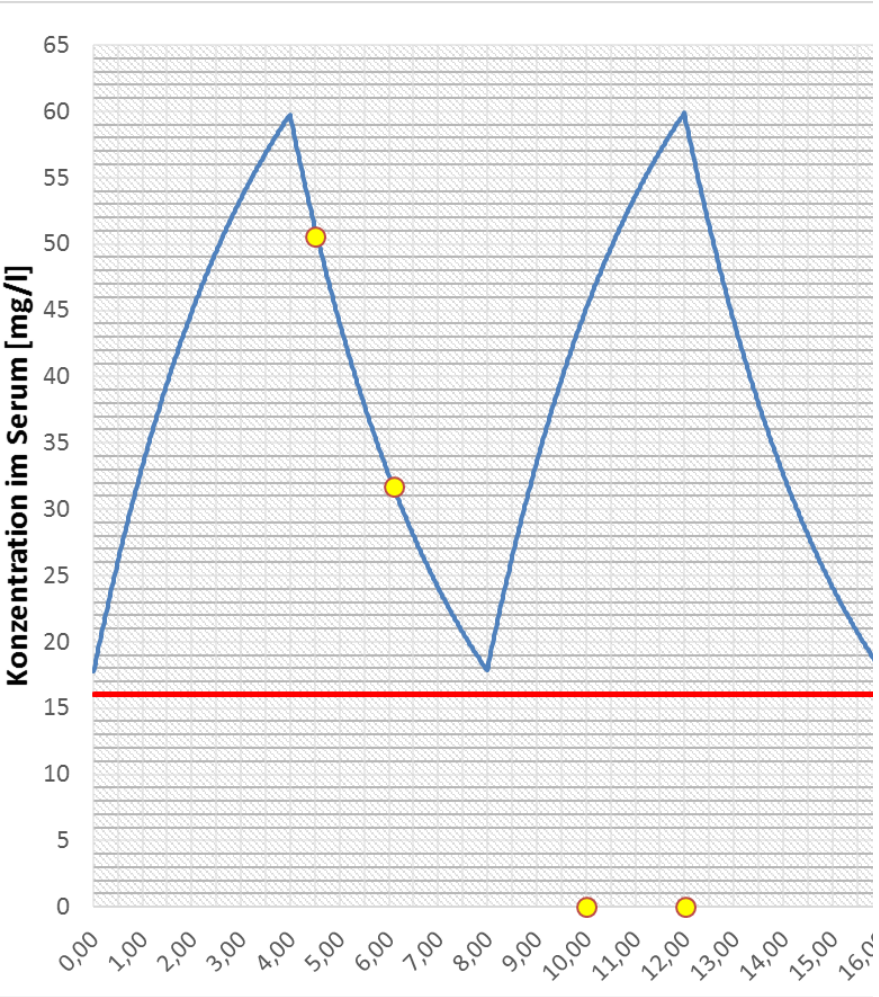
…. as seen in second TDM …

Day 13

Second TDM!

- target is still 16mg/L (nothing changed i.t. Pseudomonas susceptibility!)

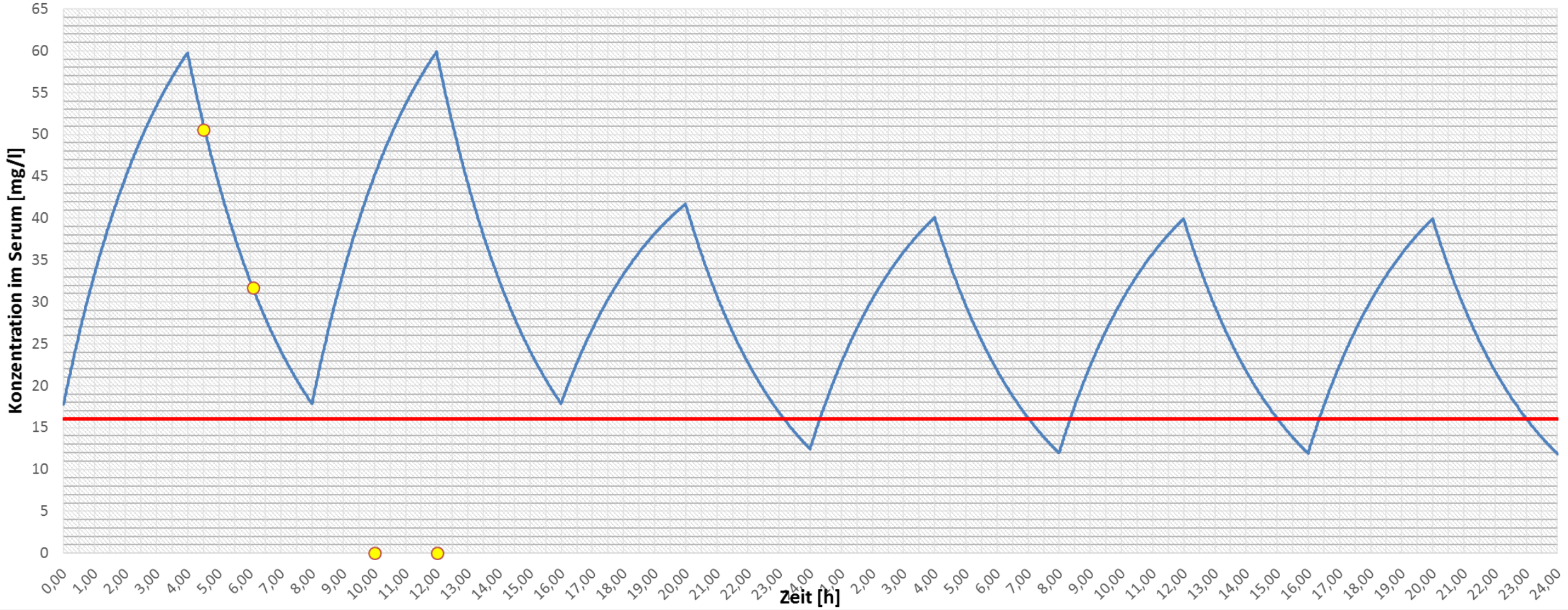But now we measure two concentrations of **50.6** and **31.7** mg/L !!!

=> Overdosage!

=> *cause* = Drop in eGFR! New eGFR = 58 ml/min (following surgery)

Day 13: TDM no. 2

Day 13: TDM no. 2

=> DOSE REDUCTION   here: to 3 x 2 gramm meropenem i.v.

Day 15

Discharchge from ICU to gyn-ward.

Day 16: stop meropenem i.v

=> Infection under controll (for now…)

THANK YOU FOR YOUR INTEREST!