Dr. Eva Meyle
Heidelberg University Hospital - Pharmacy
Heidelberg University Hospital

A souvenir from Africa – cSSTI in a young woman

22nd congress of the EAHP - 2017 Synergy Satellite Event
Good Morning Pharmacists!
Case Studies on Antimicrobial Resistance
23 March 2017

Conflicts of interest

Nothing to declare

cSSTI, ♀, 25y, BMI 37, 95 kg

- 14d holiday (Tanzania + Zanzibar)
- Last holiday: spontaneous painful redness of the left thigh and beginning the right flank
- Flight back: chills and severe vomiting → Hospitalisation in Adis Abeba
- Physical condition deteriorating → transfer to University Hospital of Nairobi
- Diagnosed with anaerobic gas gangrene (no pathogen identified)
- Multiple surgical interventions (debridement, pus evacuation)
- Empirical antibiotic therapy:
  - Vancomycin, Clindamycin, Meropenem
- After 19d: Repatriation to Germany (Heidelberg University Hospital – Department of Orthopedics)

cSSTI, ♀, 25y, BMI 37, 95 kg

Admission to Heidelberg - Physical state

- Multiple wound drainages and pleural drainage
- Oxygen ventilation 2 l/min (non-invasive)
- No fever
- No catecholamines

Initial Blood results:

- CL_{Cr}: 147 [ml/min]
- Na^+: 140, K^+: 4,07, Cl^-: 101 [mmol/l]
- CRP: 311 [mg/l]
- WBC: 1,91 /nl

Anamnestic congenital leucopenia

cSSTI, ♀, 25y, BMI 37, 95 kg

Admission to Heidelberg - Medication

Meropenem	1 g	1-1-1
Vancomycin	1 g	1-0-1
Clindamycin	600 mg	1-1-1
Metformin	1 g	paused
Bisoprolol	2,5 mg	1-0-0
Pantoprazole	40 mg	1-0-0
Morphine		4 mg/h
Ibuprofen	600 mg	1-1-1

cSSTI, ♀, 25y, BMI 37, 95 kg

Q1. What do you think about the anti-infective medication?

→ **Meropenem + Vancomycin + Clindamycin**

A) Adequate empirical therapy – no change

B) Meropenem + Vancomycin would be adequate

C) Targeted therapy from the beginning – Causative pathogen of gas gangrene is always *Clostridium ssp.*

cSSTI, ♀, 25y, BMI 37, 95 kg

Q1. What do you think about the anti-infective medication?

Meropenem: Broad spectrum gram+ & gram- coverage including ESBL-Enterobacteriaceae, *Pseudomonas*

Vancomycin:

Clindamycin: ctam-antibiotic combination therapy for gram+ infection

A) Adequate empirical therapy – no change

Adequate empirical broad-spectrum-therapy in a patient with a life-threatening infection → Tarragona-Strategy

Look at your Patient
Listen to your Hospital
Hit Hard and Early
Get to the Point
Focus, Focus, Focus

Sandiumenge et *al. Crit. Care Med.* (2003) 29:876-883

cSSTI, ♀, 25y, BMI 37, 95 kg

Q2. What do you think about the dosage of Meropenem in this obese patient

→ Meropenem 1g tid; 30min infusion time

A) Adequate dosage regimen – no change

B) Single dose must be adopted to total body weight

C) Single dose should be increased and infusion time prolonged

cSSTI, ♀, 25y, BMI 37, 95 kg

Dosage of Meropenem in obese patients

PK/PD target: fT_{MIC}>40%

PK/PD target in sepsis/sept. shock: fT_{MIC}>4-5x MIC for 50-100%

Steady-State Pharmacokinetics and Pharmacodynamics of Meropenem in Morbidly Obese Patients Hospitalized in an Intensive Care Unit

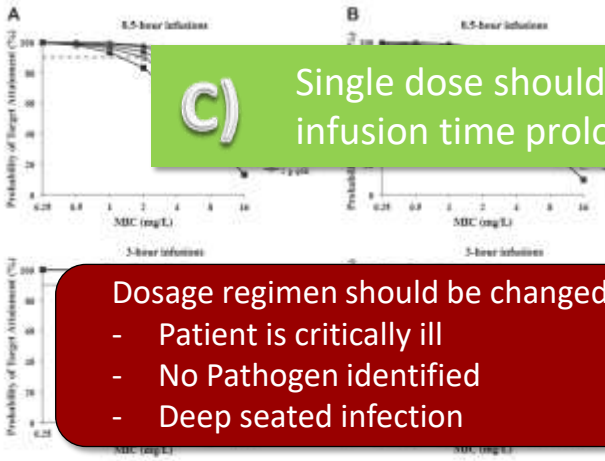
The Journal of Clinical Pharmacology 54(3) 324–330
© 2013, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.196

S. Christian Cheatham, PharmD[1], Megan R. Fleming, PharmD[2],

- 9 Patients
- BMI: 54,7 ± 8,6kg/m²
- Meropenem 0,5g or 1g every 6h or 8h over 0,5h or 3h

cSSTI, ♀, 25y, BMI 37, 95 kg

Dosage of Meropenem in obese patients



c) Single dose should be increased and infusion time prolonged

…onged
…sired
pathogens with high MIC

Dosage regimen should be changed to 2g tid over 3h
- Patient is critically ill
- No Pathogen identified
- Deep seated infection

Figure 3. Probability of target attainment (PTA) at (A) 40% fT>MIC and (B) 54% fT>MIC for five meropenem dosing regimens infused over 0.5 and 3 hours at specific minimum inhibitory concentrations (MICs). The dotted line indicates a PTA of 90%. fT>MIC, time for which the free drug concentration remains above the MIC; q8h, every 8 hours; q6h, every 6 hours.

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Day of Admission and next day

- ICU → isolation room
- Rectal and nasal swabs for MDR bacteria, urine culture
- Immediate surgical re-intervention with negative pressure wound therapy system
- Antibiotic therapy **not** changed: Meropenem, Vancomycin, Clindamycin
- Supportive therapy: 13Mio I.U. Granocyte (G-CSF)

Next day:

- CRP> 328 mg/l
- WBC: 4,91/nl

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Two days after admission

Tissue culture (deep):
Acinetobacter baumannii

→ **XDR *Acinetobacter baumannii***
(e**X**tensivly **D**rug **R**esistant)

ECDC CDC

Magiorakas et al. *Clin Microbiol Infect.* (2012) 18:268

Antibiotic	Sensitivity
~~Piperacillin/Tazobactam~~	~~R~~
~~Cefotaxime~~	~~R~~
~~Ceftriaxone~~	~~R~~
~~Ceftazidime~~	~~R~~
~~Imipenem~~	~~R~~
~~Meropenem~~	~~R~~
~~Aztreonam~~	~~R~~
~~Sulfamethoxazole/Trimethoprime~~	~~R~~
~~Gentamicin~~	~~R~~
Tobramycin	S
Amikacin	S
Colistin	S
~~Tigecyclin~~	~~R~~

cSSTI, ♀, 25y, BMI 37, 95 kg

Two days after admission

Antibiotic therapy **changed**:

STOP : Meropenem + Vancomycin + Clindamycin

GO : Colistin + Tobramycin

Tobramycin	S
Amikacin	S
Colistin	S

cSSTI, ♀, 25y, BMI 37, 95 kg

Q3. What do you think about the antibiotic regimen? Colistin + Tobramycin combination

A) Colistin monotherapy is to prefer

B) Adequate combination therapy

C) Tobramycin monotherapy is to prefer

cSSTI, ♀, 25y, BMI 37, 95 kg

Q3. Colistin + Tobramycin combination

OPEN Meta-analysis of colistin for the treatment of *Acinetobacter*

[…] Colistin may be **as safe and as efficacious** as standard antibiotics for the treatment of *A. baumannii* infections. […]
[…] In clinical practice, in order to improve antibacterial activity, colistin is **frequently used as combination therapy**[…]
[…] data from relevant human studies suggest **non-inferiority of colistin monotherapy** as compared with combination therapy […]

Figure 8. Risk ratios of mortality between colistin combination and alone groups.

cSSTI, ♀, 25y, BMI 37, 95 kg

Q3. Colistin + Tobramycin combination

GO Colistin + Tobramycin

- patient critical ill
- maximum activity of antiinfective therapy
- **risk of heteroresistant *A. baumannii* strain**

B) Adequate combination therapy

cSSTI, ♀, 25y, BMI 37, 95 kg

Q4. How would you dose Colistin? (no renal impairment)

A) Loading dose 9 Mio I.U., followed by 4.5 Mio I.U. bid

B) 4.5 Mio I.U. bid

C) Loading dose 3 Mio I.U., follwed by 2 Mio I.U. tid

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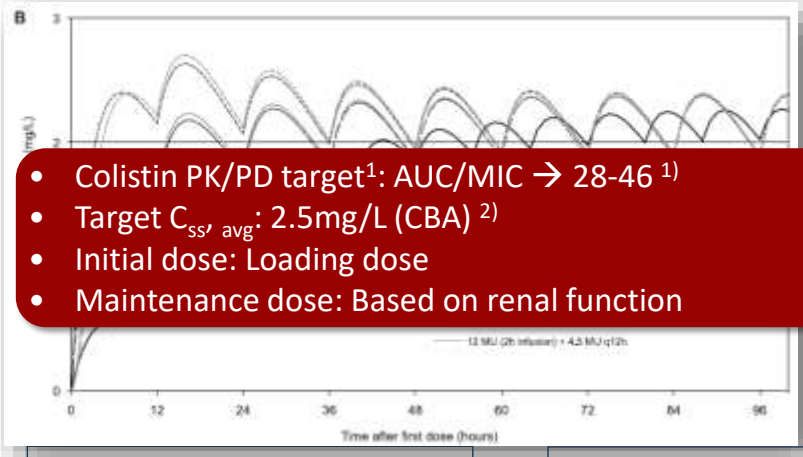
Q4. Colistin Dosage



Plachouras et al. *Antimicrob Agents Chemother* (2009); 53(8):3430-6

- Colistin PK/PD target[1]: AUC/MIC → 28-46 [1)]
- Target $C_{ss, avg}$: 2.5mg/L (CBA) [2)]
- Initial dose: Loading dose
- Maintenance dose: Based on renal function

1) Dudhani et al. J. *Antimicrob. Chemother* (2010); 65(9):1984-90

2) Garonzik et al. *Antimicrob. Agents Chemother* (2011); 55(7):3284-94

cSSTI, ♀, 25y, BMI 37, 95 kg

Q4. Colistin Dosage – How we do it

A) 9 Mio I.U., followed by 4.5 Mio I.U. bid

Therapietag	*Dosis*	*Dosisintervall*
d 1	Loading Dose 9 Mio IE	
ab d 2	4,5 Mio IE	12h

Kreatinin-Clearance 30-60 ml/min

Therapietag	*Dosis*	*Dosisintervall*
d 1	Loading Dose 9 Mio IE	
ab d 2	4 Mio IE	12h

Kreatinin-Clearance 15-30 ml/min

Therapietag	*Dosis*	*Dosisintervall*
d 1	Loading Dose 9 Mio IE	
ab d 2	3 Mio IE	12h

Kreatinin-Clearance <15 ml/min

Therapietag	*Dosis*	*Dosisintervall*
d 1	Loading Dose 9 Mio IE	
ab d 2	2 Mio IE	12h

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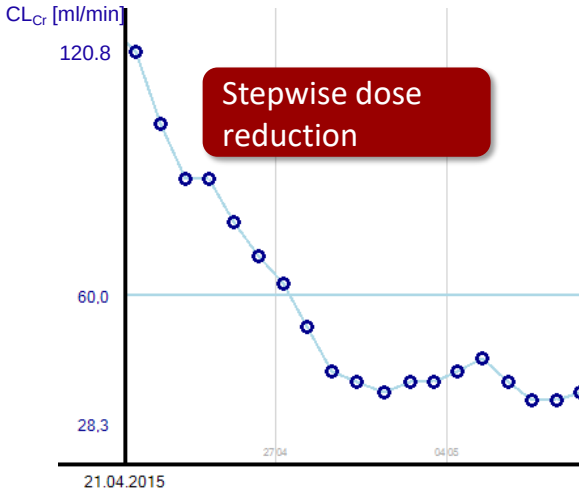
Colistin + Tobramycin - Nephrotoxicity



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Colistin + Tobramycin - Nephrotoxicity