Optimising Antibiotic Treatment of Bone & Joint Infections :

Pharmacokinetics of antibiotics in osteoarticular infections

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Osteomyelitis : different territories

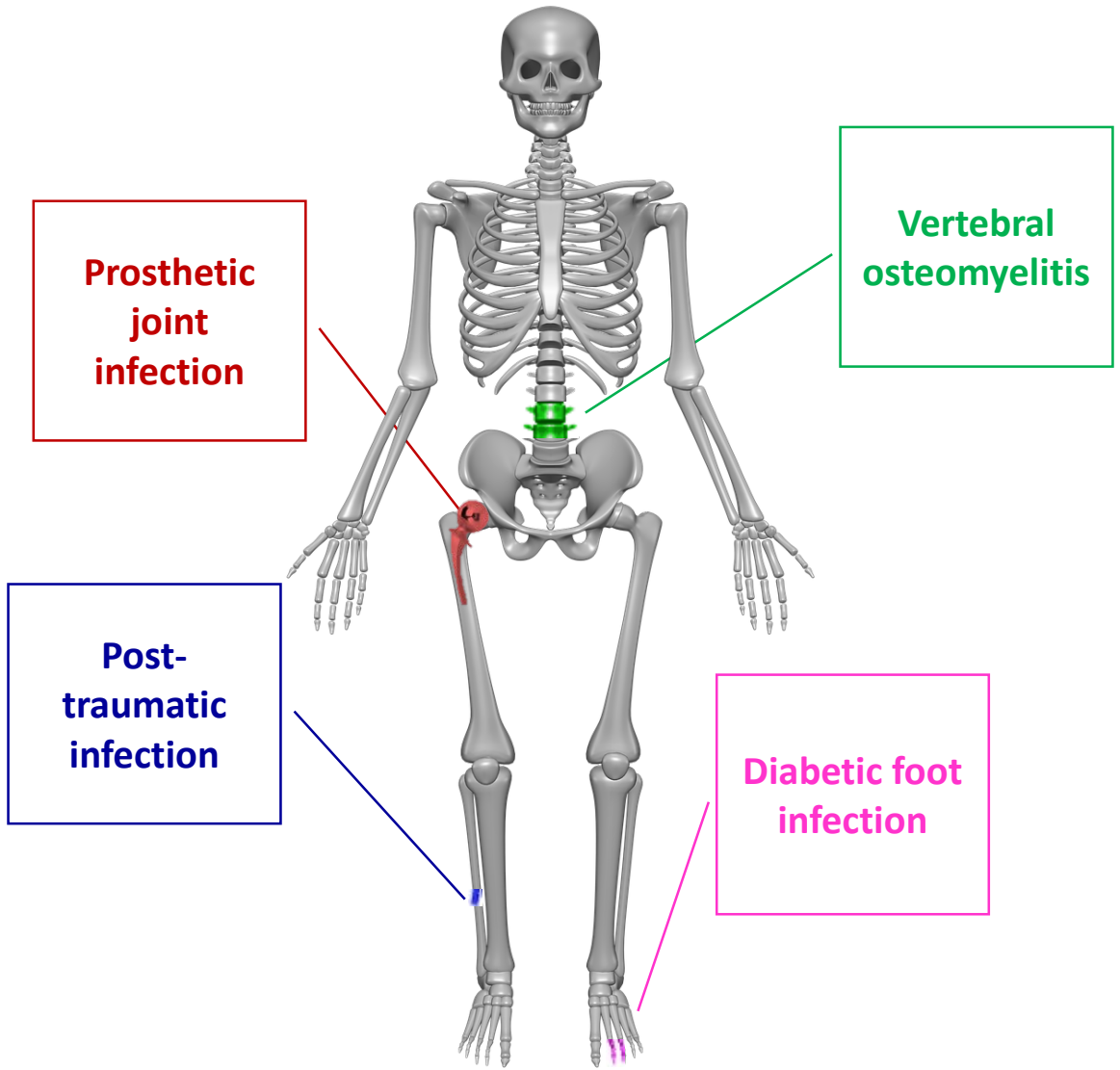
One pathology but possible several PK/(PD) issues!

- Different locations

→ different access of drugs …

- Different environments

→ different expression of activity of drugs



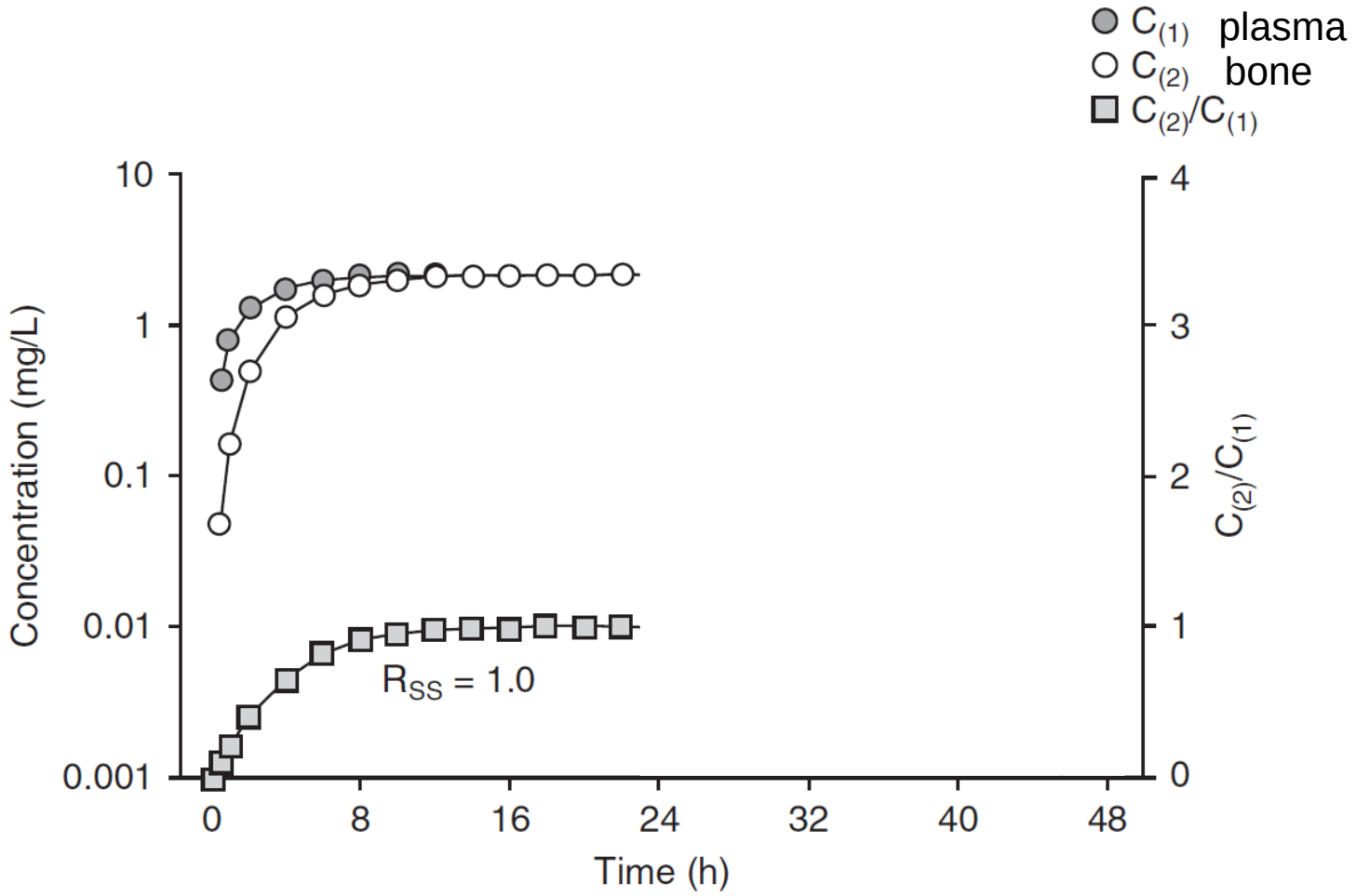
Adapted from Boucher et al., Clin Infect Dis (2010) 51 (S2) :S183-S197

A few relevant PK Questions ….

- When to take samples ?

Time points for sampling matter !

1. Drug given by continuous infusion



At equilibrium, bone:plasma ratio remains constant

Landersdorfer et al., Clin Pharmacokinet (2009) 48: 89-124

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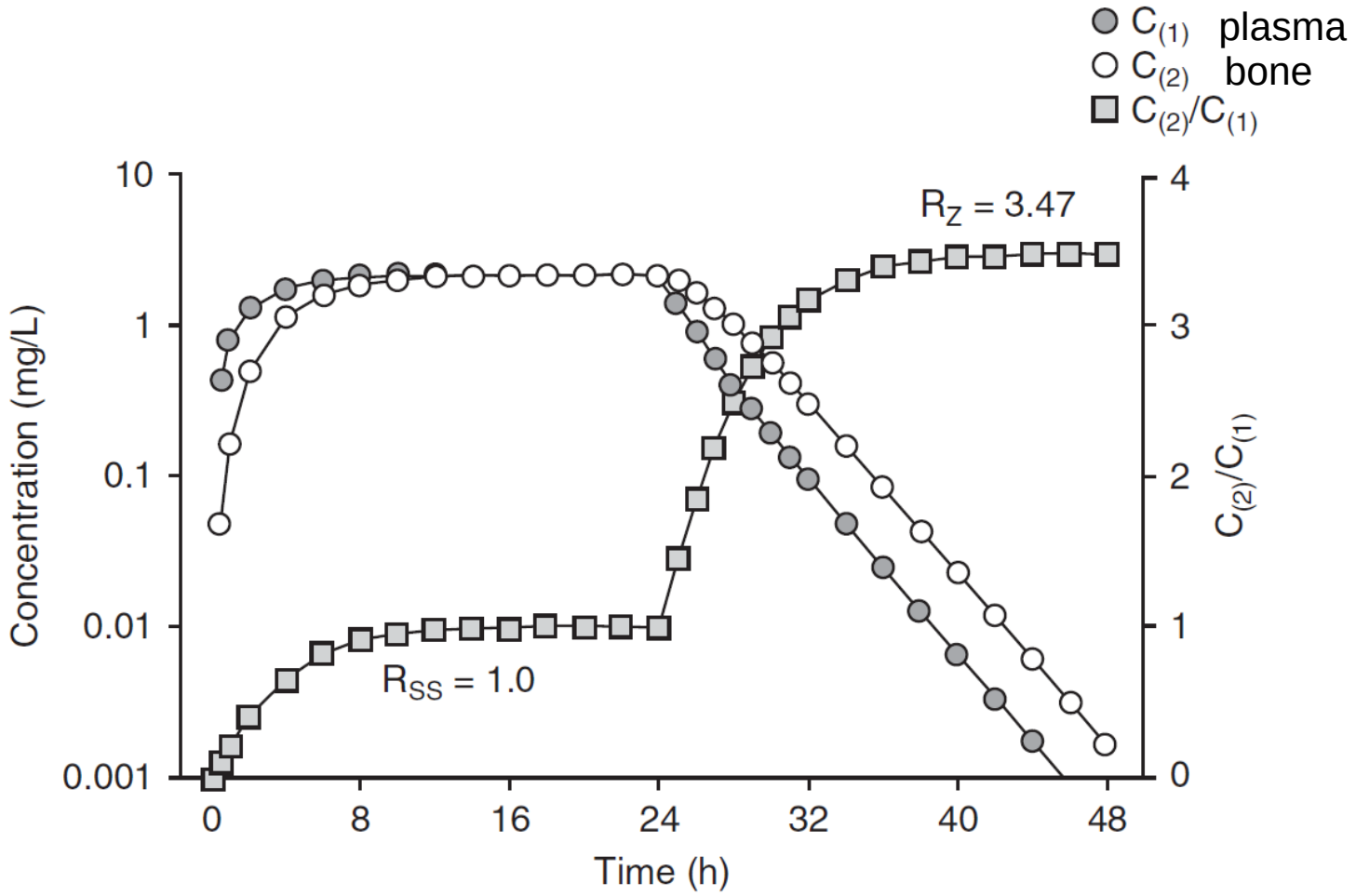
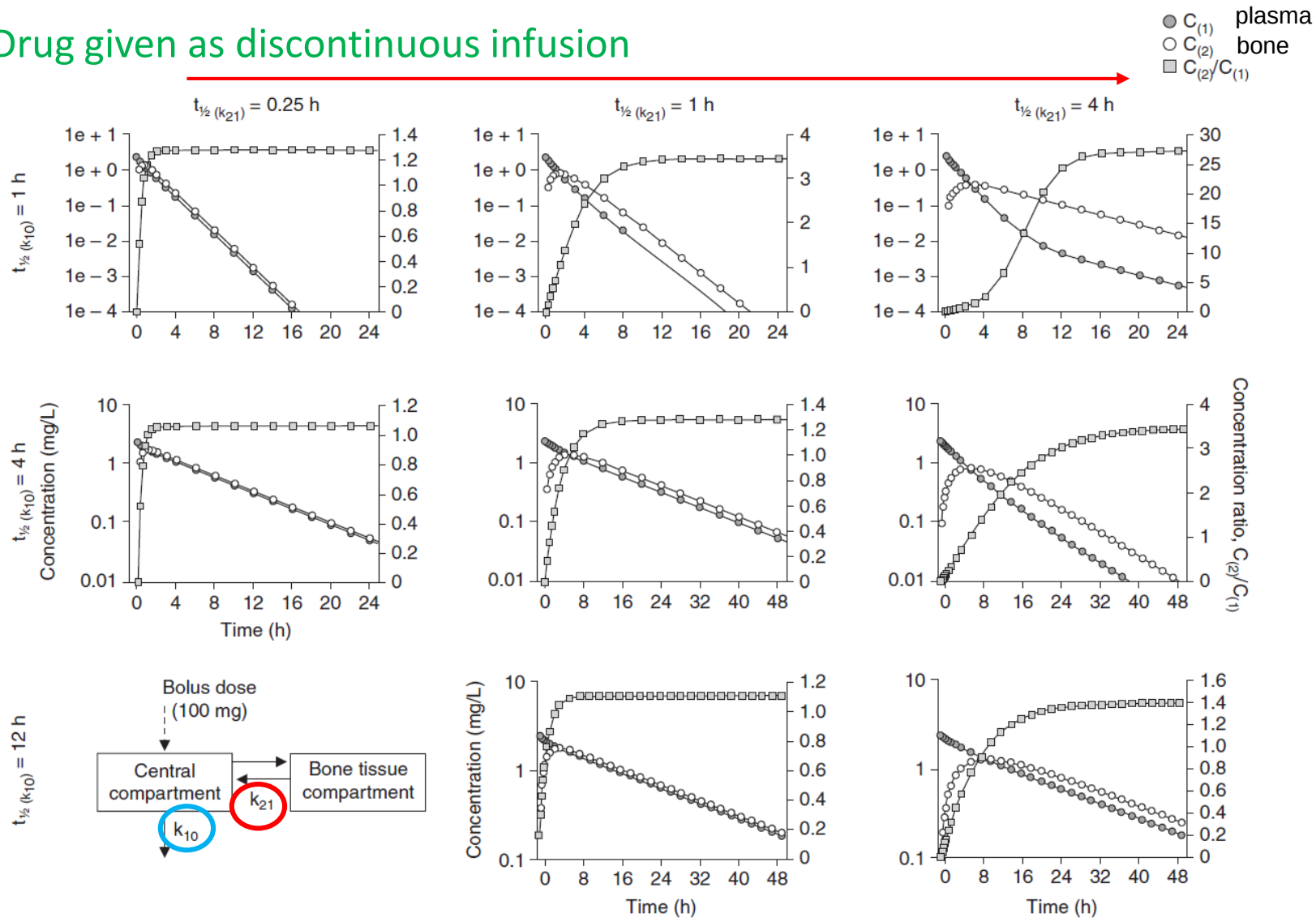


During the elimination phase, bone:plasma ratio changes over time

Landersdorfer et al., Clin Pharmacokinet (2009) 48: 89-124

Time points for sampling and administration scheme matter !

2. Drug given as discontinuous infusion



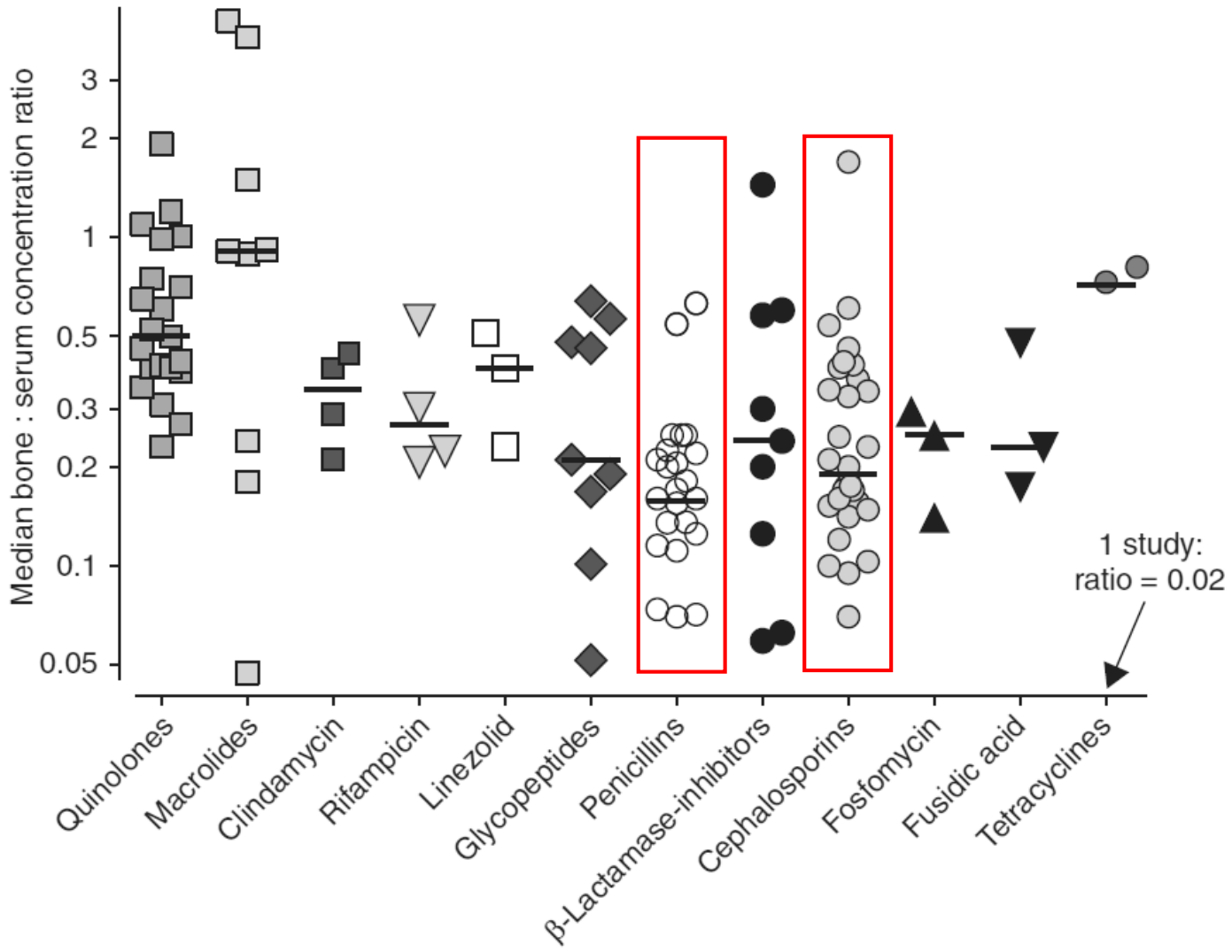
Multiple sampling times are needed to get a global picture

Landersdorfer et al., Clin Pharmacokinet (2009) 48: 89-124

A few relevant PK Questions ….

- When to take samples ?
- Which drugs ?

Antibiotic bone penetration: a global picture



Relative values … but plasma concentrations highly variable among drugs !

Landersdorfer et al., Clin Pharmacokinet (2009) 48: 89-124

Antibiotic bone concentrations: a global picture

antibiotic	Average cancellous//cortical bone or global conc. (mg/L)	Resistance Bkpt (mg/L) for *S. aureus* (R >)
Amoxi/clav	27.8/3.5 // 37.4/3.6	-
(Flu)/Cloxacillin	89.5 // 3.8	[2]
Cefazolin	75.4 // detectable	-
Vancomycin	3.8 // 4.5	2
Dalbavancin	13.4 // 4.2	0.125
Oritavancin	27 // 65.6	0.125
Daptomycin	21.4	1
Linezolid	6.4	4
Gentamicin	detectable	1
Rifampicin	6.5	0.5
Clindamycin	6.9	0.5
Moxifloxacin	2.8	0.25
Doxycycline	3	2
TMP/SMX	6.8/35.8	4

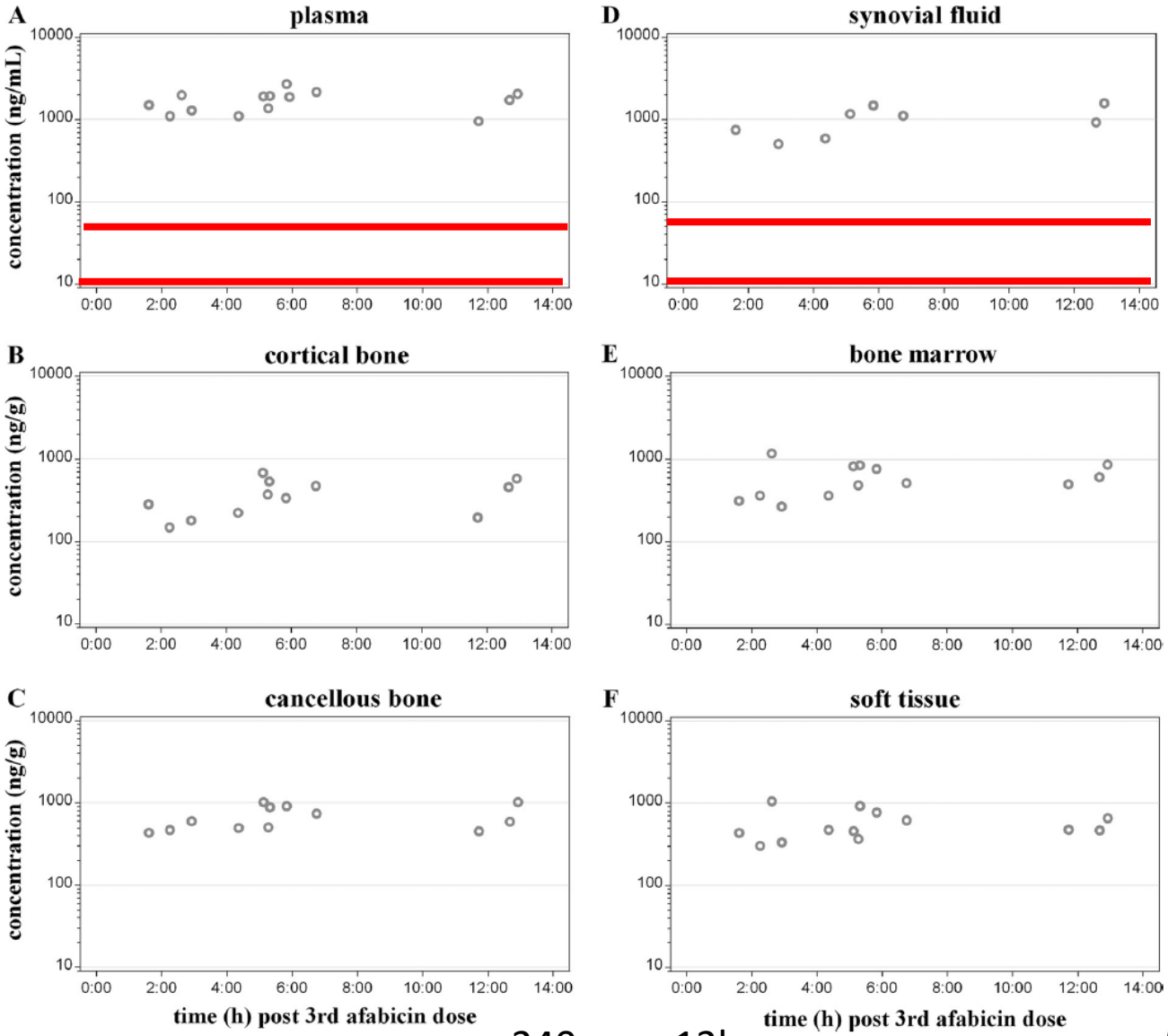
Adapted from Thabit et al., Int J Infect Dis (2019) 81: 128-136

Antibiotic bone concentrations: a global picture

antibiotic	Average cancellous//cortical or global bone conc. (mg/L)	Resistance Bkpt (mg/L) for enterobacterales (R >)
Amoxi/clav	27.8/3.5 // 37.4/3.6	8
Cefazolin	75.4 // detectable	4
Piperacillin/tazobactam	40.5/detect. // 35.5/detect.	8
Ceftriaxone	10.7	2
Cefepime	99.8 // 67.6	
Meropenem	10.6	8
Ertapenem	9.9 // 6.1	0.5
Gentamicin	detectable	2
TMP/SMX	6.8/35.8	4
Ciprofloxacin	13.8	0.5
Fosfomycin	13 // 8	8
Colistin	NA	2
Metronidazole	5.6 // 5.7	-

Adapted from Thabit et al., Int J Infect Dis (2019) 81: 128-136

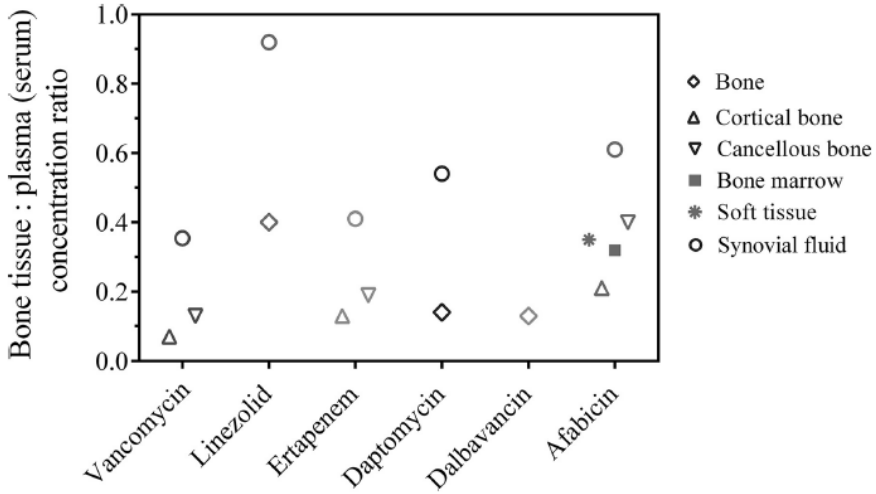
A new drug in the arsenal: afabicin (spectrum= *S. aureus* only!)



240 mg q12h

MIC_{99} *S. aureus*: 60 ng/mL

MIC_{90} *S. aureus*: 8 ng/mL



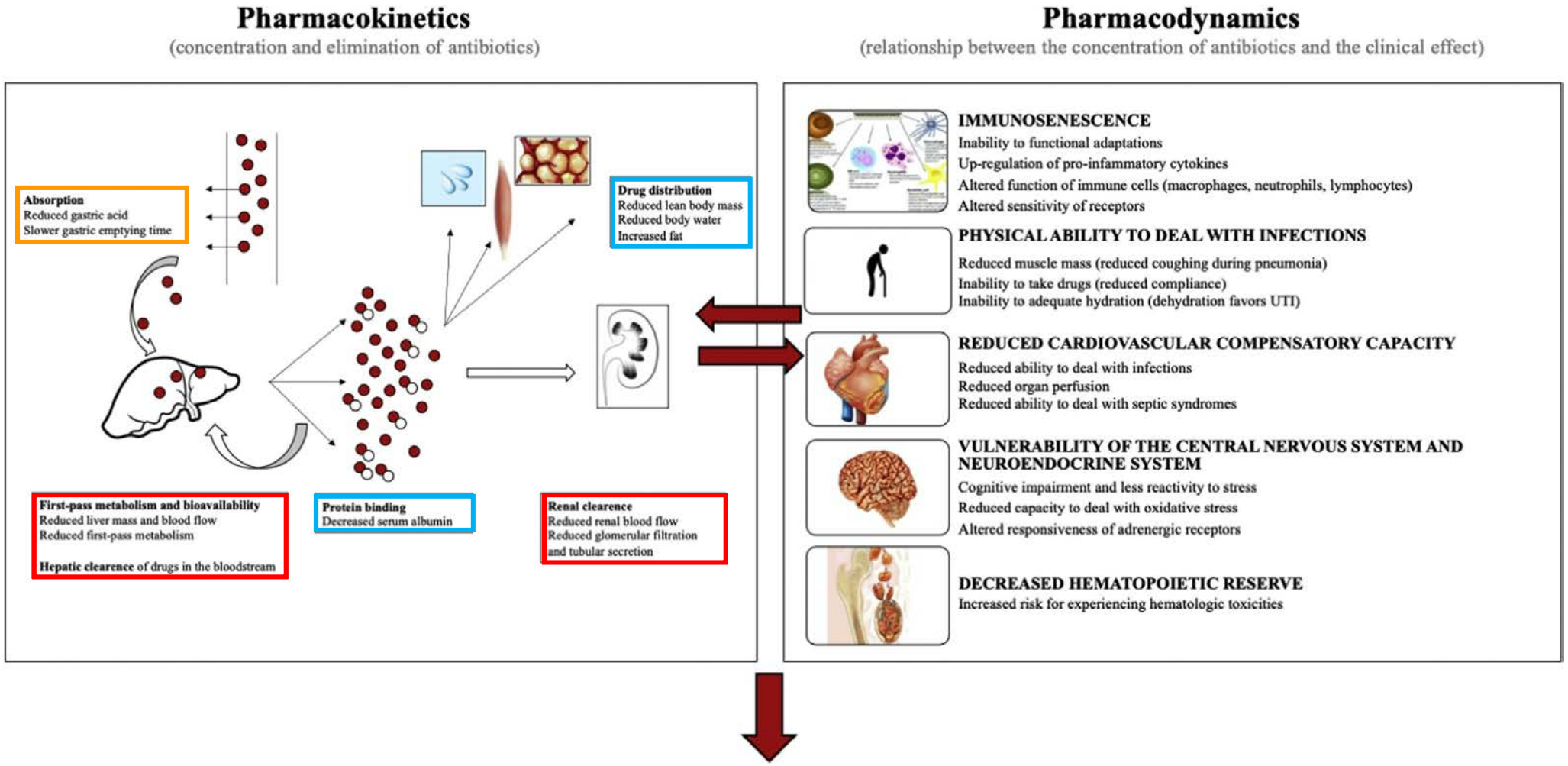
Menetrey et al., Antimicrob Agents Chemother (2019) 63:e01669-18

A few relevant PK Questions ….

- When to take samples ?
- Which drugs ?
- Which causes of variability ?

Inter-individual variability

1. Physiological changes in elderly affecting drug PK/PD



Falcone et al., J Glob Antimicrob Res (2020) 22: 325-333

Inter-individual variability

1. Physiological changes in elderly affecting drug PK/PD

antibiotic
(Flu)/Cloxacillin
Vancomycin
Dalbavancin
Oritavancin
Daptomycin
Linezolid
Rifampicin
Clindamycin
Moxifloxacin
Doxycycline
TMP/SMX

antibiotic
Amoxi/clav
Cefazolin
Piperacillin/tazobactam
Ceftriaxone
Meropenem
Ertapenem
Gentamicin
Ciprofloxacin
Fosfomycin
Colistin
Metronidazole

Adapted from Macias-Valcayo et al., Expert Opin Pharmacother. (2019) 20: 1109-1121

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Adjust in case of renal insufficiency

Adapted from Macias-Valcayo et al., Expert Opin Pharmacother. (2019) 20: 1109-1121

Inter-individual variability

1. Physiological changes in elderly affecting drug PK/PD

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Meropenem
Ertapenem
Gentamicin
Ciprofloxacin
Fosfomycin
Colistin
Metronidazole

Adjust in case of hepatic insufficiency

Adapted from Macias-Valcayo et al., Expert Opin Pharmacother. (2019) 20: 1109-1121

Inter-individual variability

1. Physiological changes in elderly affecting drug PK/PD

antibiotic
(Flu)/Cloxacillin
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Metronidazole

Highly protein bound

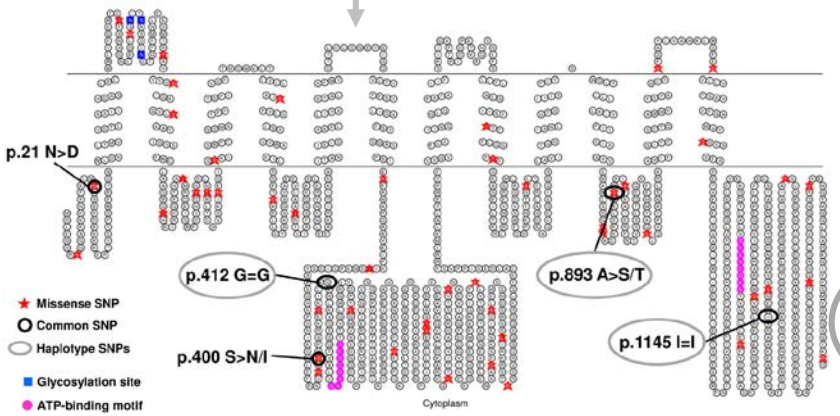
Adapted from Macias-Valcayo et al., Expert Opin Pharmacother. (2019) 20: 1109-1121

Inter-individual variability

2. Pharmacogenomics (transporters – metabolism) and gender

Simulated exposure and probability to achieve efficacy and toxicity targets stratified by categorical covariates

Daptomycin dosage and sex/*ABCB1* haplotype	C_{max} (mg/L)	C_{min} (mg/L)	AUC (mg·h/L)	CFR[b] fC_{max}/ MIC ≥12	PTA C_{min} ≥24.3 mg/L
10 mg/kg					
F/other	91.8 ± 14.2	28.1 ± 9.9	1225 ± 265	0.982	0.611
M/other	83.2 ± 12.9	20.1 ± 8.1	1001 ± 222	0.974	0.264
F/CGC	104.9 ± 15.8	24.9 ± 9.9	1233 ± 273	0.987	0.465
M/CGC	96.2 ± 14.5	17.2 ± 7.8	1005 ± 226	0.985	0.17



3 SNP in most frequent haplo-type (~15%)

Higher probability of success in
- Females
- CGC haplotypes

Higher probability of toxicity in
- Females (lower if CGC haplotype)

Wolking et al., Clin Pharmacokinet (2015) 54: 709–735
Kroetz et al., Pharmacogenetics (2003) 13:481–494

Bricca et al., J Antimicrob Chemother (2019) 74: 1012–1020

A few relevant PK Questions ….

- When to take samples ?
- Which drugs ?
- Which causes of variability ?
- Which target concentrations ?

Hidden reservoirs

1. Biofilms

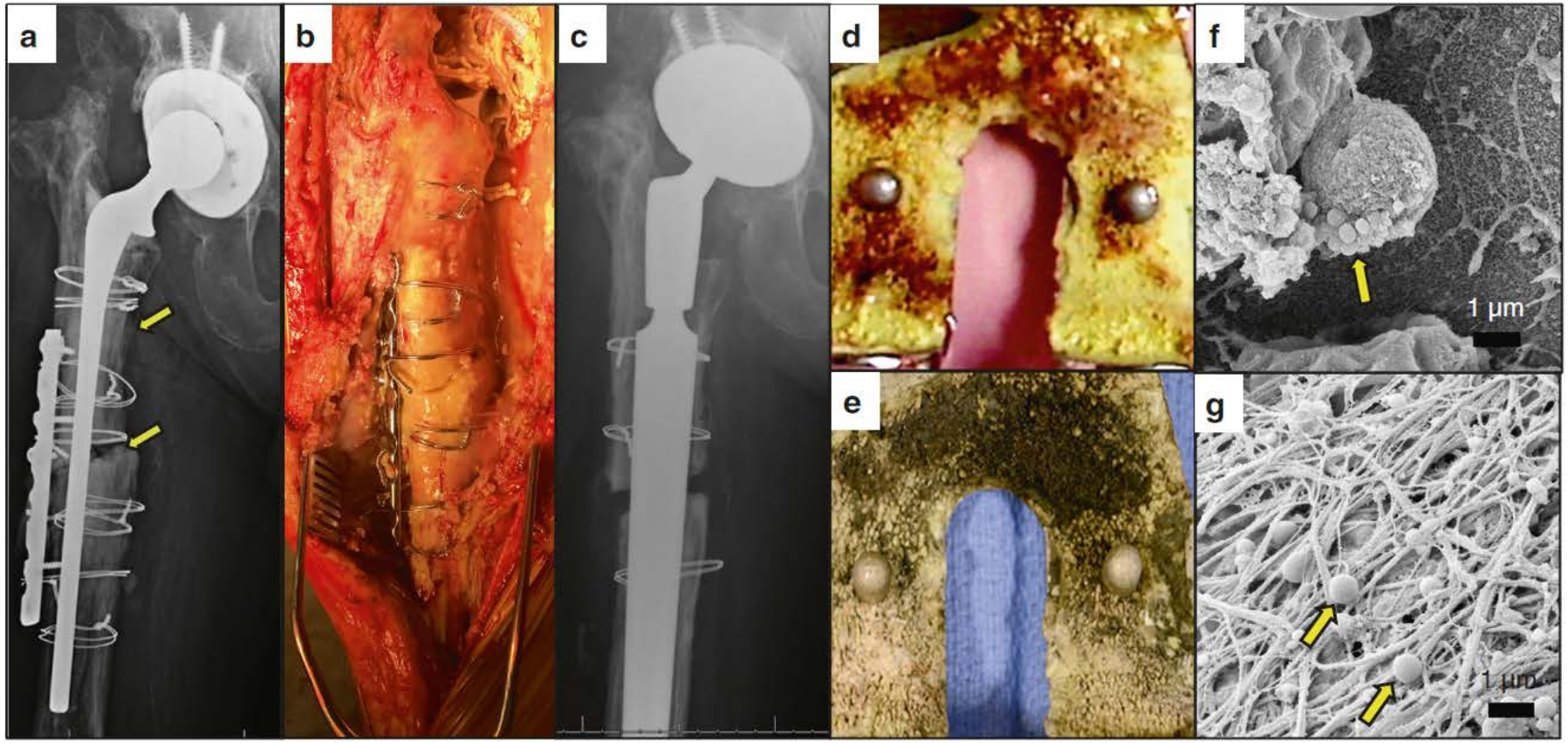


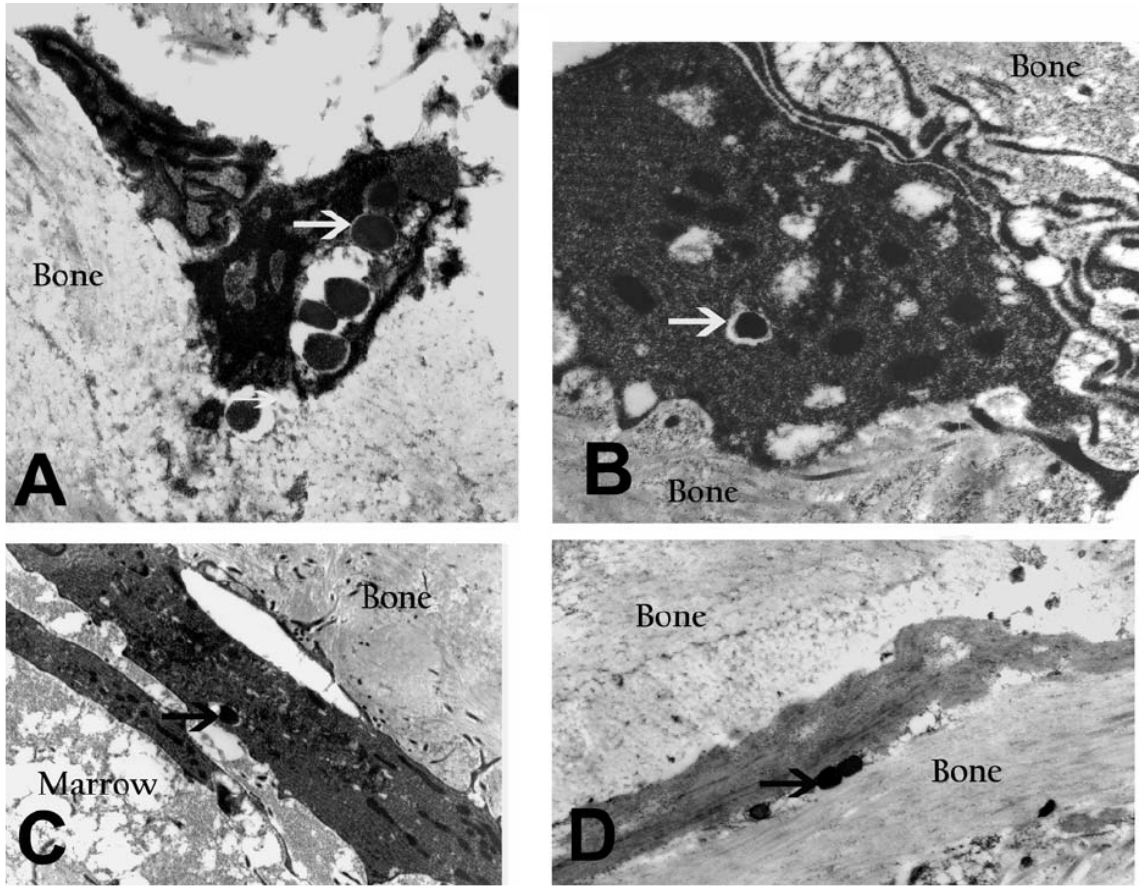
Fig. 1 Removal of necrotic bone and biofilm contaminated components during revision surgery for MRSA-infected total joint replacements (TJR). **a**–**c** The indications for this single-stage revision for a MRSA-infected total hip replacement is shown. **a** Radiographic evidence of the septic TJR in the pre-op X-ray are periosteal reaction and a non-united femoral fracture (yellow arrows). **b** The open infected thigh requires removal of necrotic soft tissue and white (dead) bone, adjacent to live (red) bone that needs to be retained for successful limb salvage. Complete removal of the dead bone, cement, and necrotic tissues creates a healthier environment for the new prosthesis. **c** Post-op X-ray of the femoral defect with modular hip prosthesis. **d**–**g** Bacterial biofilm on explanted hardware components. Photographs of the surface of a femoral total knee replacement component before (**d**) and after (**e**) osmium tetroxide staining identifying bacterial biofilm on the bone cement. **f** SEM of the explanted hardware reveals biofilm bacteria (yellow arrow) on the surface of the implant (x10 000) and **g** bacteria attached to fibrin on the explanted hardware (x10 000)

Masters et al., Bone Research (2019) 7:20

Hidden reservoirs

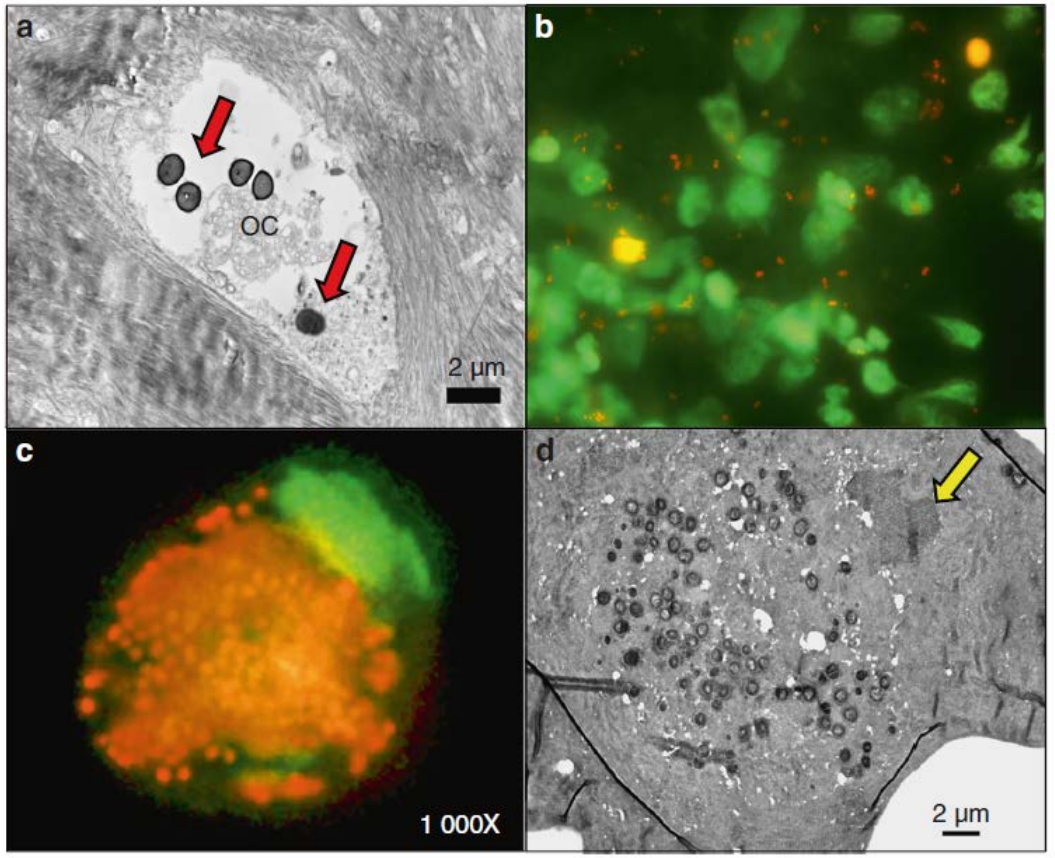
2. Intracellular survival

Evidence of an intracellular reservoir
in osteocytes (A,B), osteoblasts (C) and bone matrix
of a patient with recurrent osteomyelitis



Bosse et al., J Bone Joint Surg Am. (2005) 87: 1343-7

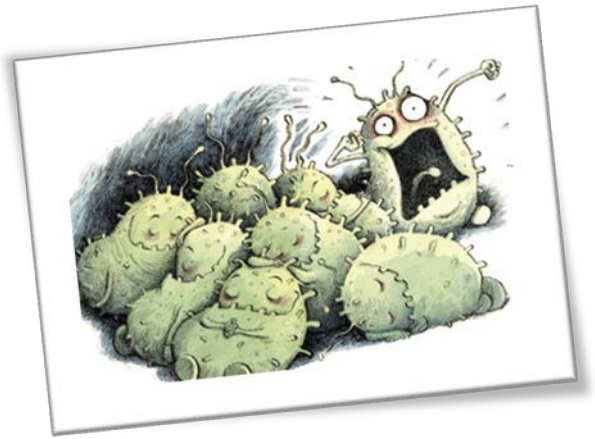
Evidence of bacteria in osteocyte-lacuno canalicular network (A-B)
and of 'Trojan horses' macrophages (C-D)



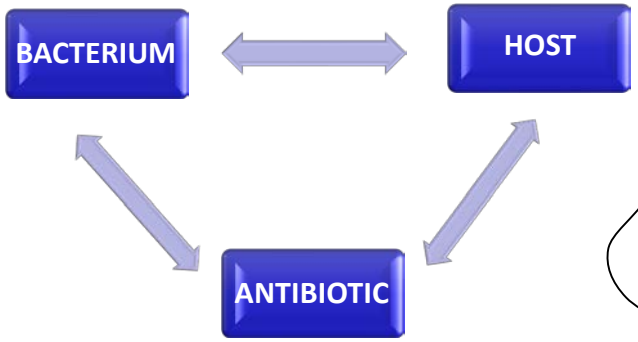
Masters et al., Bone Research (2019) 7:20

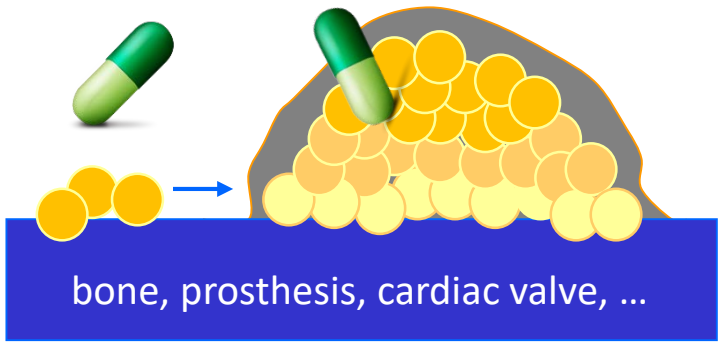
Antibiotic PK/PD against persistent forms of infection

PK parameters:
Access and accumulation at the infection site

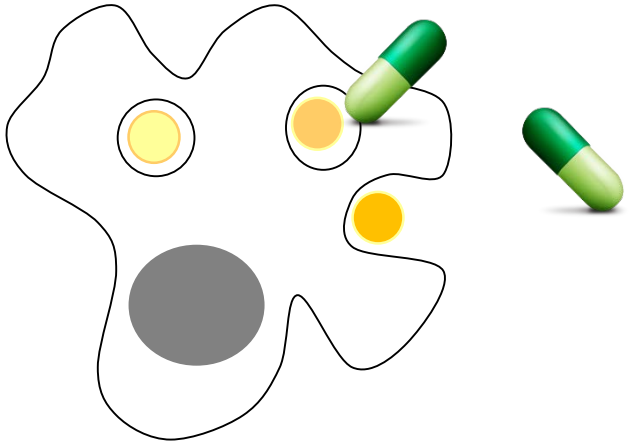


PD parameters:
- Expression of antibiotic activity
- Bacterial responsiveness
- Cooperation with the host





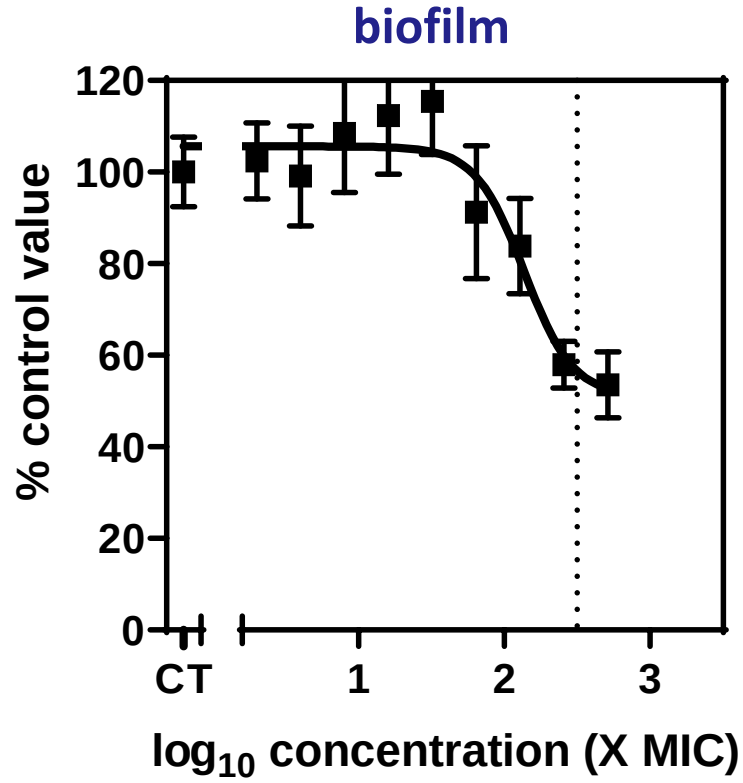
biofilm

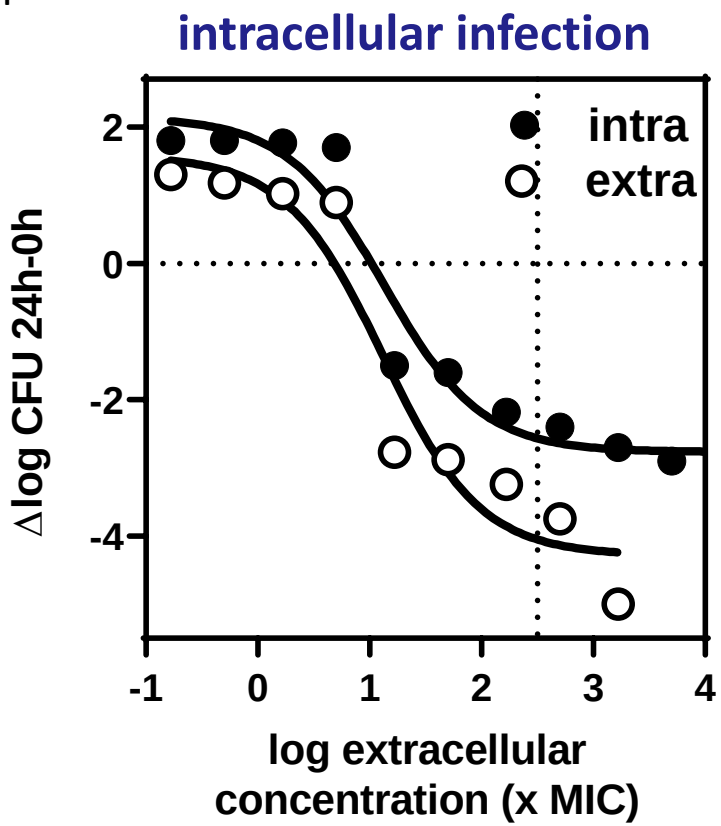


intracellular infection

Antibiotic PK/PD against persistent forms of infection

moxifloxacin





In general, maximal effect reached at conc. ~ 300 x MIC

Adapted from Bauer et al., Antimicrob Ag Chemother (2013) 57:2726-2737, Barcia-Macay et al., Antimicrob Ag Chemother (2006) 50: 841-851

Antibiotic bone concentrations: a global picture

~ 100 MIC

> 100 MIC

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Moxifloxacin	2.8	0.25
Doxycycline	3	2
TMP/SMX	6.8/35.8	4
Afabicin	0.370 // 0.640	[0.008]

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Colistin	NA	2
Metronidazole	5.6 // 5.7	-

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Still more questions than answers ….

- Local bioavailability ?
- Duration of treatment ?
- Expression of activity ?
- PD criteria for efficacy ?