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au vendredi 7 juin 2019

Therapeutic drug monitoring (TDM) of the beta-lactam antibiotics: "It's about time"

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5 June 2019

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No financial conflict of interest

Possible intellectual conflict of interest:

Working on beta-lactam TDM for a few years now…

Outline: beta-lactam TDM

RATIONALE

TARGET POPULATIONS

PRACTICAL ASPECTS

CURRENT SITUATION

CURRENT ISSUES

- **Why** perform TDM of beta-lactam antibiotics
- **Who** should undergo beta-lactam TDM
- **How** should beta-lactam TDM be done
- **Where** beta-lactam TDM is being done
- **What** are the outstanding/understudied issues
- Not covered: continuous versus intermittent infusion

Why perform beta-lactam TDM?

A clinical case (I)

- 32 year-old man with no past medical history admitted to the intensive care unit with polytrauma from a motor vehicle accident
  - Multiple surgeries, long intubation

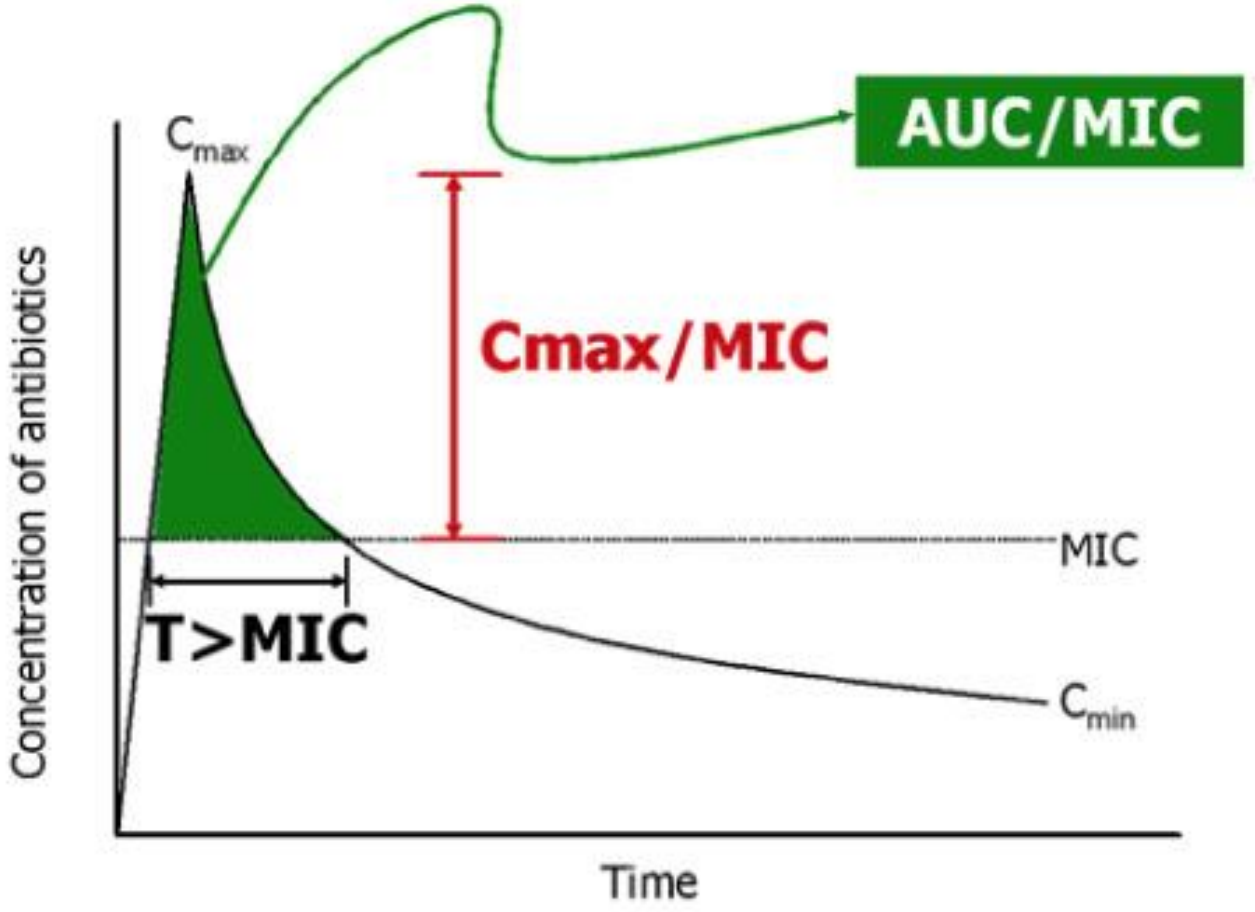
- Day 10: ventilator-associated pneumonia diagnosed
  - Extended-spectrum beta-lactamase+ *Klebsiella pneumoniae* grows from broncho-alveolar lavage cultures
  - Imipenem 500 mg qid begun

Why perform beta-lactam TDM?

A clinical case (II)

- Patient remains febrile, Klebsiella persists in tracheal aspirates
- On day 5 of imipenem therapy, creatinine clearance is calculated: 305 ml/min
- The next morning, blood is drawn for a trough level of imipenem: the drug is undetectable (<0.5 mg/L)…

The pharmacokinetic indices



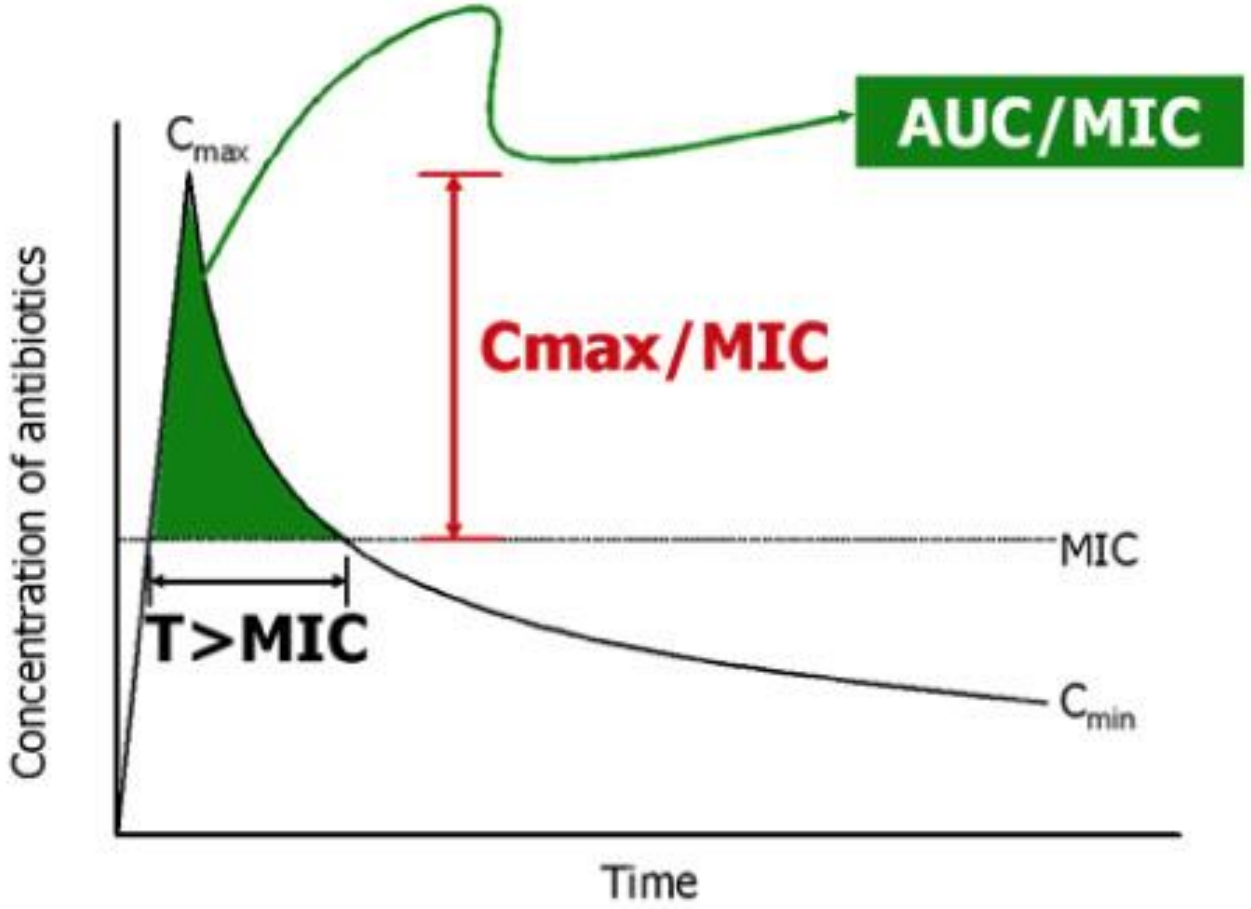
Traditional categorization:

T > MIC
beta-lactams
vancomycin
(It's about time!)

Cmax/MIC
aminoglycosides
fluoroquinolones
daptomycin
metronidazole

AUC/MIC
linezolid
tigecycline

The pharmacokinetic indices



May be something more like this:

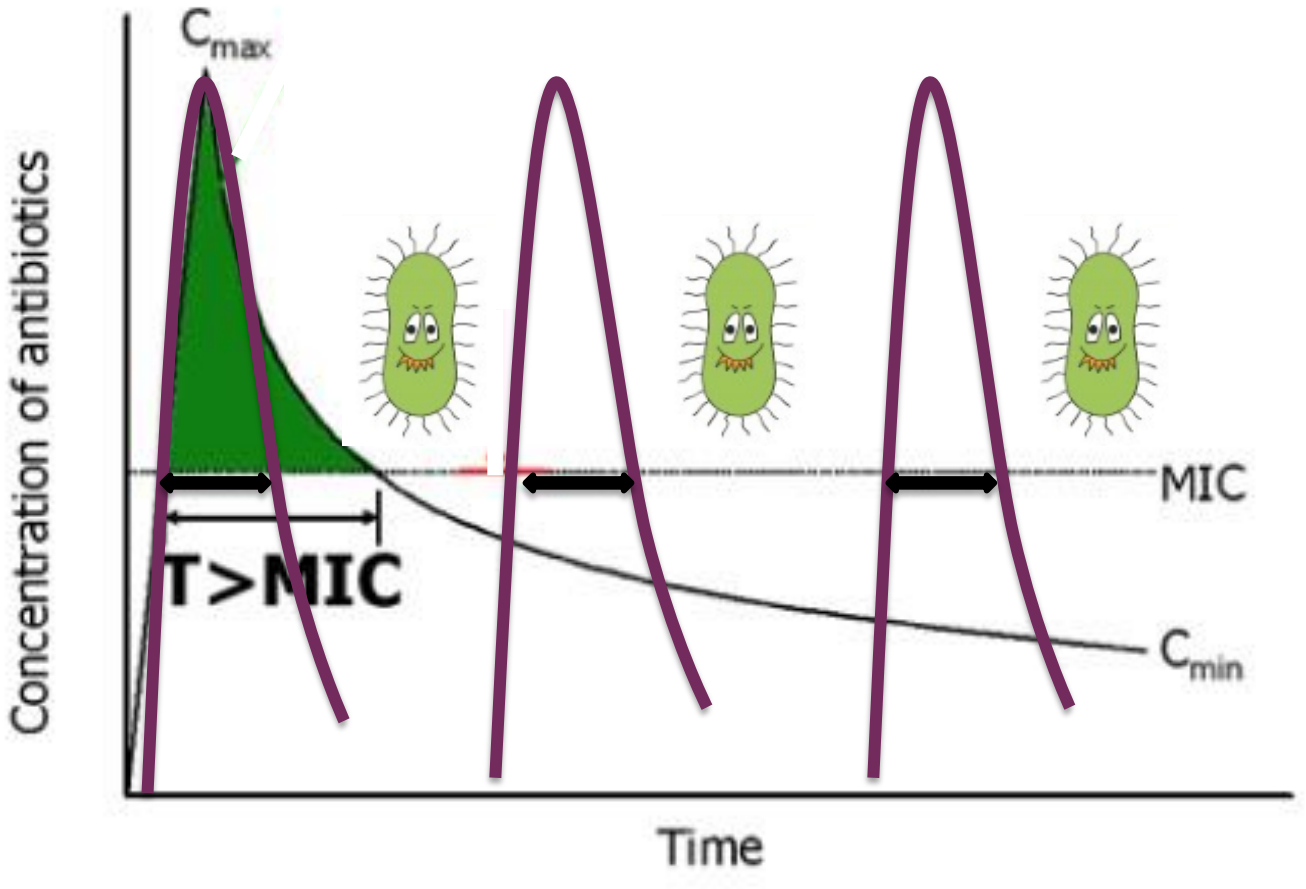
T > MIC

beta-lactams
vancomycin

AUC/MIC

beta-lactams
vancomycin
linezolid
tigecycline
aminoglycosides
fluoroquinolones
daptomycin
metronidazole

Augmented renal clearance
(or an increased volume of distribution)



Augmented renal clearance: glomerular hyperfiltration, by consensus >130 ml/min

Rationale for now measuring levels of antibiotics we'd used blindly for 20 years

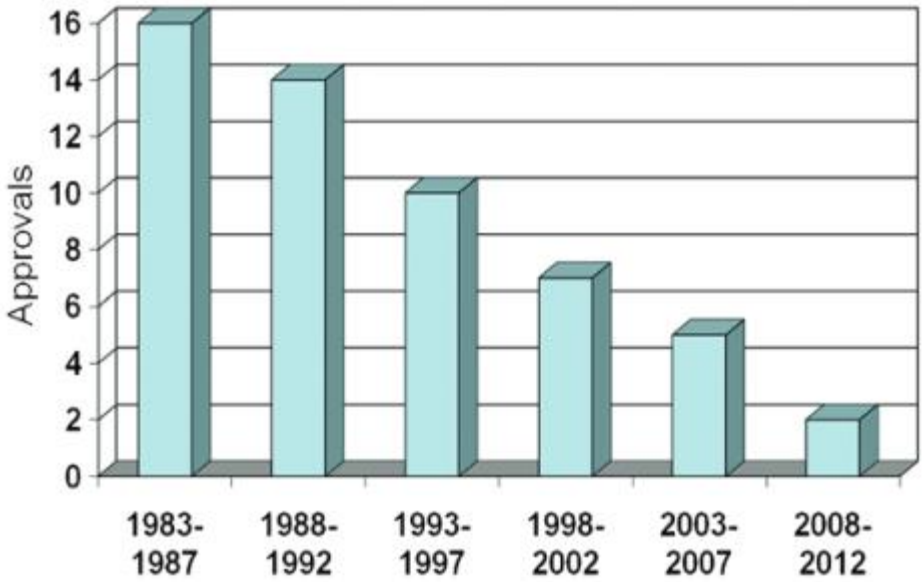
- We need to do better for our individual patients
  - Mortality of sepsis still unacceptably high in 2018
  - Populations are changing (obesity, dialysis/CRRT, immunosuppression)
- Preserving what we still have: as a society we are in a fine mess

Antibacterial resistance Us! Antibiotic pipeline

Brun-Buisson et al, *Intens Care Med* 2004

Rationale for measuring levels of antibiotics we'd used blindly for 20 years

- That dry antibiotic pipeline



New systemic antibacterial agents approved by the US FDA per 5-year period.

Boucher et al. *Clin Inf Dis* 2013

Who needs beta-lactam TDM?

- The <u>critically ill</u>
  - Post-trauma, post-operative, burn, ECMO patients
  - <u>Hyperdynamic pathophysiologic states</u>:
    - Augmented renal clearance→ early elimination
    - Capillary leak syndrome→ increased & changing volumes of distribution (Vd)

These patients look nothing like the phase I, healthy volunteers whose beta-lactam concentrations inform approved dosing regimens

Who needs beta-lactam TDM?

A clinical case (III)

- Patient remains febrile, Klebsiella persists in tracheal aspirates
- On day 5 of imipenem therapy, creatinine clearance is calculated: 305 ml/min
- The next morning, blood is drawn for a trough level of imipenem: the drug is undetectable (<0.5 mg/L)
- An intermediate level (t 3h) is 0.88 mg/L…

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study

Angela Huttner[a,*], Elodie Von Dach[a], Adriana Renzoni[a], Benedikt D. Huttner[a], Mathieu Affaticati[b], Leonardo Pagani[a], Yousef Daali[c], Jerôme Pugin[d], Abderrahim Karmime[e], Marc Fathi[e], Daniel Lew[f], Stephan Harbarth[a]

- Prospective observational study of 100 ICU patients
  - aged 18-60 years, severe infection, creatinine clearance ≥60 ml/min
- Primary outcome: clinical response at day 30
  - (in relation to levels of one of 4 measurable beta-lactams)
- Secondary outcomes: incidence of ARC, incidence of "subthreshold" beta-lactam concentrations

Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study

- Mean age 45 years
- Median creatinine clearance 144 ml/min
  - 64% had ARC at inclusion
- Most had imipenem (> piperacillin/tazobactam > meropenem > cefepime)

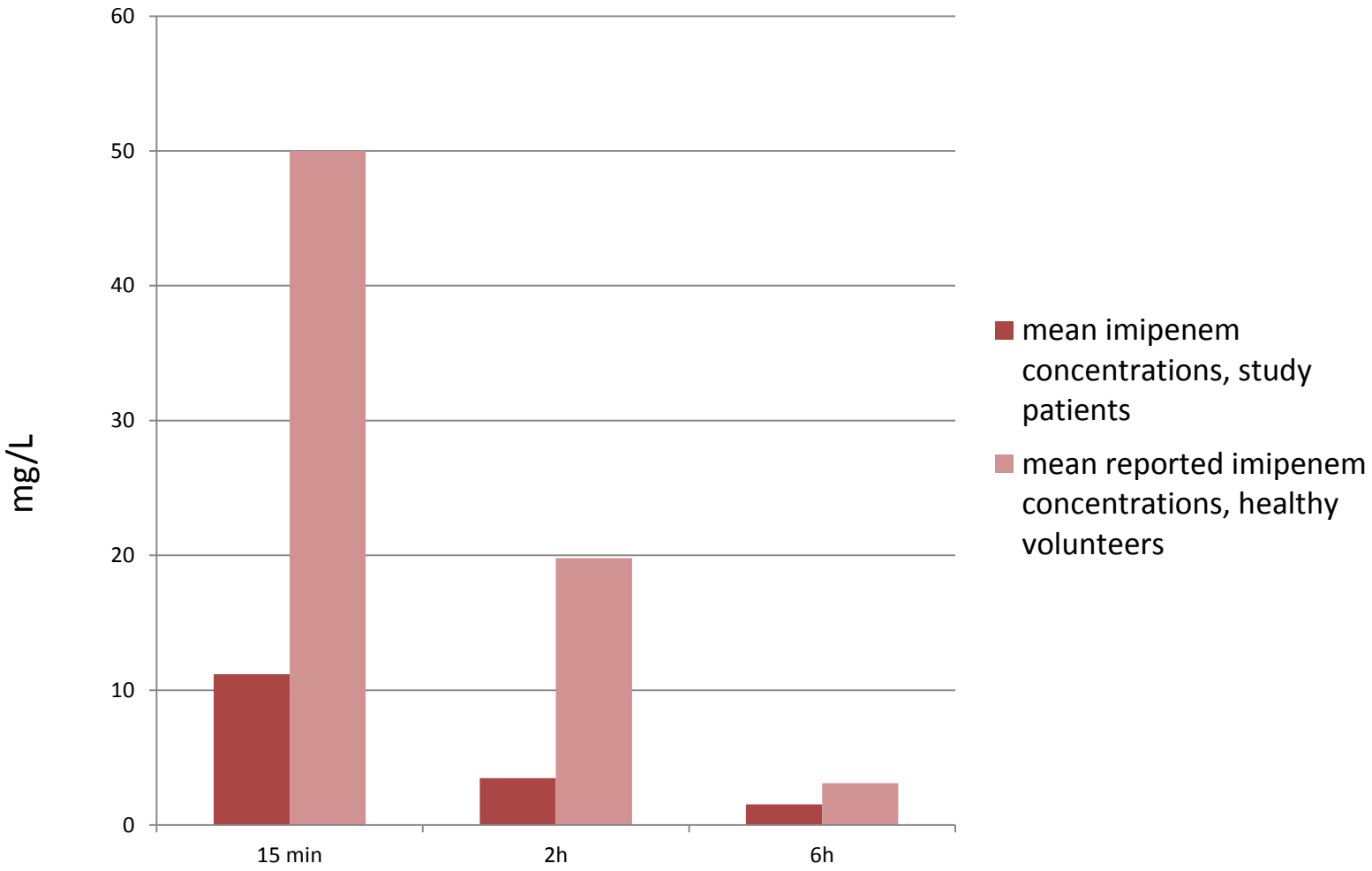
Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study

Table 3
Characteristics of pooled antibiotic concentrations.

	Peak (C_{max})	Intermediate ($T_{40-60\%}$)	Trough ($T_{100\%}$)
All antibiotics			
No. of samples	162	135	217
Undetectable concentrations (%)	0	4	20.0
Subthreshold concentrations (%)	2.6	16	71.4
Imipenem/cilastatin[a,b]			
No. of samples	84	70	120
Mean concentration (mg/L)	11.2	3.5	1.52
Median concentration (mg/L)	9.6	2.8	0.93
IQR of concentrations (mg/L)	7.1–13.1	2.07–4.7	0.4–1.88
Concentration range (mg/L)	1.3–88.6	0.88–13.2	0–12.2
Undetectable concentrations (%)	0	0	24
Subthreshold concentrations (%)	1.2	22.9	77
Piperacillin/tazobactam[b,c]			
No. of samples	61	49	74
Mean concentration (mg/L)	96.8	22.2	6.3
Median concentration (mg/L)	93	15.1	3.0
IQR of concentrations (mg/L)	58.8–120	7.5–26.3	1.4–6.87
Concentration range (mg/L)	1.5–241.2	1.8–166.1	0–84.3
Undetectable concentrations (%)	0	0	6.7
Subthreshold concentrations (%)	1.6	6.1	60.8
Meropenem[a]			
No. of samples	14	11	18
Mean concentration (mg/L)	22.9	3.11	0.89
Median concentration (mg/L)	21.08	1.91	0.33
Concentration range (mg/L)	9.6–38.5	0–16.6	0–7.4
Undetectable concentrations (%)	0	27.2	50
Subthreshold concentrations (%)	0	54.6	88.9
Cefepime[c]			
No. of samples	3	5	5
Mean concentration (mg/L)	63.86	14.0	9.2
Median concentration (mg/L)	67.4	9.5	8.1

Odds ratio for undetectable imipenem levels if augmented renal clearance present = 3.3 (95%CI 1.1-9.9)

Our ICU patients vs. healthy volunteers



Who else needs beta-lactam TDM?

- Patients on dialysis or continuous renal replacement therapy
  - TDM for both exposure & safety
- Obese patients
  - Wide inter-individual variability, increased Vd
- Elderly patients
  - Impaired absorption, reduced protein binding, wide inter-individual variability
- Patients with:
  - Remote infections (e.g., osteomyelitis) or difficult pathogens (e.g., *Pseudomonas aeruginosa*)

Beta-lactam TDM: more commonly to ensure exposure but also to protect against toxicity

- Beta-lactams known for their relatively low toxicity EXCEPT cefepime…

Clinical Microbiology and Infection 23 (2017) 454–459

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

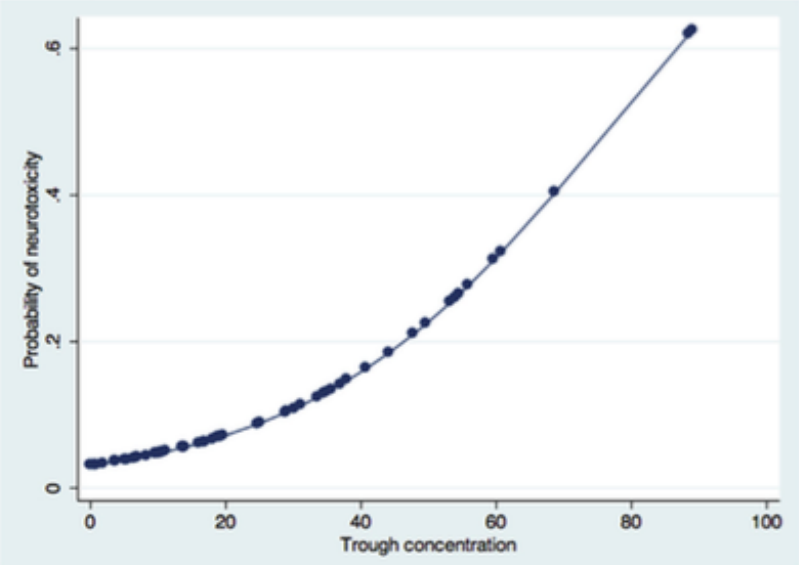
Original article

Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study

T. Huwyler [1,6], L. Lenggenhager [1,6], M. Abbas [2], K. Ing Lorenzini [3], S. Hughes [5], B. Huttner [2,4], A. Karmime [5], I. Uçkay [4], E. von Dach [2], P. Lescuyer [5], S. Harbarth [2,4], A. Huttner [2,4,*]

Who else needs beta-lactam TDM?

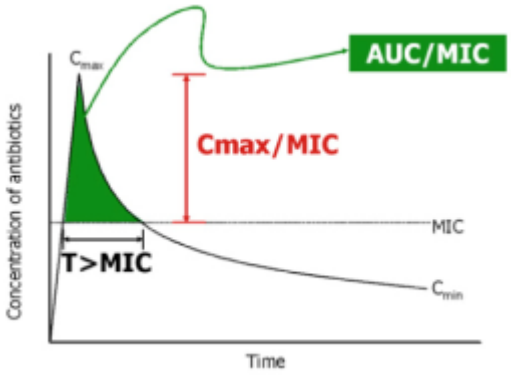
- Patients on cefepime for more than a few days
- Patients with renal insufficiency on cefepime for any period of time
- Trough levels should probably be ≤20 mg/L



How ***should*** beta-lactam TDM be done?

Logistics

- Quickly
  - (Almost never)
- In a standardized/validated fashion
  - (Currently almost all in-house)
- Cheaply
  - (Depends)
- Thoroughly → in tandem with target organism's MIC!
  - (Rarely)



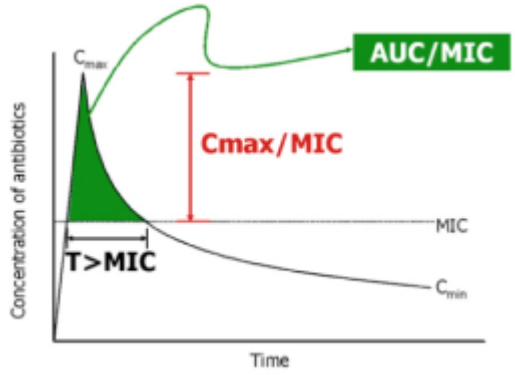
How is beta-lactam TDM currently done?

Assays

- Either high-performance liquid chromatography with ultraviolet detection (HPLC/UV) or
- Liquid chromatography–tandem mass spectrometry (LC–MS/MS)
- Rarely, microbiologic assay
- Most centers measure total (free + protein-bound) levels, though we should be going for free levels
  - Especially for highly protein-bound drugs like flucloxacillin (95%) and ceftriaxone (60%)!

Wong et al. *J Antimicrob Chemother* 2014;69(5):1416-23
Wong et al. *Antimicrob Ag Chemother* 2013; 57(12): 6165-70

What should be the PK targets?



Efficacy/exposure targets

- Most common target is 100% *ƒ* T>MIC
  - Pragmatism/feasibility versus PK information gathering
- You may not have the MIC
  - Consider EUCAST breakpoints
- May need to adjust depending on site of infection, drug's properties

Table 4. List of PK/PD targets for dose adjustment adopted by selected ICUs

	PK/PD targets
For dose increase	100% $fT_{>MIC}$ ($n=5$)
	100% $fT_{2-4\times MIC}$ ($n=1$)
	50% $fT_{>4\times MIC}$ ($n=1$)
	100% $fT_{>4\times MIC}$ ($n=2$)
	40% $fT_{>4\times MIC}$ ($n=1$)
	50% $fT_{>4\times MIC}$ ($n=1$)
	70% $fT_{>4\times MIC}$ ($n=1$)
Threshold of potential toxicity for dose reduction	100% $fT_{10\times MIC}$ ($n=4$)
	100% $fT_{8\times MIC}$ ($n=1$)
	100% $fT_{6\times MIC}$ ($n=1$)
	100% $fT_{4-5\times MIC}$ ($n=1$)
	steady-state concentration exceeding 2 × maximum exposure expected in general population; e.g. piperacillin >100 mg/L (>32 g/24 h in normal patients), meropenem >32 mg/L (>12 g/24 h in normal patients) ($n=1$)

% $fT_{>x\times MIC}$, percentage of the dosing period during which the free (unbound) concentration

Wong et al. *J Antimicrob Chemother* 2014;69(5):1416-23
Muller et al. *Drugs* 2018;78(4):439-451

The minimum inhibitory concentration: be careful!

- Just one MIC is a very imperfect measure

J Antimicrob Chemother 2018; **73**: 564–568
doi:10.1093/jac/dkx427 Advance Access publication 5 December 2017

Journal of Antimicrobial Chemotherapy

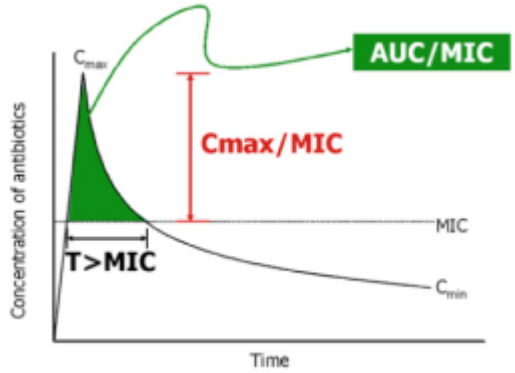
MIC-based dose adjustment: facts and fables

Johan W. Mouton[1]*, Anouk E. Muller[1,2], Rafael Canton[3], Christian G. Giske[4], Gunnar Kahlmeter[5] and John Turnidge[6]

[1]Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands; [2]Department of Medical Microbiology, Haaglanden Medical Centre, The Hague, The Netherlands; [3]Servicio de Microbiologia, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYIS), Madrid, Spain; [4]Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden; [5]Department of Clinical Microbiology, Central Hospital, 351 85, Växjö, Sweden; [6]Adelaide Medical School, University of Adelaide, Adelaide, Australia

"We must free ourselves from the misconception that there is such a thing as a 'true' MIC for a strain. Instead, each measurement of an MIC generates a value that is a member of a probability distribution."

What should be the PK targets?

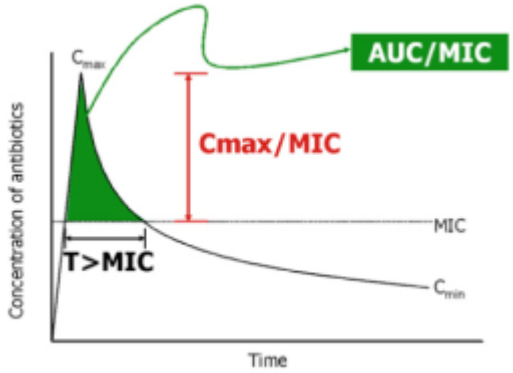


Toxicity thresholds

- "Work is ongoing." (=We don't really know.)
  - Even for cefepime (that was just one small retrospective study!)
- We know there is a lot of variability for some antibiotics
  - piperacillin, amoxicillin, flucloxacillin
- Some antibiotics don't seem to have (discernibly) concentration-dependent toxicity
  - The example of imipenem…

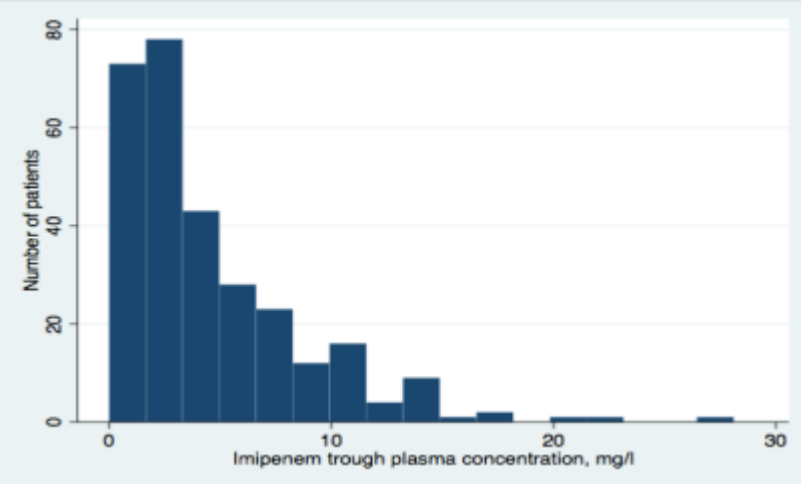
Huttner, von Dach, Renzoni et al. *Int J Antimicrob Ag* 2015; 45(4):385-92
Muller et al. *Drugs* 2018;78(4):439-451

What should be the PK targets?



Toxicity thresholds

- Of 300 patients in Geneva undergoing imipenem TDM, 8 (3%) had toxicity considered likely related
  - No real differences in imipenem levels (median 5.2 mg/l versus 4.8 mg/l, p=0.78) or duration of therapy (9 vs 10 days)
  - Everyone had low levels!



Summary: targets for beta-lactam TDM

- We don't yet have exact therapeutic windows for all beta-lactams
- But beta-lactams are not highly toxic (with some exceptions) and toxicity is reversible
  - → So high numbers should not scare you
  - → Numbers can get very high if you are measuring total levels

- Efficacy (upper limit): current paradigm is to target 100% *f* T>MIC (but one MIC is not always reliable)

- Toxicity (lower limit): for cefepime, avoid trough levels >20 mg/l, for other drugs the limit may be much higher

Defining upper & lower TDM limits: we're working on it!

OPTIMAL TDM

The OPTIMAL TDM Study: Determining Optimal Beta-lactam Plasma Concentrations Through Therapeutic Drug Monitoring (OPTIMAL TDM)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03790631

Recruitment Status : Recruiting
First Posted : December 31, 2018
Last Update Posted : February 22, 2019

See Contacts and Locations

Sponsor:
University of Geneva, Switzerland

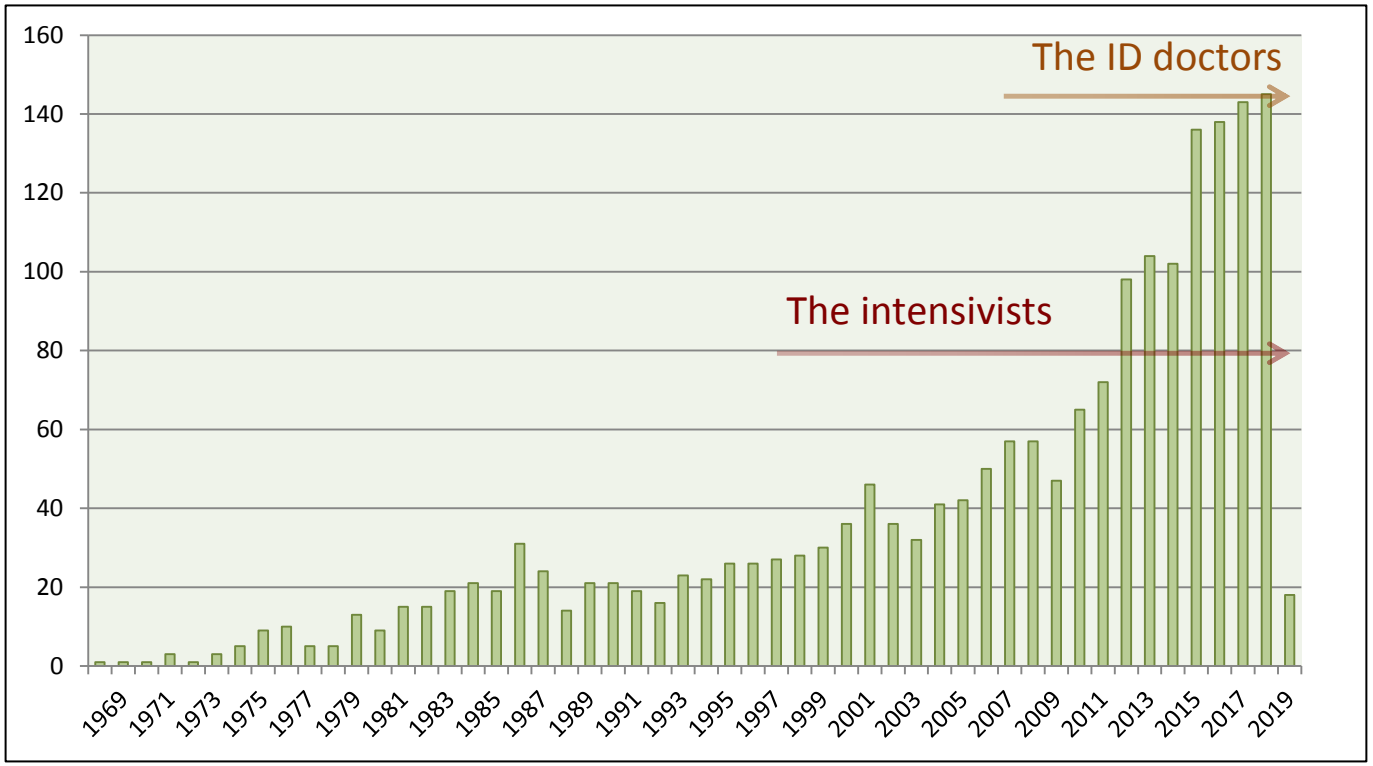
- Single→multicenter (?) study following >700 patients clinically in the 30 days after ≥2 TDM levels for **clinical response** & potential **toxicity**

Imipenem
Meropenem
Piperacillin
Flucloxacillin
Amoxicillin
Ceftazidime
Cefepime

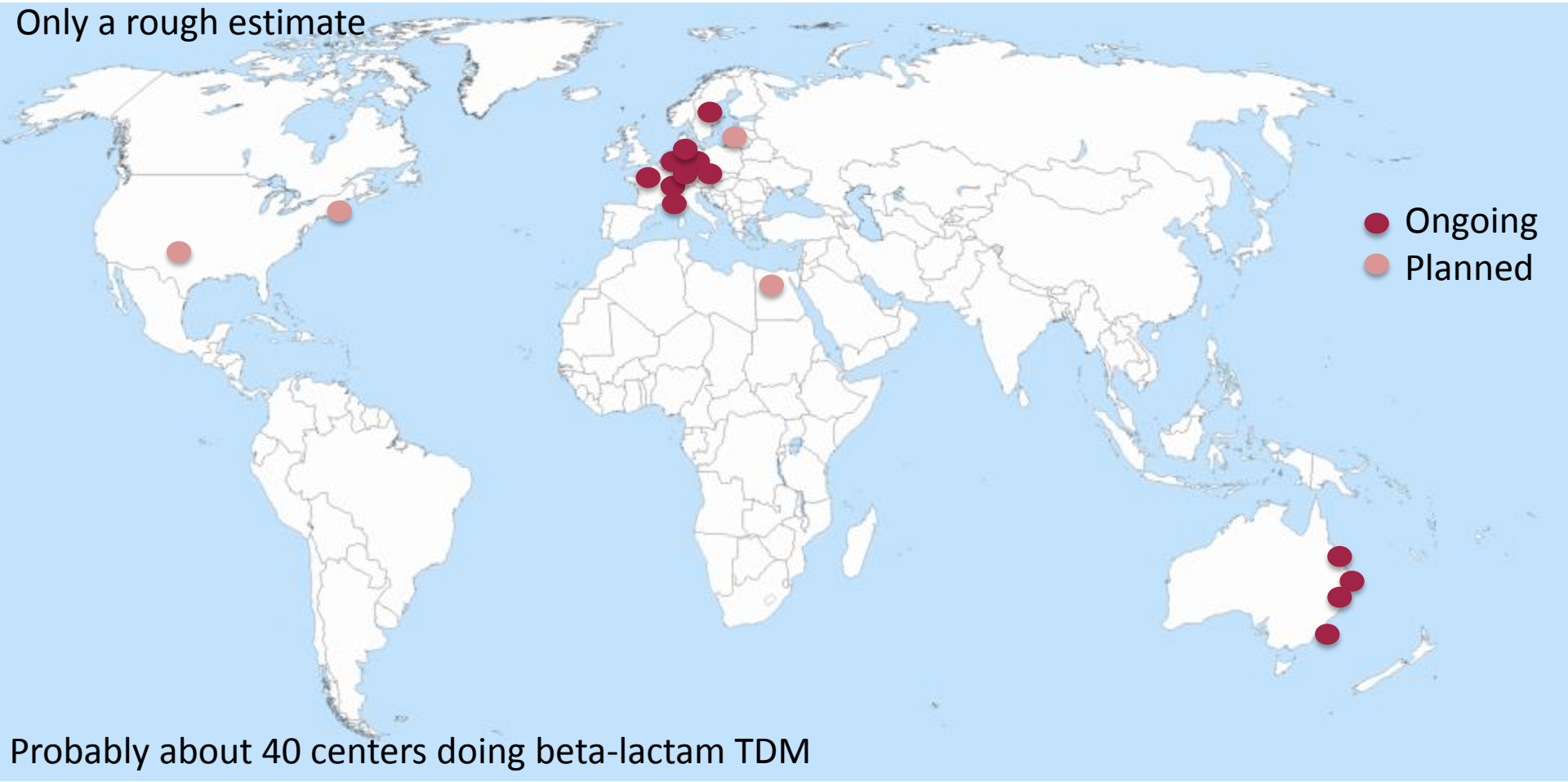
Beta-lactam TDM: current status

Articles published on beta-lactam TDM

Search = “beta-lactam therapeutic drug monitoring”



Beta-lactam TDM: current status



Outstanding issue #1:

Does beta-lactam TDM improve clinical outcomes?

- We know it improves pharmacologic outcomes
  - Sime et al. Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial. *J Antimicrob Chemother* 2015; 70(8):2369-75
  - Patel et al. Therapeutic drug monitoring of beta-lactam antibiotics in burns patients--a one-year prospective study. *Ther Drug Monit* 2012; 34(2):160-4

- But we can't easily show differences in clinical outcomes
  - No randomized trial has yet shown superior outcomes
    - Getting harder to do (local culture changes, clinical equipoise lost)
  - That patient with *Klebsiella pneumoniae*…

Clinical case: our young man (IV)

- Day 6 of imipenem therapy: spontaneous improvement before any dose change
  - Defervescence, weaning from ventilator
- Day 10: infection fully resolved, imipenem 500 mg qid discontinued
- Day 12: transferred to the floor

Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study

- Primary outcome: clinical response
  - Patients with low imipenem levels did not have more failure!
    - Failure in 18/98 (18%), no difference in imipenem levels
    - Augmented renal clearance was actually protective—or a marker of something protective
- There are other studies like this…
  - Difficult population to study (polypharmacy, differing comorbidities & severities, diagnoses unclear, etc.)

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

(Best evidence – but still not enough)

Jason A. Roberts,[1,2] Sanjoy K. Paul,[3,4] Murat Akova,[5] Matteo Bassetti,[6] Jan J. De Waele,[7] George Dimopoulos,[8] Kirsi-Maija Kaukonen,[9] Despoina Koulenti,[1,8] Claude Martin,[10,11] Philippe Montravers,[12] Jordi Rello,[13] Andrew Rhodes,[14] Therese Starr,[2] Steven C. Wallis,[1] and Jeffrey Lipman[1,2]; for the DALI Study[a]

- Point-prevalence study of intermediate (50% fT>MIC) & trough (100% fT>MIC) beta-lactam serum concentrations
- 384 patients across 68 ICUs
  - Of 248 patients treated for infection, 16% did not achieve 50% fT>MIC & were 32% less likely to have positive clinical outcome (OR 0.68, 95%CI 0.52-0.91, P=.009)
- + Association between positive clinical outcome and an increasing 100% fT>MIC ratio (OR 1.56, 95%CI 1.15-2.13, P=0.03)

Outstanding issues:
Does beta-lactam TDM improve other outcomes?

What about ecologic outcomes?

Sensibilité (%) des isolats de *Pseudomonas aeruginosa* Unité de soins intensifs Laboratoire de Bactériologie HUG (abch)	2010	2011	2012*	2013	Sensibilité (%) des isolats de *P. aeruginosa* Tous les services HUG en 2013
ATB / Σ patients	55	68	56	84	1071
Pipéracilline	84	89	83	75	86
Pipéracilline/Tazobactam	86	91	85	74	88
Céftazidime	83	91	88	76	91
Céfépime	92	94	98	82	92
Imipénème	72	79	85	70	82
Méropénème	72	85	84	66	84
Aztréonam	73	78	80	65	80
Amikacine	91	100	96	94	93
Gentamicine	91	97	85	87	88
Tobramycine	98	100	98	100	98
Ciprofloxacine	87	97	92	89	90

2016:
76
81
90
76
76

27th ECCMID Vienna, Austria 22 – 25 April 2017 | ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

Emergence of *Pseudomonas aeruginosa* resistance in patients with imipenem therapeutic drug monitoring

Lauriane Lenggenhager, Mohamed Abbas, Carolina Fankhauser, Benedikt Huttner, Stephan Harbarth, Angela Huttner

Background: Antibiotic overuse drives antibiotic resistance. Resistance to carbapenem antibiotics among *Pseudomonas aeruginosa* strains appears to be rising in step with their increased use. We examined the transition from imipenem susceptibility to resistance among *P. aeruginosa* strains detected in hospitalised patients, exploring imipenem duration and plasma concentrations determined by therapeutic drug

Patients in whom IRP emerged had significantly more days of imipenem therapy than those whose strains remained sensitive (median 11 days [IQR 5-10] vs. 5 [IQR 3-7], P=.044). **They trended toward lower imipenem levels (mean minimum concentration 3.97 mg/l [SD ±3.85] vs. 5.31 mg/l [SD ±5.36])…**

significant.

Results: We identified 67 adult patients with imipenem TDM (median number of measurements 1, range 1-6) and at least one specimen yielding *P. aeruginosa* (median 2, IQR 1-4). Most (49/67, 73%) were male; mean age was 63 years (SD ±16). A slight majority (34/67, 51%) were surgical patients and nearly half (32/67, 48%) were hospitalized in the intensive care unit….

Other outstanding issues

- No commercial beta-lactam assay
- MICs are difficult to perform—and one alone is not always reliable
- Therapeutic ranges have not been defined
- Technical issues
  - stability

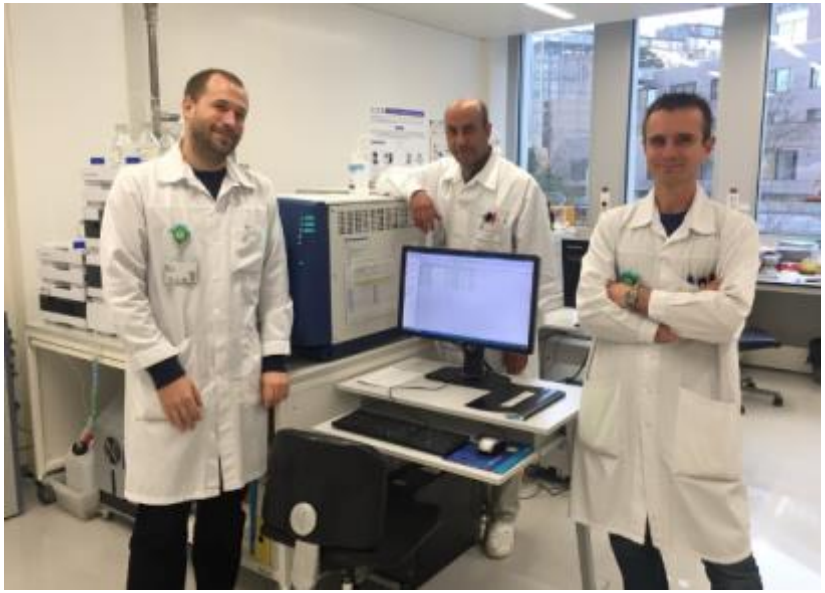
Where more work is needed

- TDM isn't the intervention; it's the guide
- More needs to be done for the <u>group</u>
  - Effects of optimized dosing ±shorter durations on resistance development
- More needs to be done for the <u>individual</u>
  - The approach of "Go hard and go home"/"Hit hard and hit fast" has not been studied in a randomized trial…

Conclusions

- Pharmacokinetic data from healthy volunteers are not representative of critically ill & other populations
- Beta-lactam TDM is a tool that, in the individual patient, can help ensure adequate antibiotic exposure and protect against toxicity (e.g., cefepime)
  - But logistic & technical issues need addressing
- TDM is the guide and should be used to revisit our old assumptions about dosing and pharmacokinetics
- There may be a role for improving ecologic outcomes for the group
  - But more data are needed

Thank you!



David Tonoli Abderrahim Karmime Pierre Lescuyer

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