TDM versus no TDM
Intermittent without TDM

BVIKM/SBIMC symposium, March 2017

Deborah Konopnicki, CHU St Pierre, Brussels

+ Disclosure

Ladies and gentleman members of the jury, my client is innocent

TDM vs. no TDM

No TDM

- Is there an evidence-based rationale to perform TDM?
- Is it easily feasible to perform TDM?
- Is it useful in all situations?

No TDM

Is there an evidence-based rationale in clinical studies?

- **YES:** Elevat
  higher toxic
  - Vancomyc
  - Aminoglyc

Cefepim

Through concentrations >20 mg/L after

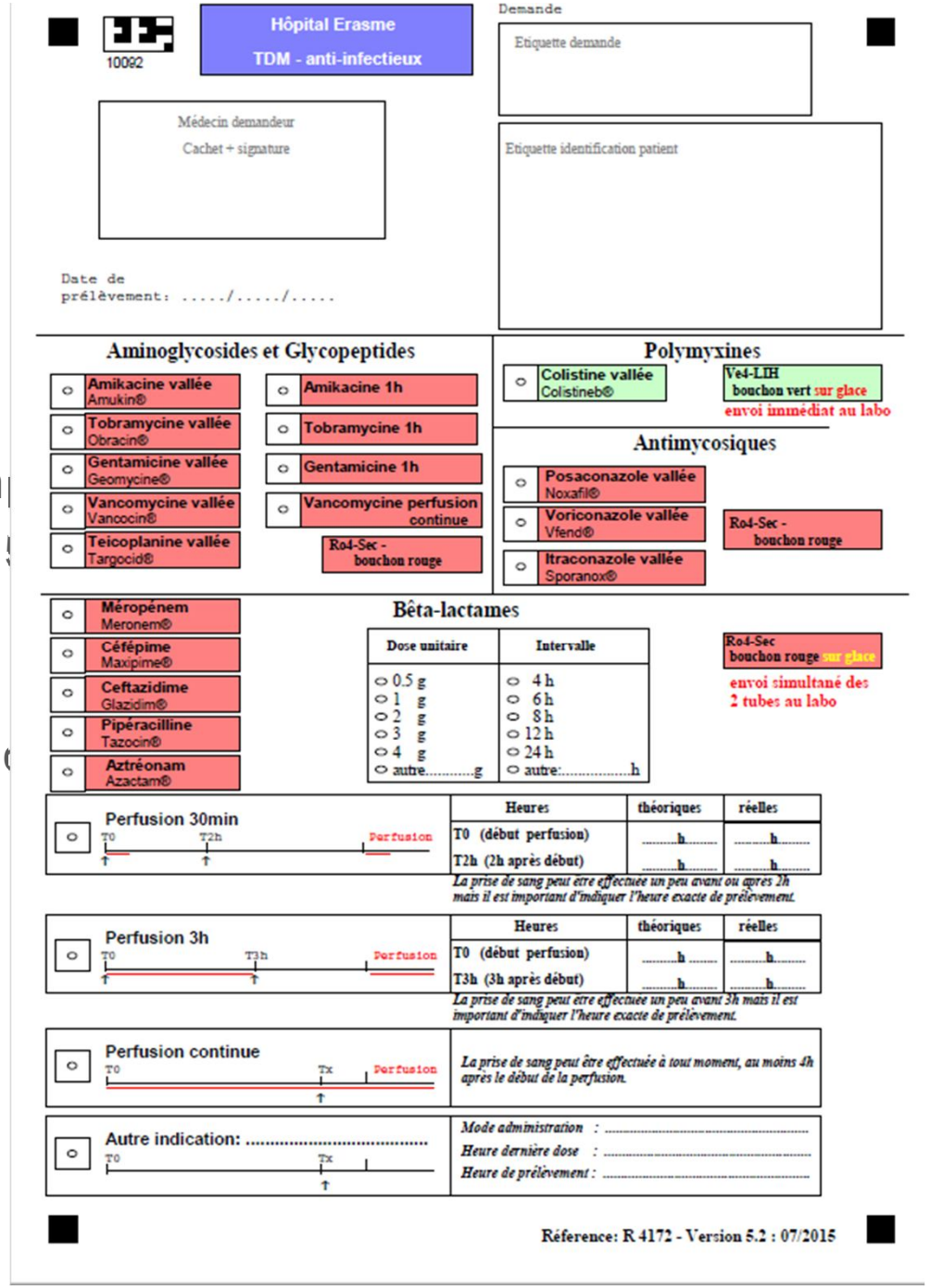
Direct or indirect evidences

that TDM are clinically usefull

- **YES**: to attain PK/PD targets in ICU patients (look at the continuous vs intermittent administration studies)

No TDM

- **Is TDM easily feasible?**
  - When should we take our sam
    Timing to get to **steady state**:
    - Voriconazole 5 days
  - How many samples? Is one en



10092

Hôpital Erasme
TDM - anti-infectieux

Demande
Etiquette demande

Médecin demandeur
Cachet + signature

Etiquette identification patient

Date de prélèvement: ...../...../.....

Aminoglycosides et Glycopeptides

- Amikacine vallée — Amukin®
- Tobramycine vallée — Obracin®
- Gentamicine vallée — Geomycine®
- Vancomycine vallée — Vancocin®
- Teicoplanine vallée — Targocid®
- Amikacine 1h
- Tobramycine 1h
- Gentamicine 1h
- Vancomycine perfusion continue

Ro4-Sec - bouchon rouge

Polymyxines

- Colistine vallée — Colistineb®

Ve4-LIH bouchon vert sur glace
envoi immédiat au labo

Antimycosiques

- Posaconazole vallée — Noxafil®
- Voriconazole vallée — Vfend®
- Itraconazole vallée — Sporanox®

Ro4-Sec - bouchon rouge

Bêta-lactames

- Méropénem — Meronem®
- Céfépime — Maxipime®
- Ceftazidime — Glazidim®
- Pipéracilline — Tazocin®
- Aztréonam — Azactam®

Dose unitaire	Intervalle
0.5 g	4 h
1 g	6 h
2 g	8 h
3 g	12 h
4 g	24 h
autre.....g	autre:.....h

Ro4-Sec bouchon rouge sur glace
envoi simultané des 2 tubes au labo

Perfusion 30min

Heures	théoriques	réelles
T0 (début perfusion)	.....h.....	.....h.....
T2h (2h après début)	.....h.....	.....h.....

La prise de sang peut être effectuée un peu avant ou après 2h mais il est important d'indiquer l'heure exacte de prélèvement.

Perfusion 3h

Heures	théoriques	réelles
T0 (début perfusion)	.....h.....	.....h.....
T3h (3h après début)	.....h.....	.....h.....

La prise de sang peut être effectuée un peu avant 3h mais il est important d'indiquer l'heure exacte de prélèvement.

Perfusion continue

La prise de sang peut être effectuée à tout moment, au moins 4h après le début de la perfusion.

Autre indication: .....

Mode administration : .....
Heure dernière dose : .....
Heure de prélèvement : .....

Référence: R 4172 - Version 5.2 : 07/2015

Intra-individual variation

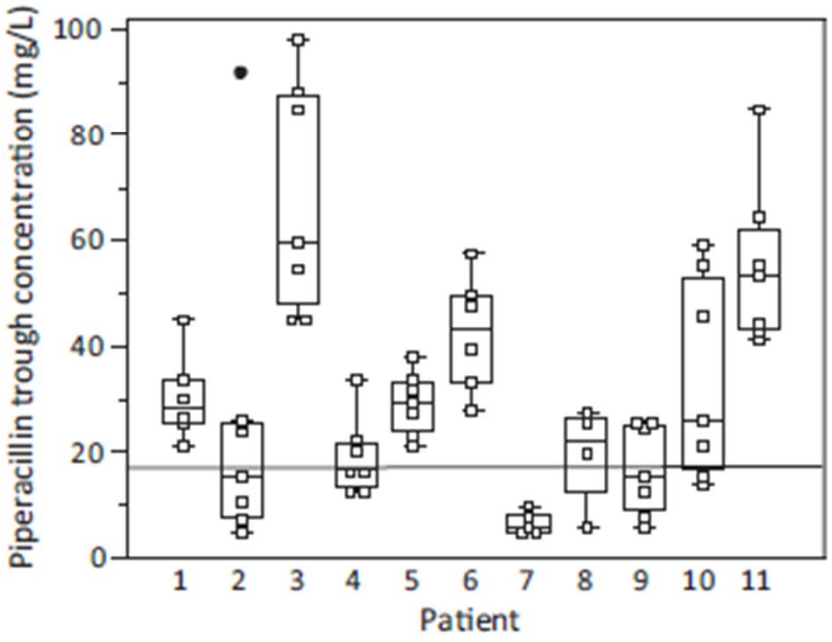
International Journal of Antimicrobial Agents

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

Short Communication

Does consistent piperacillin dosing result in consistent therapeutic concentrations in critically ill patients? A longitudinal study over an entire antibiotic course

Mieke Carlier[a,b,*], Sofie Carrette[b], Veronique Stove[c], Alain G. Verstraete[a,c], Jan



Zoller et al. Critical Care 2014, 18:R148
http://ccforum.com/content/18/4/R148

CRITICAL CARE

RESEARCH Open Access

Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study

Michael Zoller[1], Barbara Maier[2], Cyrill Hornuss[1], Christina Neugebauer[1], Gundula Döbbeler[1], Dorothea Nagel[2], Lesca Miriam Holdt[2], Mathias Bruegel[2], Thomas Weig[1], Béatrice Grabein[3], Lorenz Frey[1], Daniel Teupser[2], Michael Vogeser[2] and Johannes Zander[2*]

eGFR>80 ml/'

Pip/tazo
loading dose: 4g
followed by 4g given in 3 hours
q6h

Variability was
40% within patients
57% between patients

Inversely correlated to SOFA score: the less sick patients had the greatest variability

No TDM

- **Is TDM easily feasible?**
  - When should we take our samples?
  - Timing to get to steady state
  - How many samples? Is one enough?
  - Which lab is going to analysis my sample?
  - Delay answers?
  - How much does it cost? Reimbursment?

Médicament	Laboratoire	Délai réponse	Remboursement
Vancomycine	LHUB-ULB	2 heures (7/7)	X
Téicoplanine	CHU Liège	2 jours (5/7)	X
Gentamicine	LHUB-ULB	3 heures (7/7)	X
Amikacine	LHUB-ULB	2 heures (7/7)	X
Tobramycine	LHUB-ULB	3 heures (7/7)	X
Pipéracilline	LHUB-ULB	1 jour (5/7)	X
Céfépime	LHUB-ULB	1 jour (5/7)	X
Ceftazidime	LHUB-ULB	1 jour (5/7)	X
Méropénem	LHUB-ULB	1 jour (5/7)	X
Aztréonam	LHUB-ULB	1 jour (5/7)	X
Amoxicilline	UZ Gent	?	X
Ampicilline	UZ Gent	?	X
Cefuroxime	UZ Gent	?	X
Isoniazide	UZ Brugge	2 jours (5/7)	X
Colistine	LHUB-ULB	7 jours (1/7)	X
Voriconazole	LHUB-ULB	7 jours (1/7)	15€ patient
Posaconazole	LHUB-ULB	7 jours (1/7)	15€ patient
Itraconazole	LHUB-ULB	7 jours (1/7)	15€ patient
Fluconazole	LHUB-ULB	7 jours (1/7)	15€ patient

Clinica Chimica Acta

Volume 468, May 2017, Pages 215–224

Development and validation of a measurement procedure based on ultra-high performance liquid chromatography-tandem mass spectrometry for simultaneous measurement of β-lactam antibiotic concentration in human plasma

Raül Rigo-Bonnin[a], Alba Ribera[b, c], Ariadna Arbiol-Roca[a], Sara Cobo-Sacristán[d], Ariadna Padullés[d], Òscar Murillo[b, c], Evelyn Shaw[b, c], Rosa Granada[e], Xosé L. Pérez-Fernández[e], Fe Tubau[f, g], Pedro Alía[a]

Show more

http://dx.doi.org/10.1016/j.cca.2017.03.009

7 min

simultaneous measurement of amoxicillin, ampicillin, cloxacillin, piperacillin, cefepime, ceftazidime, cefuroxime, aztreonam and meropenem concentrations in plasma

No TDM

Is TDM usefull in all situations?

- **In particular, is it useful in all situations**
  - **mild or moderate infection**
  - **normal body weight**
  - **no kidney failure**
  - **no sepsis**
  - **intravenous antibiotics prescribed according to guidelines**
  - **for a classical infection (pyelonephritis or pneumonia) that is to say extensively studied**
  - **Bacteria sensitive to AB**
  - **no major drug-drug interaction suspected**

Intermittent without TDM

International Journal of Antimicrobial Agents

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

2014

Review

Prolonging β-lactam infusion: A review of the rationale and evidence, and guidance for implementation

Shawn H. MacVane [a], Joseph L. Kuti [a], David P. Nicolau [a,b,*]

[a] Center for Anti-Infective Research and Development, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102, USA
[b] Division of Infectious Diseases, Hartford Hospital, Hartford, CT, USA

Reference	Study design	Patients	Infection	Dosing regimen	PI findings
Arnold et al., 2013 [36]	Retrospective, single centre	503, ICU	Gram-negative bacteria	FEP or TZP or MEM 3-h inf. vs. FEP or TZP or MEM 30-min inf.	No difference in treatment success rates or mortality
Bauer et al., 2013 [37]	Retrospective, single centre	87, bacteraemia or pneumonia	*Pseudomonas aeruginosa*	FEP 2 g q8h 4-h inf. vs. FEP 2 g q8h 30-min inf.	Significantly lower mortality (20% vs. 3%)
Chastre et al., 2008 [20]	Prospective, multicentre, randomised	531, VAP	Gram-positive and -negative bacteria	DOR 500 mg q8h 4-h inf. vs. IMI 500 mg q6h 30-min inf. or IMI 1 g q8h 1-h inf.	Comparable clinical (68.3% vs. 64.8%) and microbiological (73.3% vs. 67.3%) cure rates; no difference in mortality (10.8%

Non randomised studies

Not ICU?

Not resistant/difficult to treat bacteria?

	multicentre			2.25–4.5 g q6–8 h 30-min inf.	mortality (19% vs. 38%)
Lodise et al., 2007 [24]	Retrospective, single centre	194, *P. aeruginosa* infections	*P. aeruginosa*	TZP 3.375 g q8h 4-h inf. vs. TZP 3.375 g q4h or q6h 30-min inf.	Significantly lower mortality (12.2% vs. 31.6%) in severely ill (APACHE II score ≥17)
Nicasio et al., 2010 [27]	Prospective, single centre	168, VAP	Gram-positive and -negative bacteria	Empirical VAP pathway with PI β-lactam vs. empirical VAP therapy with TI β-lactam	Significantly lower infection-related mortality (8.5% vs. 21.6%)
Patel et al., 2009 [31]	Retrospective, multicentre	129, mixed infections (mainly UTI and respiratory infection)	Gram-negative bacteria	TZP 3.375 g q8h 4-h inf. vs. TZP 3.375–4.5 g q6h or q8h 30-min inf.	No difference in mortality (5.7% vs. 8.5%)
Wang, 2009 [30]	Retrospective, single centre	30, HAP (ICU only)	*A. baumannii*	MEM 500 mg q6h 3-h inf. vs. MEM 1 g q8h 1-h inf.	No difference in clinical response
Yost and Cappelletty, 2011 [34]	Retrospective, multicentre	359, mixed infections	Gram-negative bacteria	Antipseudomonal β-lactam[a] EI vs. antipseudomonal β-lactam TI	Significantly lower mortality (9.7% vs. 17.9%)

More adverse reactions if continuous administration compared to intermittent?

- Beta-lactams: NO!

  Falagas M. Systematic review and meta-analysis. Clin Infect Dis 2013

  Carbapenem/piptazo

  Teo J. Meta-analysis. Int J Antimicrob Agents 2014

  Beta-lactams

- Vanco: Significantly less nephrotoxicity with continuous vancomycin

  Hao J. Meta-analysis. Int J Antimicrob Agents. 2016

Practical issues

- Continuous or extended infusion
- Good venous access
- Continuous infusion:
  - Pump and adapted nurse care…cost issues
  - Another line for other drugs
  - Stability of the drug
    - meropenem 4h at room temperature/24h in refrigerated
  - Problems of compatibility (turbidity, white precipitate) between Pip/Tazo and Vanco
    - Branded Pip/tazo: EDTA increases stability and compatibility
    - Generic Pip/Tazo and vanco concentration ≤ 4-7 mg/mL are compatible

The ANTIBIOPERF study

Charmillon A Clin Microbiol Infect 2016

On line questionnaire about current practices on Intermittent, extended or continuous infusions and TDM

Beta-lactams antibiotics and vancomycin

>500 ICU in France mid-2015

Results

- Extended or continuous infusions: 76% (ceftazidim), 57% (Pip/tazo)
- Access to TDM was :
  - very limited for beta-lactams: 16.5% cloclaxicillin 30% ceftazidim
  - 97% for vanco
- Gaps in knowledge about the duration of stability
  - Correct answers for cloxacillin 8%, Ceftazidim 33%
- 48% had no access to practical guidelines

Intermittent without TDM

- Is not a good choice in ICU, or for severe infections, or infections with resistant bacteria, patients with as obesity, sepsis, renal failure, drug-drug interaction…etc
- Good and practical (stability, IV lines compatibility, dosage interpretation,…etc) guidelines are needed for continuous/prolonged administration and TDM interpretation
- However intermittent without TDM could be applied in non severe infection, in particular,
  - mild or moderate infection
  - Normal body weight
  - No kidney failure
  - No sepsis
  - Intravenous antibiotics prescribed according to guidelines
  - Bacteria sensitive to AB
  - For a classical infection (pyelonephritis) that is to say extensively studied
  - No major drug-drug interaction expected