How to Adjust Antibiotics & Antifungals Doses during CRRT : Practical Aspects

1.-Scope of the Problematic

2.- IHD versus CRRT:

Overdosing vs Underdosing

3.- What Are the General Rules to Follow ?

4.Important Antibiotics to Adapt in our Daily Practice …

5.- Antifungals to Adapt during CRRT….

6.- Membrane Adsorption of Antibiotics…..

6.- Conclusions-Perspectives

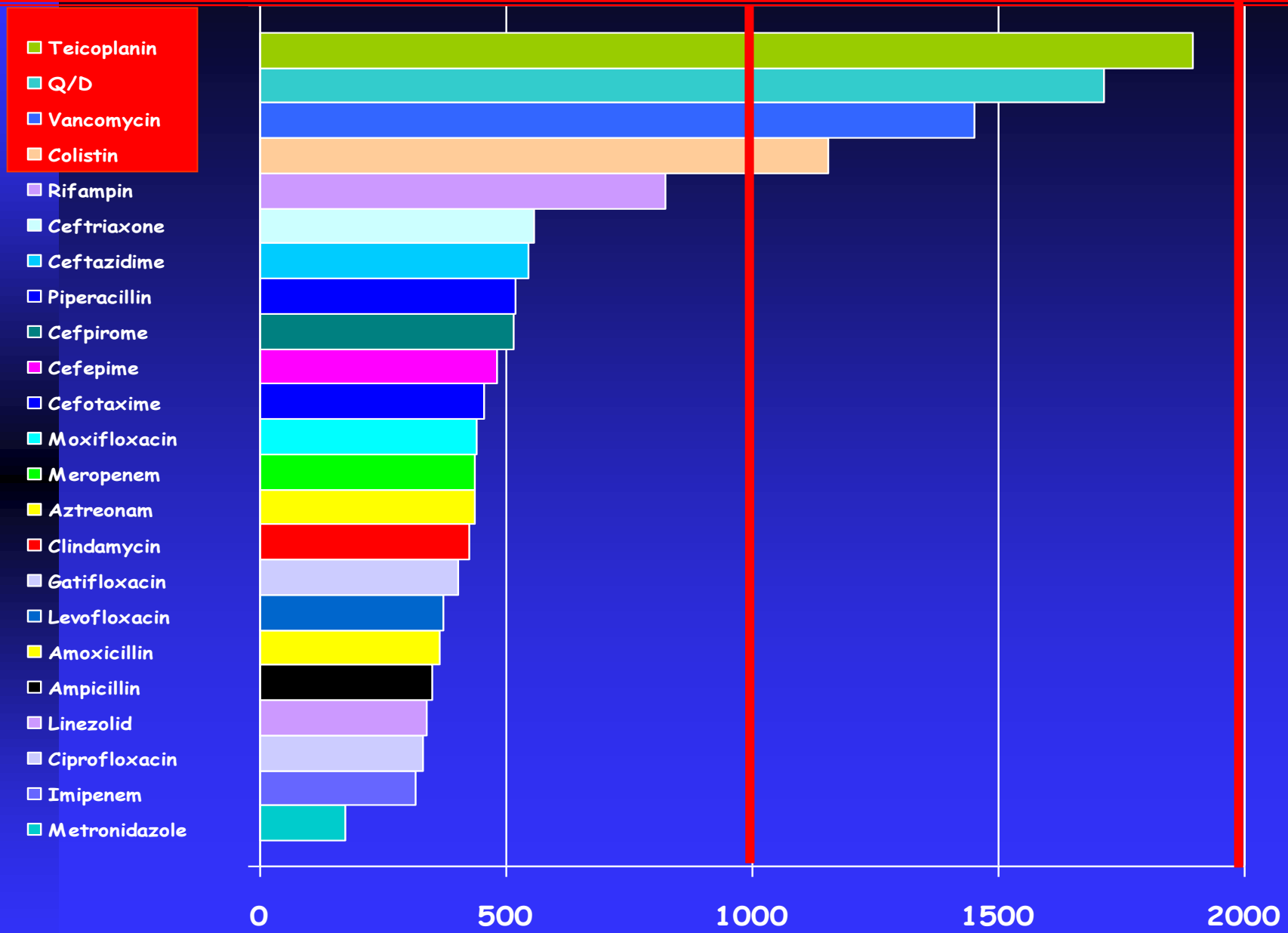
Prof P.M. Honoré,MD,PhD,FCCM Intensivist-Nephrologist

Prof of ICU Med,Senior Lecturer,VUB University ,Bxl(Bel)

2° International Intercongress Conference of the PTAIT

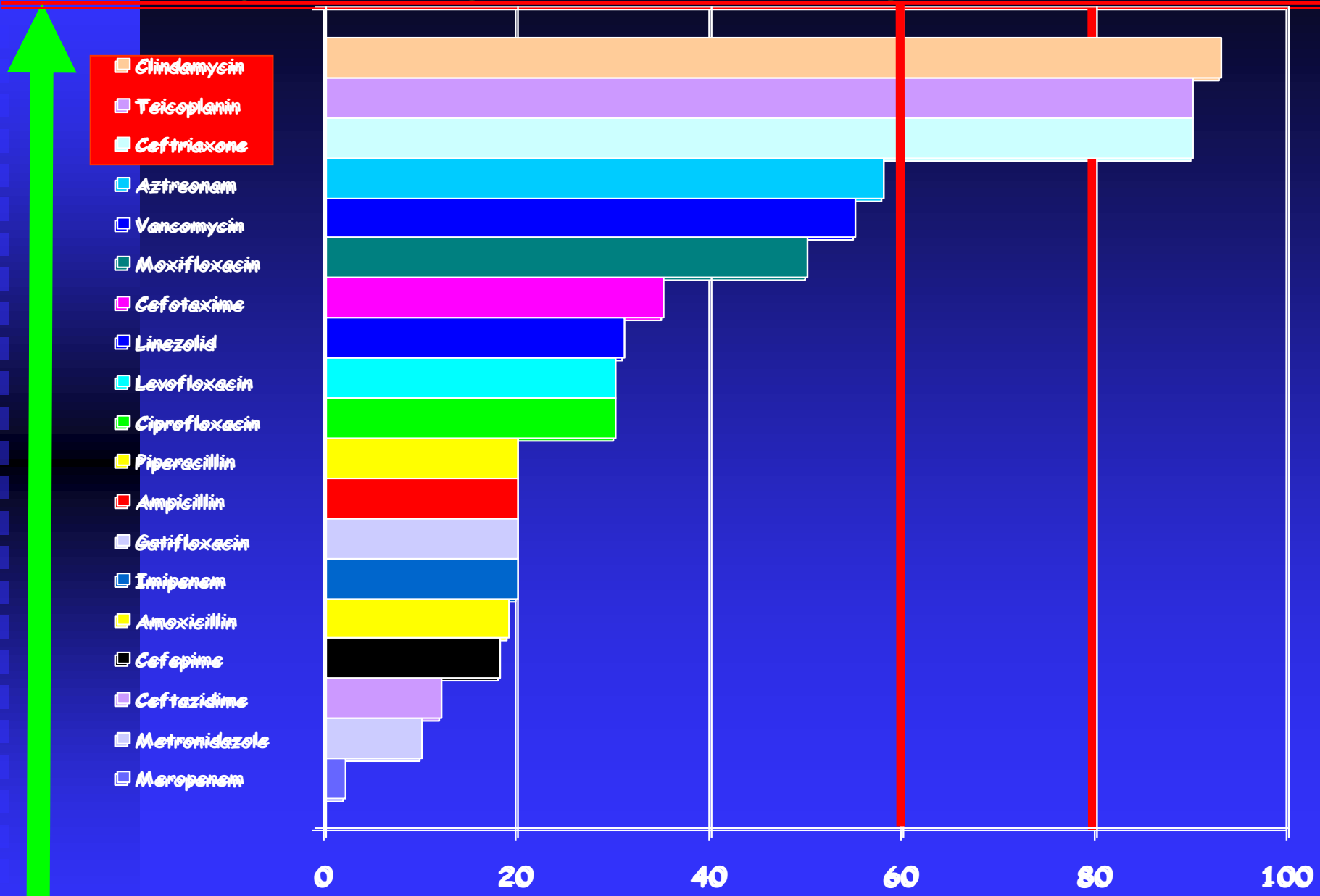
Karpacz,24-26 Nov 2016-Poland

MOLECULAR WEIGHT



Pea F et al. *Clin Pharmacokinet* 2007;12: 997-1038

PLASMA PROTEIN BINDING



Pea F et al. *Clin Pharmacokinet* 2007;12: 997-1038

HYDROPHILIC ANTIBIOTICS

- **BETA-LACTAMS**
  - ✓ PENICILLINS
  - ✓ CEPHALOSPORINS
  - ✓ CARBAPENEMS
  - ✓ MONOBACTAMS
- **GLYCOPEPTIDES**
- **AMINOGLYCOSIDES**

- ✓ LOW VOLUME OF DISTRIBUTION
- ✓ INABILITY OF DIFFUSING THROUGH MEMBRANES
- ✓ INACTIVITY AGAINST INTRACELLULAR PATHOGENS
- ✓ RENAL ELIMINATION AS UNCHANGED DRUG

LIPOPHILIC ANTIBIOTICS

- MACROLIDES
- FLUOROQUINOLONES
- TETRACYCLINES
- CHLORAMPHENICOL
- RIFAMPICIN
- LINEZOLID

- ✓ HIGH VOLUME OF DISTRIBUTION
- ✓ ABILITY OF DIFFUSING THROUGH MEMBRANES
- ✓ ACTIVITY AGAINST INTRACELLULAR PATHOGENS
- ✓ ELIMINATION AFTER LIVER METABOLIZATION

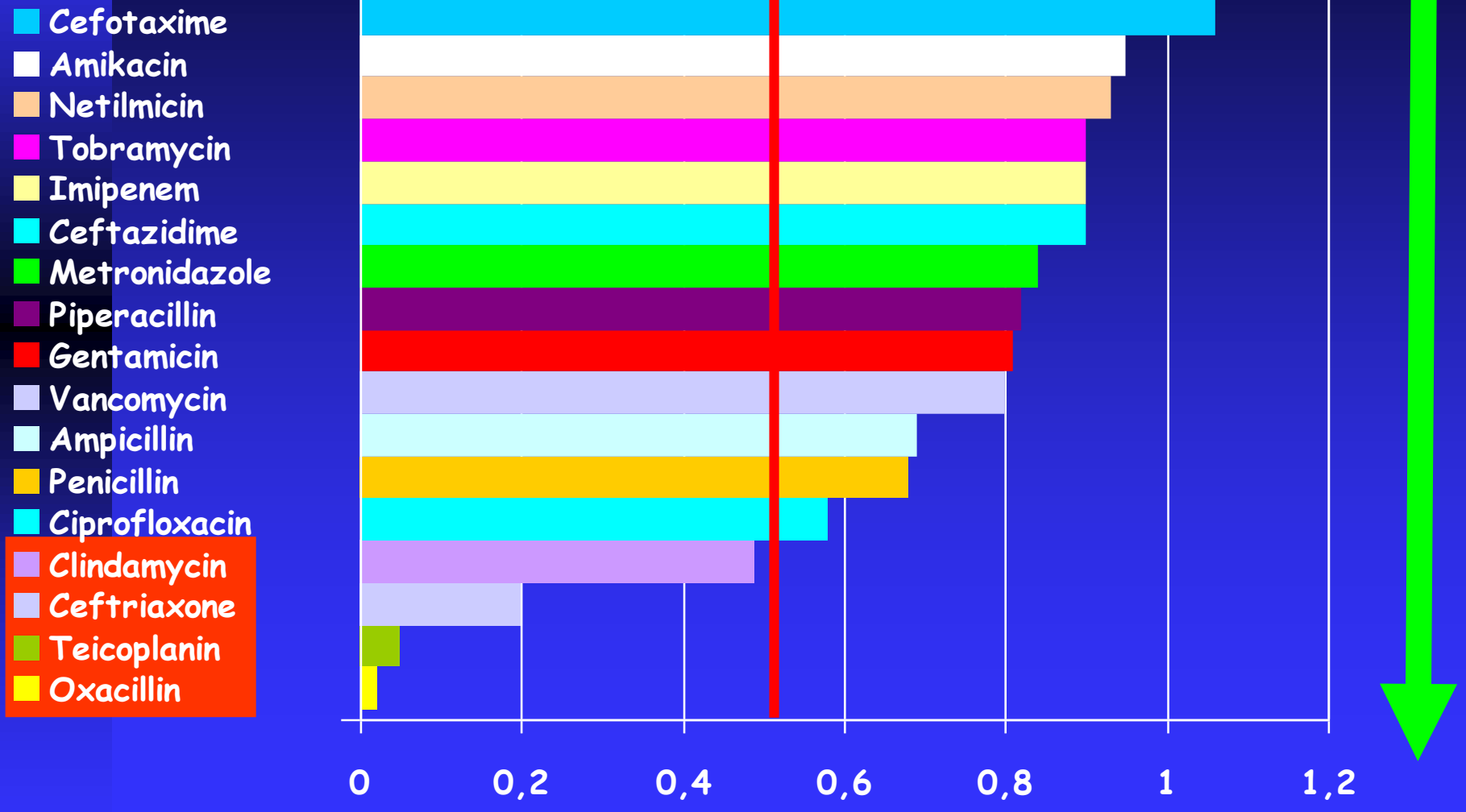
Pea F & Viale P. *Clin Infect Dis* 2006; 42: 1764-1771

Roger C, Roberts JA et al.JAC 2016 ;7:364-370

Kreiebbuehl L et al.Annals of Inttensive Care 2011 ;1-52

SIEVING COEFFICIENT DURING CVVH

$$Sc = \frac{C_{UF}}{C_P}$$



Golper TA & Marx MA. *Kidney Int* 1998; Suppl.66: 165-168

Honore PM,.Antibiotic Dosage During CRRT..Lambert Academic Publisining Book Released in Feb 2016

In the critically ill－Pharmacodynamics

- Pattern of Bactericidal Activity
- Post-Antibiotic Effect（PAE）

Most Abx	Time-dependent No PAE （except Carbapenems）	Continuous Infusions
Aminoglycosides Quinolones Metronidazole	Conc.-Dependent With PAE	High Doses with prolonged dosing interval

Dosing of Antibiotics :What about Beta-Lactams ?

- Piperacillin-tazobactam is not so good regarding tissue penetration..alveolar space …VAP…
- Time-dependent bactericidal activity
- Removal of Piptazo during CRRT very effective
- Loading dose most often neglected (4 Gr)
- Maintenance Infusion of 16-2 gr/24 H
- Several studies (including a substudy from the IVOIRE trial) indicate underdosing of β-lactams in 80 % of patients when administered in bolus

Boselli E et al.Crit Care Med 2008;36:1500-1506

Joannes-Boyau O, Honore PM et al.ICM 2013;39:1535-1546

Brielh D, Jacobs R, Honore PM, Roberts JA,Joannes-Boyau O et al.To be submiited

Dosing of Antibiotics :What About Vancomycin ?

- Poor tissue penetration of Vancomycin –Alveolar..
- New loading dose of 35 mg/kg in 4 h –Following by 15 mg/24 H…and according to the trough value..
- Elimination of Vancomycin under CRRT effective.
- Is Vancomycin effective for treatment of VAP in patients undergoing CRRT -You need to go for higher trough of 25-30 mg/L(MIC of 1-1.5 mg/L)
- Higher loading dose of 25 mg/kg in 2 H for IHD..

Beumier M et al. J Antimicrob Chemother 2013;68:2859-2865
Kalil AC et al.BMJ open 2013;Oct 14-
Spapen HD, Honore PM et al.Ann Intensive Care 2011;1-21
Vandecasteele S et al.Clin Infect Dis 2011;53:124-129

Dosing of Antibiotics : The Case for Amikacin

- Concentration(peak!)-dependent bactericidal activity
- 500 mg Amikacin in AKI under CRRT ?
- At Least 25 mg/kg = Loading dose and after according to TDM..(1000 mg should be discard..)
- Recent Data are Suggesting 30-35 mg/kg in MDR
- Toxicity more related to amikacin exposure time rather than to peak Intensity….less if once daily..
- What about Higher Dosages Under Preventive CRRT….

Taccone F et al.Int J Antimicrob Agents 2011;37:531-533
Honore PM et al AIC 2015;1:51-
de Momtmollin E et al.ICM 2014 ;40 : 995-1005

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Journal of Antimicrobial Chemotherapy

A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens: a proof-of-concept study

Alexandre Brasseur[1], Maya Hites[2], Sandrine Roisin[3], Frédéric Cotton[4], Jean-Louis Vincent[1], Daniel De Backer[1], Frédérique Jacobs[2] and Fabio Silvio Taccone[1]*

Table 2. Characteristics of infections and drug regimens

Patient	Site of infection	MDR pathogen	Mechanism of resistance	Previous anti-GN drugs	Susceptibility to aminoglycosides	MIC (mg/L)	Initial dose (mg/kg)	Maximal dose (mg/kg)	Time to optimal C_{peak}/MIC (day)	Total dose (mg)	Clinical response
1	tertiary peritonitis	*P. aeruginosa*	VIM	FOF, IPM, MEM, RIF	AMK	8	26	26	5	27 500	yes
2	empyema post-oesophagectomy	*P. aeruginosa*	VIM	ATM, CST	AMK	16	27	54	5	39 500	yes
3	VAP	*P. aeruginosa*	—	CAZ, CIP, CST, TZP	TOB	8	16	20	3	12 480	yes
4	VAP	*P. aeruginosa*	—	CIP, MEM	AMK	8	37	67	5	39 000	no
5	necrotizing pancreatitis	*P. aeruginosa*	—	CAZ, CST	AMK	8	31	52	0	52 250	no
6	tertiary peritonitis	*P. aeruginosa*	—	ATM, CST, TZP	GEN	4	7	13	4	16 880	yes
7	tertiary peritonitis	*P. aeruginosa*	—	ATM, CST	GEN	4	18	18	0	14 400	no
8	tertiary peritonitis	*P. aeruginosa*	—	ATM, CAZ, MEM	AMK	8	30	50	0	22 500	yes
9	tertiary peritonitis	*P. aeruginosa*	—	CAZ, CIP	AMK	8	29	29	0	7500	yes
10	VAP	*P. aeruginosa*	VIM	ATM, CAZ, CIP, CST, MIN	GEN	2	11	11	0	7900	yes
11	tertiary peritonitis	*E. coli E. aerogenes*	OXA48	CAZ, CST, MEM, TGC	AMK	8	29	29	0	13 500	no
12	VAP	*P. aeruginosa*	VIM	ATM, CST	AMK	8	33	57	0	15 000	no
13	necrotizing pancreatitis	*K. oxytoca*	OXA48	CST, MEM, SXT, TGC	AMK	8	29	29	0	8000	no
14	HAP	*A. baumannii*	—	CIP, CST, MEM, TGC	AMK	8	25	28	0	22 000	yes
15	necrotizing pancreatitis	*E. coli*	—	ATM, CST, MEM, SXT, TGC, TZP	AMK	4	28	28	0	36 750	no

VAP, ventilator-associated pneumonia; HAP, hospital-associated pneumonia; AMK, amikacin; AMP, ampicillin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; FOF, fosfomycin; GEN, gentamicin; IPM, imipenem; LZD, linezolid; MEM, meropenem; MIN, minocycline; RIF, rifampicin; SXT, trimethoprim/sulfamethoxazole; TOB, tobramycin; TZP, piperacillin/tazobactam; TGC, tigecycline.

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Table 4. Characteristics of CVVHDF parameters in individual patients

Patient	Duration (days)	Initial blood flow (mL/min)	Initial dialysate rate (mL/h)	Initial ultrafiltrate rate (mL/h)	Initial CVVHDF dose (mL/h)	Initial CVVHDF dose (mL/kg/h)
1	13	150	2000	2000	4000	41
2	13	180	2000	2500	4500	41
3	22	130	1500	1500	3000	75
4	26	130	2000	1500	3500	78
5	52	130	2500	2500	5000	63
6	22	180	2000	1500	3500	42
7	49	180	3200	1000	4200	47
8	13	130	1500	1500	3000	60
9	9	150	2000	2000	4000	47
10	13	120	1500	1500	3000	41
11	10	150	2000	2000	4000	31
12	31	150	1500	1500	3000	43
13	4	130	1500	2500	4000	57
14	22	160	1500	3000	4500	50
15	22	130	2500	2400	4900	79

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Table 5. Differences between patients with clinical response and clinical failure during HDA therapy

	Clinical response ($n=8$)	Clinical failure ($n=7$)	P values
Demographics			
age (years)	65 (58–67)	58 (56–60)	0.14
male	5 (67)	6 (86)	0.56
weight (kg)	84 (67–92)	70 (66–85)	0.63
BMI (kg/m^2)	28 (23–32)	24 (22–28)	0.59
ICU length of stay (days)	34 (22–53)	24 (13–27)	0.16
Comorbidities			
immunosuppressive drugs	3 (37)	2 (29)	1.0
solid organ transplantation	2 (25)	2 (29)	1.0
hypertension	3 (37)	2 (29)	1.0
heart failure	1 (12)	2 (29)	0.57
diabetes	1 (12)	2 (29)	0.57
malignancy	1 (12)	2 (29)	0.57
On HDA initiation			
APACHE II score	23.5 (18–24)	21 (19–23)	0.76
SOFA score day 1	10 (9–12)	12 (10–18)	0.14
mechanical ventilation	8 (100)	5 (71)	0.2
use of vasopressors	4 (50)	7 (100)	0.08
HDA			
% days with daily administration	96 (82–100)	82 (73–94)	0.38
total dose (mg)	19 440 (11 335–23 750)	15 000 (13 950–37 875)	0.43
first C_{peak}/MIC	6.9 (4.7–10.1)	10.7 (9.1–14.2)	0.18
mean C_{peak}/MIC	9.9 (8.1–14.0)	11.5 (9.9–15.6)	0.14
time to optimal peak (days)	1.5 (0–4.2)	0 (0–0)	0.28
microbiological response	3 (37)	—	0.2
CRRT			
previous CRRT	3 (37)	3 (43)	1.0
CRRT dose (mL/kg/h)	44 (41–52)	57 (45–70)	0.29
30 day renal recovery	4 (50)	—	0.08

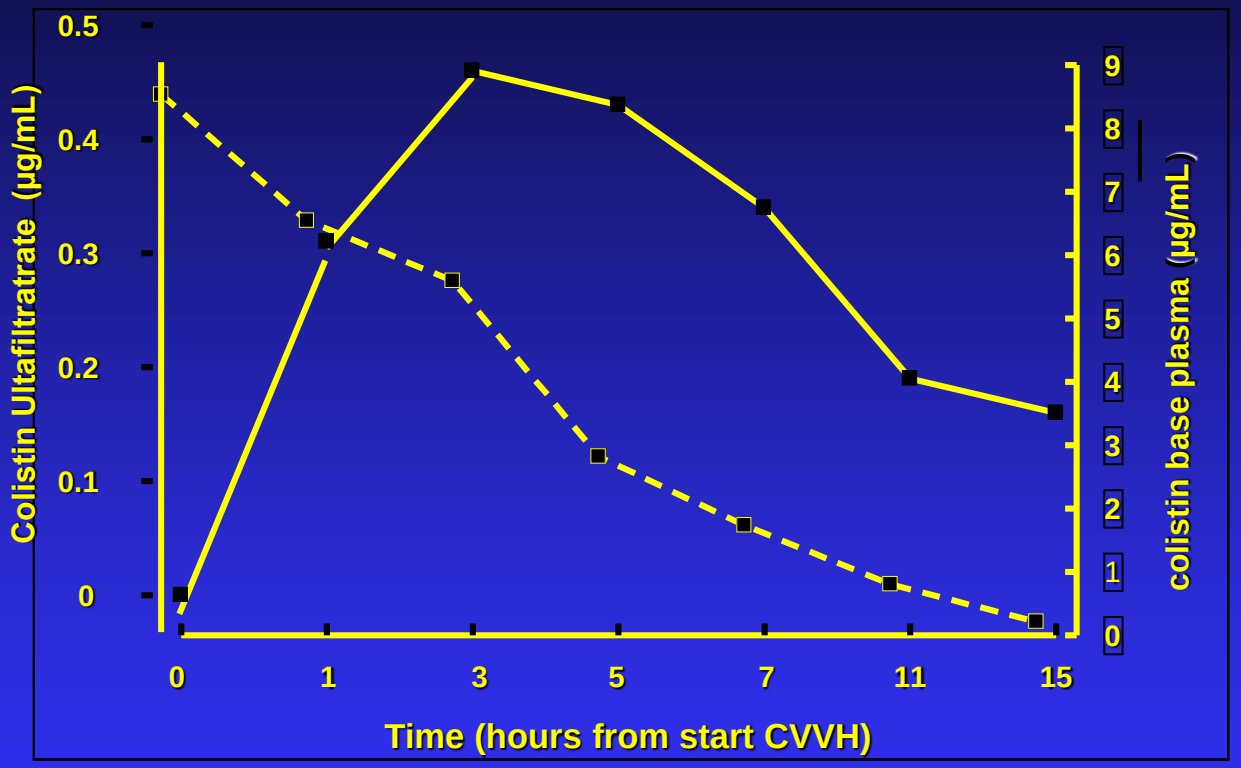
CRRT, continuous renal replacement therapy.
Data are presented as median (range) or n (%).

Plasma Binding of Drugs:Colistin

- Crucial to understanding of PK/PD relationship
- Two plasma proteins commonly involved
- Human serum albumin (HSA): binds weak organic acids & bases and neutral compounds
- Alpha-1-Acid Glycoprotein (AAG)
  - An acute-phase reactant protein
  - Often important for the binding of weak organic basic drugs
  - Plasma concentrations of AAG (~0.75 g/L) are normally much lower than those of HSA (~45 g/L)
  - Concentrations of AAG are increased (~15 to 30 fold) in a number of stressful conditions, including infection
  - Therefore binding goes from around 50 % up to Closed to 95 %

Cao et al, JAC 2008 ; 62 :1009-1014
Elias L et al, JAC 2010 ;65:2231-2237

COLISTIN ELIMINATION DURING CRRT



Colistin base concentrations in plasma and ultrafiltrate during continuous venovenous hemofiltration (CVVH)
Ultrafiltrate: Plain Line
Plasma: Dotted Line

Honore PM ,Spapen HD et al.Int J Nephrol Renovasc Dis 2013;6:107-111
Honore PM et al.Indian J Crit Care Med 2014 ;7:415-417

Dosing of Colistin in Res Strains Using CRRT as A Shield..

- Colistin is difficult to eliminate by convection through CRRT during infection …
  - Concentrations of Alpha -1 Acid Glyoprotrein are increased (~15 to 30 fold) in a number of stressful conditions, including infection
  - Therefore binding goes from around 50 % up to Closed to 95 %
- When using AN-69 ST , 85 % eliminated by Adsorption….
- Loading dose of 9 MI
- Maintenance dose of 4.5 Mi three time a day (CRRT)
- No toxicity founded using HAM like AN69 ST and RCA –Change of Filter every three days..
- Regimen has been infused for 15 days under CRRT without any toxicity…(No saturation of Mb Bulk during 3 days.…)
- No greater incidence of Renal Toxicity observed using this regimen…Amongst Survivors (Retrospective Study of 25 cases)

Honore PM et al.Blood Purif 2014;37:291-295

Cao et al, JAC 2008 ; 62 :1009-1014

Elias L et al, JAC 2010 ;65:2231-2237

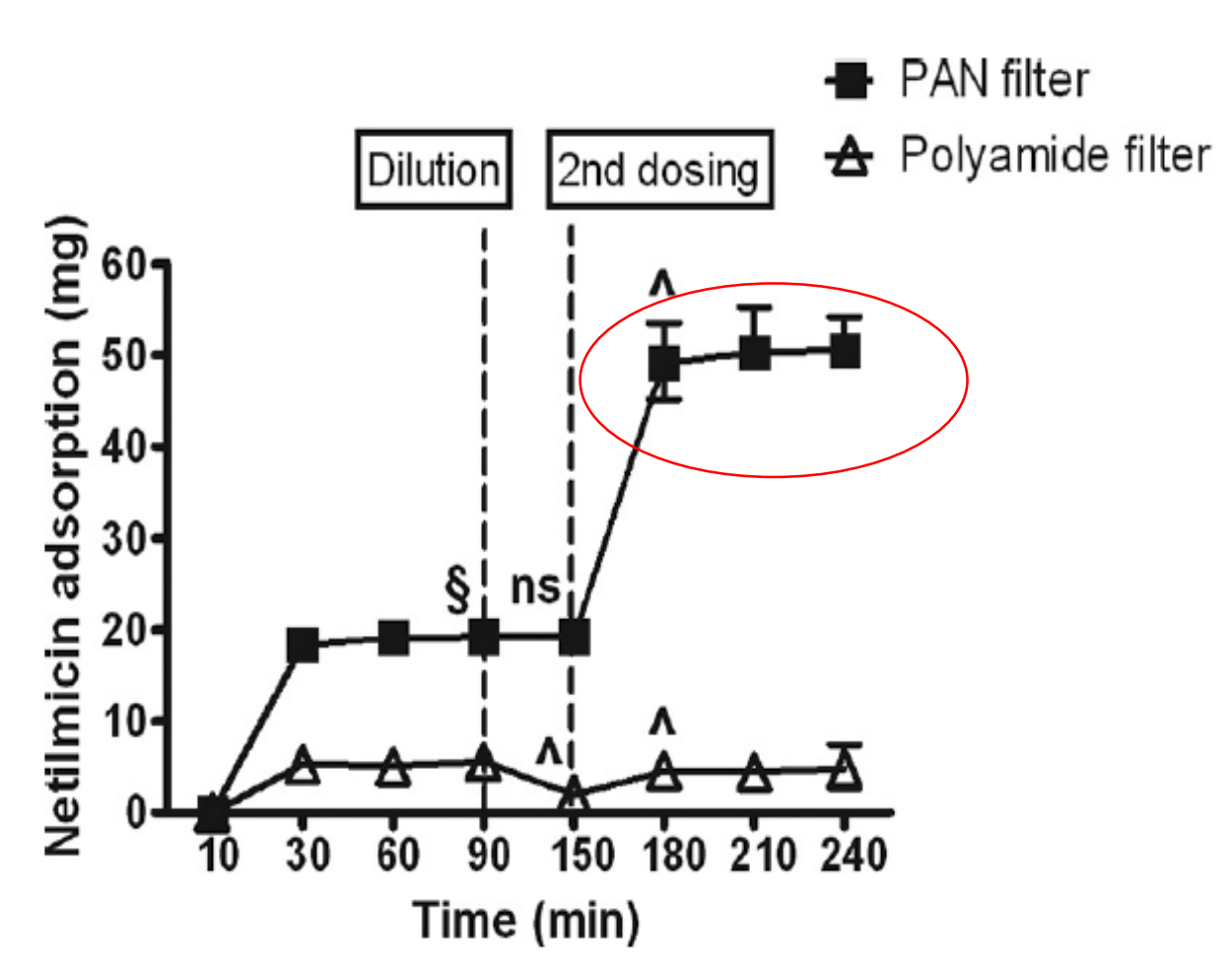
Discart H,Honore PM, Jacobs R, Hendrickx I, Spapen HD.To be submitted

Dosage of Antibiotics & Antifungals during CVVH

Antibiotique/Antifungal	Loading Dose	Maintenance Dose
Amikacin	25 mg/kg	TDM
Meropenem	2g	2g over 8h tid
Piperacillin-tazobactam	4g/0.5g	16g/2g (CI)
Vancomycin	35mg/kg over 4h	15 mg/kg (TDM=25-30mg/L)
Teicoplanin	10mg/kg 12 hourly (2 x)	8 mg/kg/ bid
Linezolid		600mg tid
Ciprofloxacin	800mg	400mg tid
Tigecyclin	150mg	100mg bid
Colistin	9 MIU	4,5 MIU tid
Voriconazole	8 mg/kg bid	6mg/kg bid
Fluconazole		600mg bid
Cefepime		2g tid
Gentamycin	10 mg	7 mg/kg od
Bactrim	1200 mg/240 mg (3amp)	800 mg/160 mg (2amp) tid
Clindamycine		900 mg qid

Honore PM et al AIC 2015;1:51-

CUMULATIVE ADSORPTION OF NETILMICIN BY HEMOFILTERS AGAINST TIME



Lam PKN et al. *Antimicrob Agents Chemother* 2010 Feb, 54: 963–965

Table 1. Characteristics of major antifungal agents including recommended dosages during continuous renal replacement therapy (CRRT)

Antifungal agent	Mechanism	Use	Adverse effects	Elimination	Dosages during CRRT
Lipid formulations of amphotericin B	Interacts with ergosterol in the fungal cell membrane	i.v.	Hepatic, renal and cardiovascular toxicity	Unaffected by CRRT	5 mg/kg/day
Fluconazole	Exhibits time-dependent activity	i.v. or oral	Hepatic toxicity	High elimination by CRRT	600 mg/12h
Voriconazole	Reduced ergosterol synthesis	i.v. or oral	Toxicity in AKI with IV use	Poor elimination of i.v. form by CRRT	Loading dose: 6 mg/kg Maintenance dose: 4 mg/kg/12h
Echinocandins	Inhibits β(1,3)-glucan synthesis	i.v.	Potential hepatic toxicity	Unaffected by CRRT	Anidulafungin: Loading dose: 200 mg Maintenance dose: 100 mg/day Caspofungin: Loading dose: 70 mg Maintenance dose: 50 mg/day

Honore PM, Jacobs R, Spapen HD. Annual Update 2012:337-344

Conclusions & Perspectives

- General Rules of Drug Dosing during CRRT can not be derived from IHD tables…(Stanford tables..)
- Most of the Classical Antimicrobials in ICU are easily removed by CRRT….
- For Time Dependent Antibiotics, use Infusions and do not Forget the loading dose in CRRT-
- For Peak Dependent Antibiotics , Loading doses are Crucial..
- For Resistant Bugs, use Higher Doses and start CRRT as a Prophylactic Ms (Amikacin, Gentamycin,Colistin,Voriconazole (SBECD /SulfoButylEther-beta-CycloDextrin..)
- The knowledge of MIC is very important and TDM is mandatory as a point of care resource (Bedside..)
- Pk/Pd & Adsorption should not be neglected anymore..but we need more data ….Especially for Aminoglycosides….