A literature review on patient covariates relevant to antibiotic PK

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Outline

1. Objectives
2. Methods
3. Covariate models for Vd
    1. Body size descriptors
    2. Hypoalbuminaemia & plasma protein binding
4. Covariate models for CL
    1. Estimated versus measured creatinine clearance
    2. Passive glomerular filtration and active secretion / re-uptake
5. Take home messages

Objectives

- ✓ Covariate relationships show us how PKs are related to patient/study characteristics

  ⇒ Identification of **patient subgroups** which are expected to be under- / over-exposed

  ⇒ **Individualized dosing** regimens (or drug monitoring)

- ✓ Covariate relationships are deduced from data and are **not necessarily generalizable** across studies (range of covariates studied)

- ✓ This literature review aims to provide a "**helicopter view**" of covariate models identified for antibiotics in ICU patients

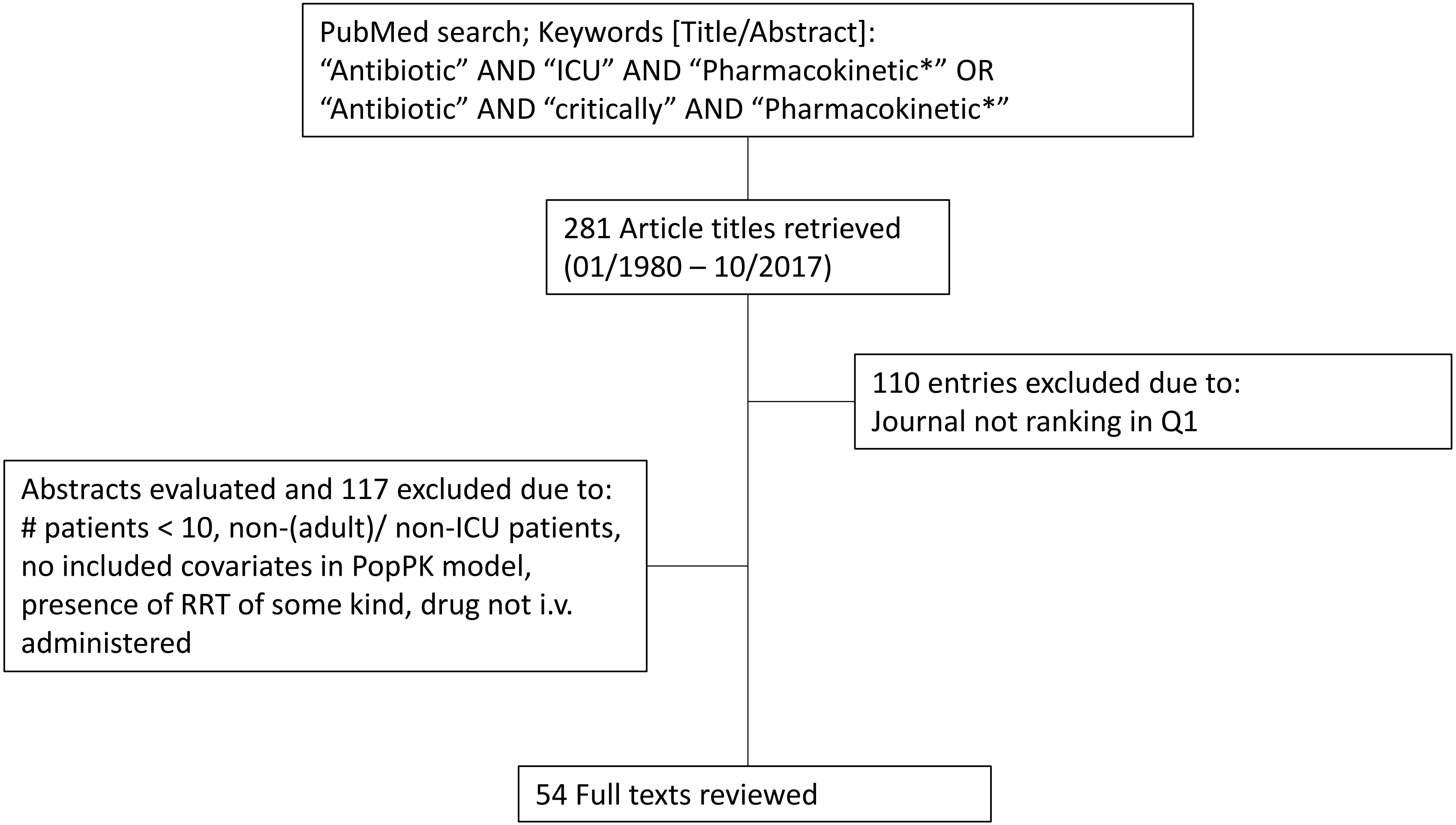
  ⇒ Assess **generalizability** of covariate models across ABs and across studies

  ⇒ Explore "**class-effects**"

  ⇒ Identify "artefacts"

  ⇒ Reveal potentially overlooked covariates

Methods


PubMed search; Keywords [Title/Abstract]:
“Antibiotic” AND “ICU” AND “Pharmacokinetic*” OR
“Antibiotic” AND “critically” AND “Pharmacokinetic*”
281 Article titles retrieved
(01/1980 – 10/2017)
110 entries excluded due to:
Journal not ranking in Q1
Abstracts evaluated and 117 excluded due to:
patients < 10, non-(adult)/ non-ICU patients,
no included covariates in PopPK model,
presence of RRT of some kind, drug not i.v.
administered
54 Full texts reviewed

Results

Table 1

Exclusion criteria: # patients ≤ 10, non-ICU patients/indications, no included covariates, RRT of some form, non-IV administration, …

Compound	# reports	V_1	CL	V_2	Q_2	Sample size
Meropenem	7	Lin_2(TBW)[1] Power(TBW)[2] Lin_2(ALB)[3] Lin_2(AGE)[3] Lin_1(ABW)[4] Lin_2(EDEMA)[5] Lin_1(TBW)[6]	Lin_2(TBW)[1] Lin_2(eCL_{Cr} - IBW)[1, 4] Lin_1(eCL_{Cr})[2, 6] Cat(SEX)[3] Cat(SEPSIS)[3] Lin_2(mCL_{CR})[5, 7]			178, 11, 27, 32, 21, 59, 57
Piperacillin	5	Lin_2(TBW)[16] Cat(SEPSIS)[17]	Lin_1(mCL_{CR})[18] Lin_2(S_{CR})[19] Lin_2(mCL_{CR})[16] Lin_2(BMI)[16] Lin_2(eCL_{CR})[17] Lin_2(DAI)[17] Lin_1(TBW)[20]			27, 48, 15, 50, 16
Vancomycin	5	Lin_1(TBW ~ Cat(AGE))[10] Allometry(TBW)[11] Lin_1(TBW)[12]	Lin_1(eCL_{CR}~ Cat(Furosemide))[10] Power(eCL_{CR})[13] Allometry(TBW)[11] Power(SAPSII)[11] Power(S_{CR})[11] Lin_1(mCL_{CR})[12] Lin_1(eCL_{CR} ~ cat(eCL_{CR}))[14]	Lin_1(TBW)[10] Allometry(TBW)[11]	Allometry(TBW)[11] Cat(Diabetes)[11]	118, 100, 30, 206, 190
Ceftazidime	4	Cat(VENT)[32]	Lin_2(eCL_{CR})[33] Lin_2(eCL_{CR} - MDRD)[32] Lin_2(eCL_{CR})[34] Lin_1($1/S_{CR}$)[35]	Cat(ADM)[32] Cat(VENT)[34] Cat(SEX)[34] Lin_2(eCL_{CR})[34]		18, 72, 50, 41
Amikacin	3	Lin_2(TBW)[25] Lin_2(PaO_2/FIO_2)[25]	Lin_2(mCL_{CR})[25] Lin_2(eCL_{CR})[26] Lin_2(eCL_{CR}-modified)[27]			60, 88, 57
Doripenem	3	Allometry(TBW)[28]	Allometry(TBW)[28] Exp(eCL_{CR})[28] Power(TBW)[29] Power(eCL_{CR})[29] Lin_2(eCL_{CR})[30]	Allometry(TBW)[28]	Allometry(TBW)[28]	12, 10, 25

Results
Covariate models for Vd

In short (oversimplification):

- ✓ *Vd is the apparent volume in which the administered dose is "diluted"*
- ✓ *Important PK parameter to derive the optimal **loading dose***
- ✓ *Patients with a higher Vd require a higher dose to achieve the target exposure*

Table 1

Exclusion criteria: # patients ≤ 10, non-ICU patients/indications, no included covariates, RRT of some form, non-IV administration, …

Compound	# reports	V_1	CL	V_2	Q_2	Sample size
Meropenem	7	Lin$_2$(TBW)[1] Power(TBW)[2] Lin$_2$(ALB)[3] Lin$_2$(AGE)[3] Lin$_1$(ABW)[4] Lin$_2$(EDEMA)[5] Lin$_1$(TBW)[6]	Lin$_2$(TBW)[1] Lin$_2$(eCL$_{Cr}$ - IBW)[1, 4] Lin$_1$(eCL$_{Cr}$)[2, 6] Cat(SEX)[3] Cat(SEPSIS)[3] Lin$_2$(mCL$_{CR}$)[5, 7]			178, 11, 27, 32, 21, 59, 57
Piperacillin	5	Lin$_2$(TBW)[16] Cat(SEPSIS)[17]	Lin$_1$(mCL$_{CR}$)[18] Lin$_2$(S$_{CR}$)[19] Lin$_2$(mCL$_{CR}$)[16] Lin$_2$(BMI)[16] Lin$_2$(eCL$_{CR}$)[17] Lin$_2$(DAI)[17] Lin$_1$(TBW)[20]			27, 48, 15, 50, 16
Vancomycin	5	Lin$_1$(TBW ~ Cat(AGE))[10] Allometry(TBW)[11] Lin$_1$(TBW)[12]	Lin$_1$(eCL$_{CR}$~ Cat(Furosemide))[10] Power(eCL$_{CR}$)[13] Allometry(TBW)[11] Power(SAPSII)[11] Power(S$_{CR}$)[11] Lin$_1$(mCL$_{CR}$)[12] Lin$_1$(eCL$_{CR}$ ~ cat(eCL$_{CR}$))[14]	Lin$_1$(TBW)[10] Allometry(TBW)[11]	Allometry(TBW)[11] Cat(Diabetes)[11]	118, 100, 30, 206, 190
Ceftazidime	4	Cat(VENT)[32]	Lin$_2$(eCL$_{CR}$)[33] Lin$_2$(eCL$_{CR}$ - MDRD)[32] Lin$_2$(eCL$_{CR}$)[34] Lin$_1$(1/S$_{CR}$)[35]	Cat(ADM)[32] Cat(VENT)[34] Cat(SEX)[34] Lin$_2$(eCL$_{CR}$)[34]		18, 72, 50, 41
Amikacin	3	Lin$_2$(TBW)[25] Lin$_2$(PaO$_2$/FIO$_2$)[25]	Lin$_2$(mCL$_{CR}$)[25] Lin$_2$(eCL$_{CR}$)[26] Lin$_2$(eCL$_{CR}$-modified)[27]			60, 88, 57
Doripenem	3	Allometry(TBW)[28]	Allometry(TBW)[28] Exp(eCL$_{CR}$)[28] Power(TBW)[29] Power(eCL$_{CR}$)[29] Lin$_2$(eCL$_{CR}$)[30]	Allometry(TBW)[28]	Allometry(TBW)[28]	12, 10, 25

Table 2:

Covariates identified for AB V_1, V_2 and V_3

- ✓ Age was found to increase V_1 (3 studies)
- ✓ Albumin was found to decrease (2 studies) and increase V_1 (2 studies)
- ✓ Body size was positively correlated with V_1
- ✓ Disease states (PaO_2/FIO_2, presence/absence of intra-abdominal infection/ sepsis/ edema, etc.) had varying effect on V_1 and V_2

			Age	ALB	Body Size descriptor			Disease state
					TBW	IBW	ABW	
Aminoglycosides		Amikacin			✓			✓
		Arbekacin	✓		✓			✓
		Gentamicin		✓	✓	✓		
		Tobramycin						
Beta-lactams	Penicillins	Amoxicillin						
		Ampicillin						
		Piperacillin			✓			✓
	Cephalosporins	**Cefazolin**		✓	✓			
		Cefepime						
		Cefpirome			✓			
		Ceftazidime						✓
		Ceftobiprole			✓			✓
		Ceftriaxone						
		Cefuroxime			✓			
	Carbapenems	Biapenem						
		Doripenem			✓			
		Imipenem		✓	✓			
		Meropenem	✓	✓	✓		✓	✓
Beta-lactamase inhibitors		Clavulanic acid						
		Sulbactam						
		Tazobactam						
Colistin								
Fosfomycin					✓			
Glycopeptides		**Teicoplanin**						
		Vancomycin	✓		✓			
Fluoroquinolones		Ciprofloxacin						
Glycylcyclines		**Tigecycline**						
Oxazolidinones		Linezolid			✓			

Table 2:

Covariates identified for AB V_1, V_2 and V_3

- ✓ Age was found to increase V_1 (3 studies)
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			Age	ALB	Body Size descriptor			Disease state
					TBW	IBW	ABW	
Aminoglycosides		Amikacin			✓			✓
		Arbekacin	✓		✓			✓
		Gentamicin		✓	✓	✓		
		Tobramycin						
Beta-lactams	Penicillins	Amoxicillin						
		Ampicillin						
		Piperacillin			✓			✓
	Cephalosporins	**Cefazolin**		✓	✓			
		Cefepime						
		Cefpirome			✓			
		Ceftazidime						✓
		Ceftobiprole			✓			✓
		Ceftriaxone						
		Cefuroxime			✓			
	Carbapenems	Biapenem						
		Doripenem			✓			
		Imipenem		✓	✓			
		Meropenem	✓	✓	✓		✓	✓
Beta-lactamase inhibitors		Clavulanic acid						
		Sulbactam						
		Tazobactam						
Colistin								
Fosfomycin					✓			
Glycopeptides		**Teicoplanin**						
		Vancomycin	✓		✓			
Fluoroquinolones		Ciprofloxacin						
Glycylcyclines		**Tigecycline**						
Oxazolidinones		Linezolid			✓			

Table 2:

Covariates identified for AB V_1, V_2 and V_3

$$V_{ss} = V_1 + V_2$$

$$V_{ss} = V_c \times \left(1 + \frac{k_{12}}{k_{21}}\right)$$

- ✓ Total body water makes up approx. 60% of TBW
- ✓ Extra- and Intracellular body water account for 27 % and 33 % of TBW
- ✓ Apart from vancomycin all compounds have a V_{ss} in line with our expectations

			Age	ALB	Body Size descriptor V_{ss} ~ TBW (v/w %)	Disease state
Aminoglycosides		Amikacin			48 %	✓
		Arbekacin	✓		36 % - 54 %	✓
		Gentamicin		✓	64 %	
		Tobramycin				
Beta-lactams	Penicillins	Amoxicillin				
		Ampicillin				
		Piperacillin			32 %	✓
	Cephalosporins	**Cefazolin**		✓	12 %	
		Cefepime				
		Cefpirome			29 %	
		Ceftazidime				✓
		Ceftobiprole			21 %	✓
		Ceftriaxone				
		Cefuroxime			21 %	
	Carbapenems	Biapenem				
		Doripenem			47 %	
		Imipenem		✓	39 %	
		Meropenem	✓	✓	24 % - 37 %	✓
Beta-lactamase inhibitors		Clavulanic acid				
		Sulbactam				
		Tazobactam				
Colistin						
Fosfomycin					64 %	
Glycopeptides		**Teicoplanin**				
		Vancomycin	✓		128 % - 664 %	
Fluoroquinolones		Ciprofloxacin				
Glycylcyclines		**Tigecycline**				
Oxazolidinones		Linezolid			67 %	

- ✓ Other body size descriptors have been proposed (taken from Hites et al., Chapter 4: Antibiotic PKPD considerations in the critically ill)

- ✓ None of these metrics take into account changes in body composition with age/ obesity

  - ➢ Amount of water in the body decreases with age and obesity

  - ➢ For ABs covariate models based on TBW might not **extrapolate** well to the elderly, obese, …

=> Other more complex covariate models, simultaneously taking into account, age, weight and body composition might be more appropriate for describing antibiotic PK

Table 4.2 Body size descriptors [86, 87]

Body size descriptor	Equation
Total body weight (TBW) (kg): total weight of the individual	Measured on a scale (kg)
Body mass index (BMI) (kg/m²): the most frequently used size descriptor	$=\text{TBW (kg)}/\text{HT (m)}^2$
Body surface area (BSA) (m²): often used to calculate doses for chemotherapy	$=\text{TBW}^{0.425} \times \text{HT}^{0.725} \times 0.007184$ or $=\sqrt{[(\text{HT(cm)} \times \text{TBW})/3600]}$
Ideal body weight for males (IBW) (kg): developed to relate body size to mortality	$=45.4 + (0.89 \times \text{HT (cm)} - 152.4) + 4.5$
Ideal body weight for females (IBW) (kg): developed to relate body size to mortality	$=45.4 + (0.89 \times \text{HT (cm)} - 152.4)$
Adjusted body weight (ABW) (kg): adds a proportion or a correction factor of excess TBW above IBW added on to IBW. The correction factor takes into account the distribution of the given antibiotic into adipose tissue	$=\text{IBW} + \text{correction factor} \times (\text{TBW} - \text{IBW})$
Free fat mass for males (FFM) (kg): body weight without any adipose tissue	$=(0.285 \times \text{TBW}) + (12.1 \times \text{HT (m)}^2)$
Free fat mass for females (FFM) (kg): body weight without any adipose tissue	$=(0.287 \times \text{TBW}) + (9.74 \times \text{HT (m)}^2)$
Lean body weight for females (LBW) (kg): developed to relate patient's size to epidemiological trends in morbidity and mortality	$=1.1 \times \text{TBW} - 0.0128 \times \text{BMI} \times \text{TBW}$ or $=(9270 \times \text{TBW})/(8780 + 244 \times \text{BMI})$ [88]
Lean body weight for males (LBW) (kg): developed to relate patient's size to epidemiological trends in morbidity and mortality	$=1.07 \times \text{TBW} - 0.0148 \times \text{BMI} \times \text{TBW}$ or $=(9270 \times \text{TBW})/(6680 + 216 \times \text{BMI})$ [88]
Percent ideal body weight (%)	$=(\text{TBW} - \text{IBW})/\text{IBW} \times 100$
Predicted normal weight for females (kg): new size descriptor, developed to better describe the PK of drugs	$=1.75 \times \text{TBW} - 0.0242 \times \text{BMI} \times \text{TBW} - 12.6$
Predicted normal weight for males (kg): new size descriptor, developed to better describe the PK of drugs	$=1.57 \times \text{TBW} - 0.0183 \times \text{BMI} \times \text{TBW} - 10.5$

Table 2:

Covariates identified for AB V_1, V_2 and V_3

- ✓ Albumin was found to decrease (2 studies) and increase V_1 (2 studies)
- ✓ Approx. 40 % of critically ill patients have albumin concentrations < 25 g/L
- ✓ A negative association between albumin and V_1 (as was found in 2 studies) often leads to the suggestion of using **higher loading doses**.

			Age	ALB	Body Size descriptor			Disease state
					TBW	IBW	ABW	
Aminoglycosides		Amikacin			✓			✓
		Arbekacin	✓		✓			✓
		Gentamicin		✓	✓	✓		
		Tobramycin						
Beta-lactams	Penicillins	Amoxicillin						
		Ampicillin						
		Piperacillin			✓			✓
	Cephalosporins	**Cefazolin**		✓	✓			
		Cefepime						
		Cefpirome			✓			
		Ceftazidime						✓
		Ceftobiprole			✓			✓
		Ceftriaxone						
		Cefuroxime			✓			
	Carbapenems	Biapenem						
		Doripenem			✓			
		Imipenem		✓	✓			
		Meropenem	✓	✓	✓		✓	✓
Beta-lactamase inhibitors		Clavulanic acid						
		Sulbactam						
		Tazobactam						
Colistin								
Fosfomycin					✓			
Glycopeptides		**Teicoplanin**						
		Vancomycin	✓		✓			
Fluoroquinolones		Ciprofloxacin						
Glycylcyclines		**Tigecycline**						
Oxazolidinones		Linezolid			✓			

Table 2:

Covariates identified for AB V_1, V_2 and V_3

- ✓ Approx. 40 % of critically ill patients have albumin concentrations < 25 g/L

- ✓ A negative association between albumin and V_1 (as was found in 2 studies) suggests the need for **higher loading doses**.

			Age	ALB	Body Size descriptor			Disease state
					TBW	IBW	ABW	
Aminoglycosides		Amikacin			✓			✓
		Arbekacin	✓		✓			✓
		Gentamicin		✓	✓	✓		
		Tobramycin						
Beta-lactams	Penicillins	Amoxicillin						
		Ampicillin						
		Piperacillin			✓			✓
	Cephalosporins	**Cefazolin**		✓	✓			
		Cefepime						
		Cefpirome			✓			
		Ceftazidime						✓
		Ceftobiprole			✓			✓
		Ceftriaxone						
		Cefuroxime			✓			

We recommend that especially for critically ill patients with hypoalbuminaemia, C_{max} should be measured immediately after the first dose to facilitate adequate dosing of the second gentamicin administration, which is likely to be a higher dose than the starting dose. At least a 150% higher starting dose may be necessary to achieve a therapeutic C_{max} in patients with albumin levels of <15 mg/L. However, this remains to be determined in a prospective setting.

Table 2:

Covariates identified for AB V_1, V_2 and V_3

- ✓ Approx. 40 % of critically ill patients have albumin concentrations < 25 g/L
- ✓ A negative association between albumin and V_1 (as was found in 2 studies) suggests the need for higher loading doses.
- ✓ The usual justification is that changes in **albumin concentrations** lead to changes in **plasma protein binding** which leads to changes in **unbound concentrations** and hence altered drug effect…

			Age	ALB	Body Size descriptor			Disease state
					TBW	IBW	ABW	
Aminoglycosides		Amikacin			✓			✓
		Arbekacin	✓		✓			✓
		Gentamicin		✓	✓	✓		
		Tobramycin						
Beta-lactams	Penicillins	Amoxicillin						
		Ampicillin						
		Piperacillin			✓			✓
	Cephalosporins	**Cefazolin**		✓	✓			
		Cefepime						
		Cefpirome			✓			
		Ceftazidime						✓
		Ceftobiprole			✓			✓
		Ceftriaxone						
		Cefuroxime			✓			

REVIEW ARTICLE

Clin Pharmacokinet 2011; 50 (2): 99-110
0312-5963/11/0002-0099/$49.95/0

The Effects of Hypoalbuminaemia on Optimizing Antibacterial Dosing in Critically Ill Patients

Marta Ulldemolins,[1,2,3] *Jason A. Roberts,*[1,4,5] *Jordi Rello,*[2,3,6] *David L. Paterson*[7,8] and *Jeffrey Lipman*[1,4]

''Pharmaceutical companies should […] consider implementing albumin-driven dose adjustments as is current practice for renal dysfunction where appropriate”

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 71 NUMBER 3 MARCH 2002

COMMENTARY

Changes in plasma protein binding have little clinical relevance

Leslie Z. Benet, PhD, and Betty-ann Hoener, PhD *San Francisco, Calif*

"Only highly protein bound - high extraction ratio drugs (either orally or intravenously administered) will exhibit changes in **unbound drug exposure** when protein binding changes."

- Most antibiotics are not highly bound and are not eliminated by high extraction processes, so no changes in unbound exposure are expected!

Clin Pharmacokinet
DOI 10.1007/s40262-017-0549-x

CrossMark

ORIGINAL RESEARCH ARTICLE

A Physiologically Based Pharmacokinetic Perspective on the Clinical Utility of Albumin-Based Dose Adjustments in Critically Ill Patients

Huybrecht T'jollyn[1,3] · An Vermeulen[1,2] · Jan Van Bocxlaer[1] · Pieter Colin[1,4]

- Most ABs are "low clearance" – "low Vd" drugs
- When comparing patients with normal and lowered albumin levels the observed effects are different between **PK_{Total} & $PK_{unbound}$** !
- When measuring **total concentrations** an increase in CL and V_{ss} is expected with decreasing albumin concentrations (due to changes in PPB)
- However, when considering the time course of the **unbound** AB concentration, exposure ($AUC_{unbound}$) is never decreased and in general also Time above MIC is unchanged
- **Theoretical PK principles** currently do not support altered dosing in hypoalbuminaemia (even if PPB is expected to be affected).
- When it comes to studying the need for altered dosing in patients with altered protein levels, **unbound AB concentrations should be measured and not total AB concentrations**

Table 2:

Covariates identified for AB V_1, V_2 and V_3

- ✓ Little evidence in favor of ALB and Disease state
- ✓ Body size (water content) is positively correlated with V_{ss}
- ✓ At present the positive correlation between age and Vd contradicts our physiological understanding

			Age	ALB	Body Size descriptor			Disease state
					TBW	IBW	ABW	
Aminoglycosides		Amikacin			✓			✓
		Arbekacin	✓		✓			✓
		Gentamicin		✓	✓	✓		
		Tobramycin						
Beta-lactams	Penicillins	Amoxicillin						
		Ampicillin						
		Piperacillin			✓			✓
	Cephalosporins	**Cefazolin**		✓	✓			
		Cefepime						
		Cefpirome			✓			
		Ceftazidime						✓
		Ceftobiprole			✓			✓
		Ceftriaxone						
		Cefuroxime			✓			
	Carbapenems	Biapenem						
		Doripenem			✓			
		Imipenem		✓	✓			
		Meropenem	✓	✓	✓		✓	✓
Beta-lactamase inhibitors		Clavulanic acid						
		Sulbactam						
		Tazobactam						
Colistin								
Fosfomycin					✓			
Glycopeptides		**Teicoplanin**						
		Vancomycin	✓		✓			
Fluoroquinolones		Ciprofloxacin						
Glycylcyclines		**Tigecycline**						
Oxazolidinones		Linezolid			✓			

Results
Covariate models for CL

In short (oversimplification):

- ✓ *CL is the main determinant for steady-state exposure*
- ✓ *Important PK parameter to derive the optimal **maintenance dose***

Table 3: Covariates identified for AB CL

			Age	Body Size descriptor					Concomitant medication	Disease state	Gender	Renal function			
				TBW	IBW	BMI	HGT	BSA				eCL_{CR}	mCL_{CR}	S_{CR}	CysC
Aminoglycosides		Amikacin										✓	✓		
		Arbekacin	✓	✓								✓			
		Gentamicin			✓*							✓	✓		
		Tobramycin					✓					✓			
Beta-lactams	Penicillins	Amoxicillin											✓		
		Ampicillin		✓											
		Piperacillin		✓		✓				✓		✓	✓	✓	
	Cephalosporins	**Cefazolin**											✓		
		Cefepime										✓	✓		
		Cefpirome											✓		
		Ceftazidime										✓		✓	
		Ceftobiprole								✓		✓			
		Ceftriaxone											✓		
		Cefuroxime		✓									✓		✓
	Carbapenems	Biapenem										✓			
		Doripenem		✓*								✓			
		Imipenem										✓	✓		
		Meropenem		✓						✓	✓	✓	✓		
Beta-lactamase inhibitors		Clavulanic acid											✓		
		Sulbactam		✓											
		Tazobactam											✓		
Colistin												✓			
Fosfomycin												✓			
Glycopeptides		**Teicoplanin**		✓								✓			
		Vancomycin		✓*					✓	✓		✓	✓	✓	
Fluoroquinolones		Ciprofloxacin										✓			
Glycylcyclines		**Tigecycline**		✓				✓			✓	✓			
Oxazolidinones		Linezolid	✓	✓											

Table 3: Covariates identified for AB CL

			Age	Body Size descriptor					Concomitant medication	Disease state	Gender
				TBW	IBW	BMI	HGT	BSA			
Aminoglycosides		Amikacin									
		Arbekacin	✓	✓							
		Gentamicin			✓*						
		Tobramycin					✓				
Beta-lactams	Penicillins	Amoxicillin									
		Ampicillin		✓							
		Piperacillin		✓		✓				✓	
	Cephalosporins	**Cefazolin**									
		Cefepime									
		Cefpirome									
		Ceftazidime									
		Ceftobiprole								✓	
		Ceftriaxone									
		Cefuroxime		✓							
	Carbapenems	Biapenem									
		Doripenem		✓*							
		Imipenem									
		Meropenem		✓						✓	✓
Beta-lactamase inhibitors		Clavulanic acid									
		Sulbactam		✓							
		Tazobactam									
Colistin											
Fosfomycin											
Glycopeptides		**Teicoplanin**		✓							
		Vancomycin		✓*					✓	✓	
Fluoroquinolones		Ciprofloxacin									
Glycylcyclines		**Tigecycline**		✓				✓			✓
Oxazolidinones		Linezolid	✓	✓							

- ✓ Age, disease states and gender have varying influence on CL
- ✓ CL increases linearly with TBW or according to allometric theory (2 studies)

=> Most studies are underpowered to compare both approaches

=> Unclear how collinearity with eCL_{CR} should be dealt with

- ✓ Concomitant medication (furosemide) decreases CL of vancomycin

Table 3: Covariates identified for AB CL

			Renal function			
			eCL_{CR}	mCL_{CR}	S_{CR}	CysC
Aminoglycosides		Amikacin	✓	✓		
		Arbekacin	✓			
		Gentamicin	✓	✓		
		Tobramycin	✓			
Beta-lactams	Penicillins	Amoxicillin		✓		
		Ampicillin				
		Piperacillin	✓	✓	✓	
	Cephalosporins	**Cefazolin**		✓		
		Cefepime	✓	✓		
		Cefpirome		✓		
		Ceftazidime	✓		✓	
		Ceftobiprole	✓			
		Ceftriaxone		✓		
		Cefuroxime		✓		✓
	Carbapenems	Biapenem	✓			
		Doripenem	✓			
		Imipenem	✓	✓		
		Meropenem	✓	✓		
Beta-lactamase inhibitors		Clavulanic acid		✓		
		Sulbactam				
		Tazobactam		✓		
Colistin			✓			
Fosfomycin			✓			
Glycopeptides		**Teicoplanin**	✓			
		Vancomycin	✓	✓	✓	
Fluoroquinolones		Ciprofloxacin	✓			
Glycylcyclines		**Tigecycline**	✓			
Oxazolidinones		Linezolid				

- ✓ Most studies (28) use eCL_{CR} to describe changes in CL and not mCL_{CR} (13)
- ✓ 22 out of 28 studies use the Cockcroft-Gault equation to predict eCL_{CR}
- ✓ 70% are based on a linear covariate model, 20% on a power model and others use a piece-wise linear or exponential model

$$P_i = \theta_1 \times \left(\frac{Cov_i}{Cov_{Std}}\right)$$

$$P_i = \theta_1 \times \left(1 + \theta_2 \times (Cov_i - Cov_{Std})\right)$$

$$P_i = \theta_1 \times \left(\frac{Cov_i}{Cov_{Std}}\right)^{\theta_2}$$

$$P_i = \theta_1 \times e^{(\theta_2 \times (Cov_i - Cov_{Std}))}$$

=> Functional form has big impact on the influence of outliers and extrapolation to specific subgroups (AKI, ARC)

Table 3: Covariates identified for AB CL

			Renal function			
			eCL_{CR}	mCL_{CR}	S_{CR}	CysC
Aminoglycosides		Amikacin	✓	✓		
		Arbekacin	✓			
		Gentamicin	1.98 mg/L vs. 1.91 mg/L			
		Tobramycin	✓			
Beta-lactams	Penicillins	Amoxicillin		✓		
		Ampicillin				
		Piperacillin	✓	✓	✓	
	Cephalosporins	**Cefazolin**		✓		
		Cefepime	29.3 % vs. 29.4 % APE			
		Cefpirome		✓		
		Ceftazidime	✓		✓	
		Ceftobiprole	✓			
		Ceftriaxone		✓		
		Cefuroxime		✓		✓
	Carbapenems	Biapenem	✓			
		Doripenem	✓			
		Imipenem	✓	✓		
		Meropenem	36.8 % vs. 28.1 % IIV			
Beta-lactamase inhibitors		Clavulanic acid		✓		
		Sulbactam				
		Tazobactam		✓		
Colistin			✓			
Fosfomycin			✓			
Glycopeptides		**Teicoplanin**	✓			
		Vancomycin	✓	✓	✓	
Fluoroquinolones		Ciprofloxacin	2 x eCL_{CR} retained, not mCL_{CR}			
Glycylcyclines		**Tigecycline**	✓			
Oxazolidinones		Linezolid				

eCL_{CR} vs. mCL_{CR}

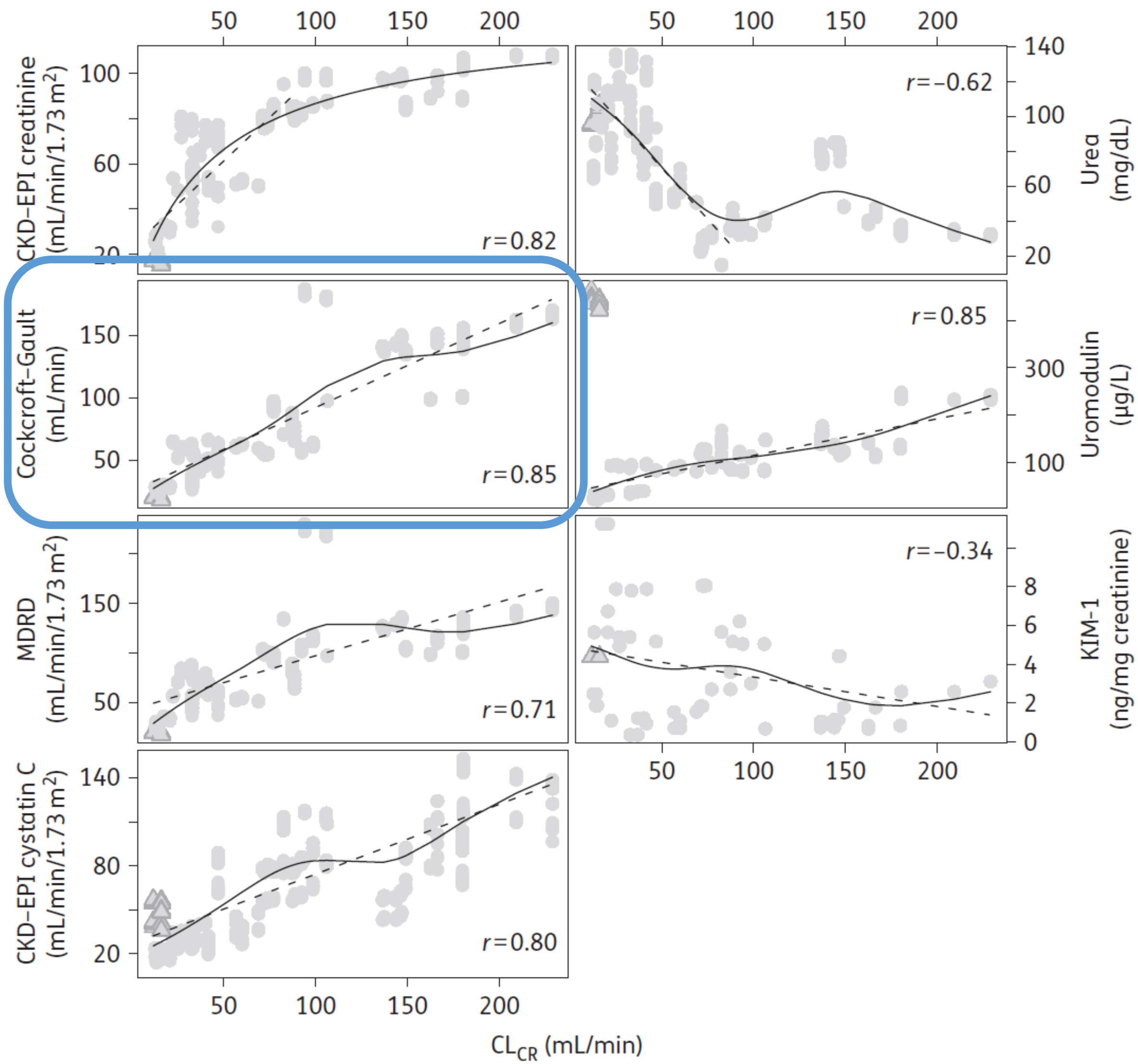
- ✓ Only 5 studies out of 54 compared the performance of mCL_{CR} vs. eCL_{CR}
- ✓ 2 studies (ciprofloxacin) retained eCL_{CR} and not mCL_{CR}
- ✓ 2 studies (gentamicin and cefepime) found (very) similar performance between eCLCR and mCLCR
- ✓ 1 study (meropenem) showed a greater reduction in unexplained inter-individual variability with mCL_{CR} compared to eCL_{CR}

=> Overall, the (potential) differences between mCL_{CR} over eCL_{CR} are not studied in a systematic manner

=> It is unlikely that mCL_{CR} provides a better correlation with CL_{AB} than eCL_{CR}

<u>Side note 1:</u>

eCL$_{CR}$ vs. mCL$_{CR}$ in 20 ICU patients



- ✓ eCL$_{CR}$ according to CG is highly correlated with mCL$_{CR}$
- ✓ Predictive performance is ± identical between covariate models with mCL$_{CR}$ and eCL$_{CR}$

Side note 1:

eCL_{CR} (Jelliffe) vs. mCL_{CR} in 14 renal transplant patients

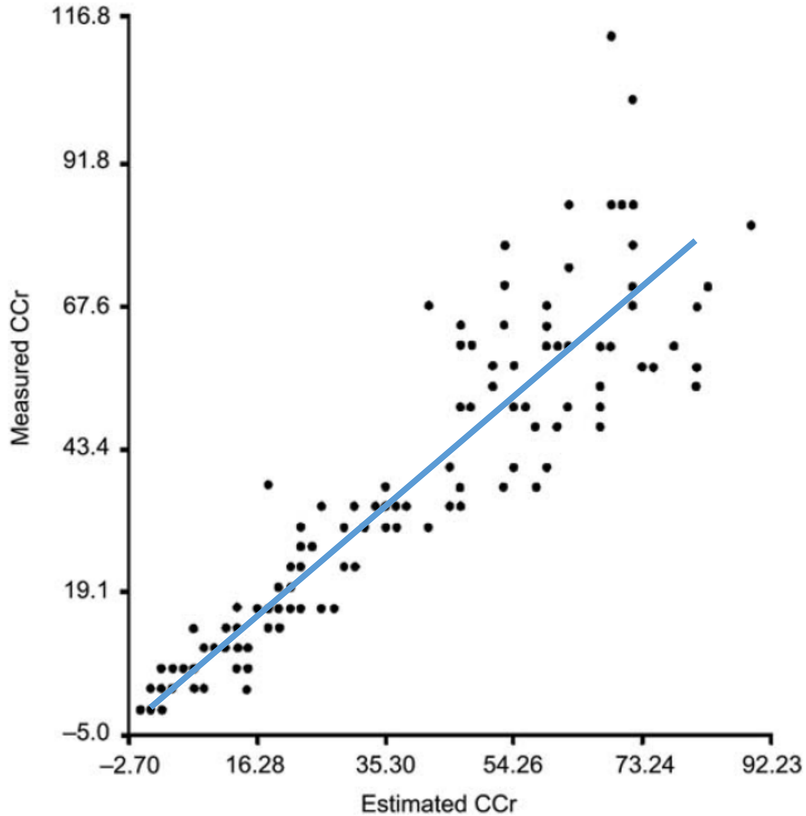


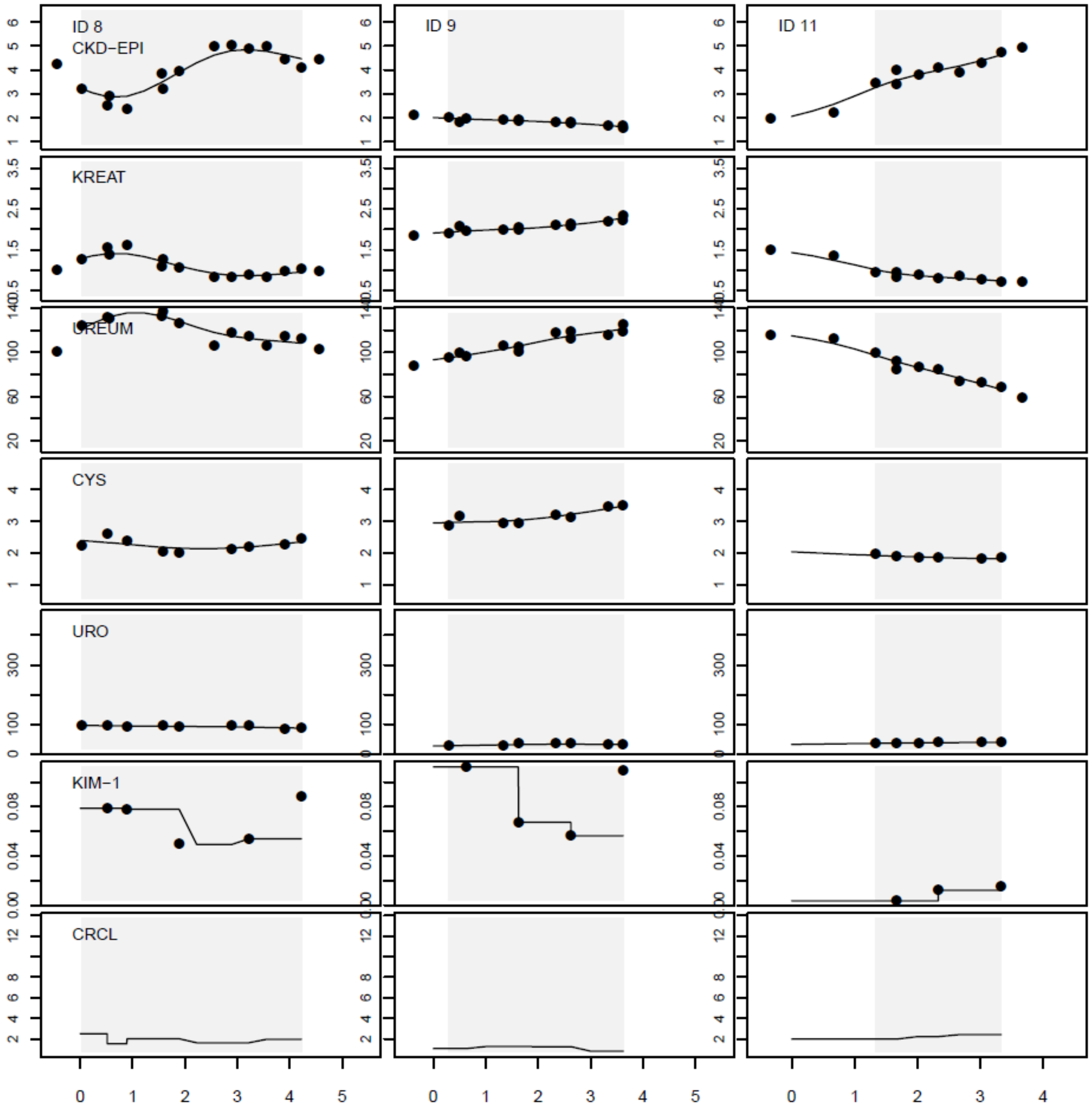
FIGURE 5.2

Comparison of CCr estimated by the method described here (horizontal axis) versus the gold standard—measured CCr using 24-h urine specimens (vertical axis) in 250 observations on 14 patients. The comparison was done starting on the day of surgery, as the transplant took hold and renal function improved thereafter. The scatter shown here is similar to that of the classical gold standard CCr based on a 24-h urine specimen (see text).

Reproduced with permission from Jelliffe R: Estimation of Creatinine Clearance in Patients with Unstable Renal Function, without a Urine Specimen. Am. J. Nephrology, 22: 320–324, 2002.

- ✓ Chapter 5: Evaluation of Renal Function (Drug Therapy for patients, Jelliffe and Neely 2017)
- ✓ A formula is derived to estimate changes in renal function based on two timed S_{CR} measurements

Side note 2:
Only 1 study evaluated the impact of intra-patient changes in renal function!



- ✓ This study (and others outside of the scope of this review) showed that often a covariate does explain **between-subject variability** but does not explain **intra-individual variability**.

Table 3: Covariates identified for AB CL

			Renal function				
			$CL_R \sim fCL_{CR}$	CL_{OTHER}	fu	Active secretion ?	Active reabsorption ?
Aminoglycosides		Amikacin	69 % - 85 %				
		Arbekacin	72 %				
		Gentamicin	78 %				
		Tobramycin	70 % - 140 %				
Beta-lactams	Penicillins	Amoxicillin	163 %				
		Ampicillin	231 %				
		Piperacillin	191 % - 272 %				
	Cephalosporins	**Cefazolin**[2]	65 %				
		Cefepime[4]	92 %				
		Cefpirome[4]	94 %				
		Ceftazidime[3]	81 % - 154 %				
		Ceftobiprole[5]	78 %				
		Ceftriaxone[4]	18 %				
		Cefuroxime[2]	150 %				
	Carbapenems	Biapenem	204 %				
		Doripenem	219 % - 309 %				
		Imipenem	126 % - 246 %				
		Meropenem	135 % - 235 %				
Beta-lactamase inhibitors		Clavulanic acid	111 %				
		Sulbactam	-				
		Tazobactam	180 %				
Colistin			-				
Fosfomycin			38 % - 103 %				
Glycopeptides		**Teicoplanin**	109 %				
		Vancomycin	49 % - 122 %				
Fluoroquinolones		Ciprofloxacin	235 % - 350 %				
Glycylcyclines		**Tigecycline**	352 %				
Oxazolidinones		Linezolid	-				

✓ If CL is dominated by GFR then:

$$CL_{AB} = f_u \times GFR$$

✓ So by comparing $\frac{CL_{AB}}{GFR}$ against f_u

we can delineate whether active processes are involved.

Table 3: Covariates identified for AB CL

			Renal function				
			$CL_R \sim fCL_{CR}$	CL_{OTHER}	fu	Active secretion ?	Active reabsorption ?
Aminoglycosides		Amikacin	69 % - 85 %		89 % - 100 %		++
		Arbekacin	72 %		> 85 %[1]		++
		Gentamicin	78 %		> 70 %		
		Tobramycin	70 % - 140 %		> 70 %		
Beta-lactams	Penicillins	Amoxicillin	163 %		80 % - 83 %	++	
		Ampicillin	231 %		75 % - 85 %	++	
		Piperacillin	191 % - 272 %		70 %	++	
	Cephalosporins	**Cefazolin**[2]	65 %		15 % - 25 %	++	
		Cefepime[4]	92 %	16 %	81 % - 84 %	+	
		Cefpirome[4]	94 %		91 %		
		Ceftazidime[3]	81 % - 154 %		83 %		
		Ceftobiprole[5]	78 %		78 %		
		Ceftriaxone[4]	18 %		5 % - 15 %		
		Cefuroxime[2]	150 %		50 % - 67 %	++	
	Carbapenems	Biapenem	204 %		97 %[2]	++	
		Doripenem	219 % - 309 %		92 %	++	
		Imipenem	126 % - 246 %	70 %	80 %	++	
		Meropenem	135 % - 235 %		98 %	++	
Beta-lactamase inhibitors		Clavulanic acid	111 %		75 %[3]	++	
		Sulbactam	-		62 %[4]		
		Tazobactam	180 %		70 %[5]	++	
Colistin			-				
Fosfomycin			38 % - 103 %		100 %		
Glycopeptides		**Teicoplanin**	109 %		5 % - 10 %	++	
		Vancomycin	49 % - 122 %		40 % - 70 %		
Fluoroquinolones		Ciprofloxacin	235 % - 350 %		60 % - 80 %	++	
Glycylcyclines		**Tigecycline**	352 %		11 % - 29 %	++	
Oxazolidinones		Linezolid	-				

Table 3: Covariates identified for AB CL

			Renal function				
			$CL_R \sim fCL_{CR}$	CL_{OTHER}	fu	Active secretion ?	Active reabsorption ?
Aminoglycosides		Amikacin	69 % - 85 %		89 % - 100 %		++
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		Gentamicin	78 %		> 70 %		
		Tobramycin	70 % - 140 %		> 70 %		
Beta-lactams	Penicillins	Amoxicillin	163 %		80 % - 83 %	++	
		Ampicillin	231 %		75 % - 85 %	++	
		Piperacillin	191 % - 272 %		70 %	++	
	Cephalosporins	**Cefazolin**[2]	65 %		15 % - 25 %	++	
		Cefepime[4]	92 %	16 %	81 % - 84 %	+	
		Cefpirome[4]	94 %		91 %		
		Ceftazidime[3]	81 % - 154 %		83 %		
		Ceftobiprole[5]	78 %		78 %		
		Ceftriaxone[4]	18 %		5 % - 15 %		
		Cefuroxime[2]	150 %		50 % - 67 %	++	
	Carbapenems	Biapenem	204 %		97 %[2]	++	
		Doripenem	219 % - 309 %		92 %	++	
		Imipenem	126 % - 246 %	70 %	80 %	++	
		Meropenem	135 % - 235 %		98 %	++	
Beta-lactamase inhibitors		Clavulanic acid	111 %		75 %[3]	++	
		Sulbactam	-		62 %[4]		
		Tazobactam	180 %		70 %[5]	++	
Colistin			-				
Fosfomycin			38 % - 103 %		100 %		
Glycopeptides		**Teicoplanin**	109 %		5 % - 10 %	++	
		Vancomycin	49 % - 122 %		40 % - 70 %		
Fluoroquinolones		Ciprofloxacin	235 % - 350 %		60 % - 80 %	++	
Glycylcyclines		**Tigecycline**	352 %		11 % - 29 %	++	
Oxazolidinones		Linezolid	-				

Q_1:
How useful are covariate models based on CL_{CR} only, knowing that CL_{CR} is (only) a good surrogate for GFR but does not take into account active secretion/ reabsorption?

Q_2:
Are these conclusions ICU-specific?

Q_3:
Why are we not more frequently identifying drug-drug interactions?

The Role of the Kidney in Drug Elimination: Transport, Metabolism, and the Impact of Kidney Disease on Drug Clearance

JO Miners[1], X Yang[2], KM Knights[1] and L Zhang[2]

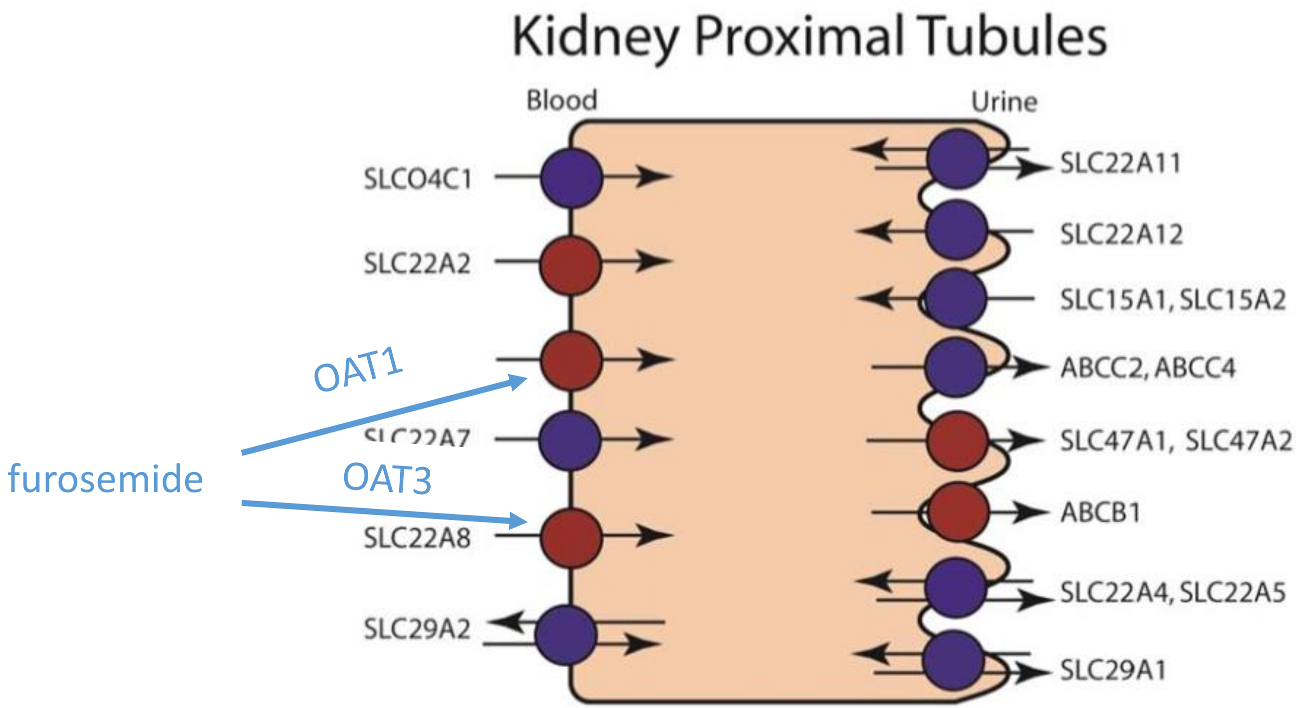

Figure 1 Renal transporters of clinical importance. Transporters are highlighted on the basis of evidence of clinical drug–drug interactions and relevance to toxicity or efficacy. Transporters recommended for evaluation in regulatory guidances for drug interactions are marked with red circles. Modified from (Hillgren, *et al.*, 2013)[6] by Dr. Sook Wah Yee, University of California, San Francisco.

Take home messages:

- ✓ TBW is associated with AB Vd, yet currently used body size metrics do not necessarily reflect our current understanding of AB distributional behaviour
- ✓ Apart from vancomycin **no signs of excessive Vd** for ABs were found in ICU patients (most compounds behave as expected)
- ✓ For ABs there is currently no evidence to suggest that changes in **albumin levels** result in changes in therapeutic efficacy. For those ABs where (theoretically) problems are suspected unbound concentrations should be measured.
- ✓ When trying to predict AB CL, **mCL_{CR} likely does not outperform eCL_{CR}** to any clinically relevant extent
- ✓ Our results show a high involvement of **active renal processes** for most ABs, yet almost none of the PopPK analyses studied the effect of concomitant medication on AB CL
- ✓ **Intra-individual variability** (in a group of patients frequently described as being hyper dynamic) is (almost) never studied, as such it remains unclear to what extend changes in renal function throughout therapy should be accounted for