Augmented Renal Clearance and Drug Dosing

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Intensive Care Services
Royal Brisbane Hospital
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NO CONFLICT OF INTERESTS
How often have you needed to increase dosing after levels were performed?
1st dose

1. Cefpirome levels lower
2. No difference between D1 vs later dose

Day 3-6
Creatinine clearance

Creatinine clearance

Lipman et al Anesth Analg 2003
Augmented Renal Clearance  
Cr Cl > 130ml/min

Lipman et al Anesth Analg 2003
How often have you needed to increase dosing after levels were performed?

That’s because vancomycin clearance mirrors creatinine clearance.
Creatinine clearance

Calculations/Predictions

or

\[
\frac{U.V}{P} = \text{Urine concentration} \times \text{volume} \quad \text{Plasma concentration}
\]
Creatinine clearance

Calculated clearances from serum creatinine are derived from patients with ABNORMAL RENAL FUNCTION
Pitfalls of using estimations of glomerular filtration rate in an intensive care population

eGFR or CG formulae to estimate renal function in ICU subjects with normal serum creatinine concentrations is inaccurate

Martin et al. *Intern Med J* 2010;41:537-43
A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance

João Pedro Baptista
Jeffrey Lipman

Figure 2 Bland-Altman plot of $\text{CL}_{CR}$ vs Cockcroft Gault formula.
Comparison of different equations to assess glomerular filtration in critically ill patients


**Conclusion:**
Estimates of GFR had low accuracy and precision in this cohort of critically ill patients ...... Urinary creatinine clearance may provide an alternative when overestimation of GFR is taken into account......
Important concept

Recommended dosages are obtained from healthy volunteers and possibly (ward) “sick” patients.
Antibiotic regimens are derived from non-critically ill volunteers. Their haemodynamic system is normal, as is their liver and kidney blood flow. They have not leaky capillaries nor have they drips and pipes in every orifice.
SEPSIS

Increased Cardiac Output

Leaky Capillaries &/or altered protein binding

Normal Organ Function

End Organ Dysfunction (e.g. renal or hepatic)

Increased CL

Increased Vd

Unchanged Vd

Decreased CL

Low Plasma Concentrations

Normal Plasma Concentrations

High Plasma Concentrations

Critical Care Medicine  March 2009
Revised from Clinical Pharmacokinetics  2006
SEPSIS

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Critical Care Medicine  March 2009
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Augmented Renal Clearance Cr Cl > 130 ml/min

Lipman et al *Anesth Analg* 2003
Augmented Renal Clearance in the ICU: Results of a Multicenter Observational Study of Renal Function in Critically Ill Patients With Normal Plasma Creatinine Concentrations

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UDY et al Critical Care Medicine March 2014: 42 : 520-527
Objective: To describe the prevalence and natural history of augmented renal clearance in a cohort of recently admitted critically ill patients with normal plasma creatinine concentrations.
**Design**: Multicenter, prospective, observational study.

**Setting**: Four, tertiary-level, university-affiliated, ICUs in Australia, Singapore, Hong Kong, and Portugal.
Patients: Study participants had to have an expected ICU length of stay more than 24 hours, no evidence of absolute renal impairment (admission plasma creatinine < 20 μmol/L), and no history of prior renal replacement therapy or chronic kidney disease. Convenience sampling was used at each participating site.
Interventions:
Eight-hour urinary Cr Cl were collected daily, as the primary method of measuring renal function. ARC was defined by a CrCl more than or equal to 130 mL/min/1.73 m².
Measurements and Main Results:
Nine hundred thirty-two patients were admitted to the participating ICUs over the study period, and 281 of which were recruited into the study, contributing 1,660 individual creatinine clearance measures.
Measurements and Main Results:

…. Overall, 65.1% manifested augmented renal clearance on at least one occasion during the first seven study days; the majority (74%) of whom did so on more than or equal to 50% of their creatinine clearance measures.
Augmented Renal Clearance in the ICU: Results of a Multicenter Observational Study of Renal Function in Critically Ill Patients With Normal Plasma Creatinine Concentrations

UDY et al. *Critical Care Medicine* March 2014
A prospective observational study in a mixed cohort of surgical and medical ICU patients receiving antimicrobial therapy at Ghent University Hospital. Of the 128 patients and 599 studied treatment days, ARC was present in 51.6% of the patients.
IF YOU DON’T LOOK PROPERLY YOU WON’T SEE IT.
ARC pictorial explanation

Inflammation
- Infection
- Burns

Pancreatitis

SIRS

Vasodilation

↑ CO

↑ RBF

IV fluids

↑ GFR

Renal reserve

→ ARC

Vasoactive medications

Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients

Andrew A Udy¹,², Jason A Roberts¹,²,³, Andrew F Shorr⁴, Robert J Boots¹,² and Jeffrey Lipman¹,²
Those manifesting ARC were younger (P <0.001), male (P = 0.012), with lower acute physiology and chronic health evaluation (APACHE) II (P= 0.008) and modified sequential organ failure assessment (SOFA) scores (P = 0.013), and higher cardiac indices (P = 0.013). In multivariate analysis, age ≤50 years, trauma, and a modified SOFA score ≤4, were identified as significant risk factors.
LOW EXPOSURE TO ANTIBIOTICS ENABLES DEVELOPMENT OF RESISTANCE

Antibiotic resistance—What’s dosing got to do with it?

Jason A. Roberts, B Pharm (Hons); Peter Kruger, MBBS, FJFICM; David L. Paterson, MBBS, FRACP, PhD; Jeffrey Lipman, MBBCh, FJFICM, MD

Critical Care Medicine  August 2008;36:2433-40
Subtherapeutic Initial \( \beta \)-Lactam Concentrations in Select Critically Ill Patients

Association Between Augmented Renal Clearance and Low Trough Drug Concentrations

Andrew A. Udy, MBChB; Julie M. Varghese, BPharm (Hons); Mahdi Altukroni, MD; Scott Briscoe, MSc; Brett C. McWhinney, MPhil; Jacobus P. Ungerer, MBChB; Jeffrey Lipman, MD; and Jason A. Roberts, PhD
AUGMENTED RENAL CLEARANCE

Trough conc/MIC ratio vs Creat Cl

CHEST 2012; 142(1):30–39
Serum antibiotic levels over a dosing interval

- Concentration dependent
- Time dependent

Concentration (mg/L)

AUC/MIC = AUIC

T > MIC

Cmax (Peak)

Cmin (Trough)
EFFECT OF ARC ON T>MIC

ARC affects AUC and $f_{T>MIC}$
CASE ONE

Mr SJ  33 M  SEVERE CLOSED HEAD INJURY

3rd week into ICU - CoNS from Bld + EVD
Off inotropes, MAP 80, P 110, T 38, Na 140
Cr 41   U/O 1-1.5ml/kg/hr

**Vancomycin**

1gm BD -> trough 6  1.5gm BD -> trough 11
3gm infusion->15  4gm infusion->steady state 21
8 hr Creat Clearance 200ml/min
Cardiac output   8 l/m

Udy et al *Int J Antimicrob Agents* 2010;35:606-8
CASE TWO

Mr IF  29 M  40% BURNS + INHALATIONAL INJURY

3rd week into ICU - Cipro sensitive CRAB
On norad 5µ/min, MAP 70, P 80, T 38°C, Na 139
Cr 60  U/O <1.5ml/kg/hr

CIPROFLOXACIN
400mg tds  level at 4hrs level 1.2mg/l
Lipman et al – should be about 2mg/l
Cardiac Output 10l/m

Udy et al Int J Antimicrob Agents 2010;35:606-8
CASE THREE

Mr RJ 29 M 28% BURNS + INHALATIONAL INJURY

2nd week into ICU - Amikacin sensitive CRAB

Off inotropes, MAP 80, P 100, T 38, Na 140
Cr 55, U/O <1.5ml/kg/hr

AMIKACIN

20mg/kg/day 14hrs 1.2
30mg/kg/day 14hrs 2.4
30mg/kg/18hourly trough <1

Udy et al Int J Antimicrob Agents 2010;35:606-8
CASE FOUR

Mr CS 19 M MULTI-TRUAMA - SEVERE CLOSED HEAD INJURY -> DECOMPRESSIVE CRANIECTOMY

3rd week into ICU - 5th day VAP
Off inotropes, MAP 100, P 116, T 38°, Na 148 Cr 56, U/O 1-1.5ml/kg/hr

MEROPENEM

2gm 8 hourly
Trough - undetectable
Creatinine Clearance 224ml/min
Cardiac Output 10l/min

Udy et al *Int J Antimicrob Agents* 2010;35:606-8
ERTAPENEM 1GM/DAY (!?..!)

DOSE INCR 1GM BD
DOSE INCR 1GM TDS
AS EXTENDED INFUSION

Level ‘therapeutic’ target = 100% \( f T_{>\text{MIC}} \)

and only then did we get adequate levels!

Hayashi, Lipman, Udy et al. IJAA 2013;41:162-6
IN SUMMARY

Younger patients who have an inflammatory response (any) with “normal” renal function
Particularly those that need fluid loading and or inotropiC support to defend a blood pressure
UNDERDOSING OF RENALLY EXCRETED DRUGS
AUGMENTED RENAL CLEARANCE – implications

1) ICU PK can be different to package insert
2) Urinary cleared drug
   Measure 8 hour creat clearance
   if high -> increase dose
3) TDM if possible
THE END!

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