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Antibiotic dosing in the 'at risk' critically ill patient: Linking pathophysiology with pharmacokinetics/pharmacodynamics in sepsis and trauma patients

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Abstract

Background: Critical illness, mediated by trauma or sepsis, can lead to physiological changes that alter the pharmacokinetics of antibiotics and may result in sub-therapeutic concentrations at the sites of infection. The first aim of this project is to identify the clinical characteristics of critically ill patients with significant trauma that have been recently admitted to ICU that may predict the dosing requirements for the antibiotic, cefazolin. The second aim of this is to identify the clinical characteristics of critically ill patients with sepsis that may predict the dosing requirements for the combination antibiotic, piperacillin-tazobactam.

Methods/Design: This is an observational pharmacokinetic study of patients with trauma (cefazolin) or with sepsis (piperacillin-tazobactam). Participants will have samples from blood and urine, collected at different intervals. Patients will also have a microdialysis catheter inserted into subcutaneous tissue to measure interstitial fluid penetration of the antibiotic. Participants will be administered sinistrin, indocyanine green and sodium bromide as well as have cardiac output monitoring performed and tetrapolar bioimpedance to determine physiological changes resulting from pathology. Analysis of samples will be performed using validated liquid chromatography tandem mass-spectrometry. Pharmacokinetic analysis will be performed using non-linear mixed effects modeling to determine individual and population pharmacokinetic parameters of antibiotics.

Discussion: The study will describe cefazolin and piperacillin-tazobactam concentrations in plasma and the interstitial fluid of tissues in trauma and sepsis patients respectively. The results of this study will guide clinicians to effectively dose these antibiotics in order to maximize the concentration of antibiotics in the interstitial fluid of tissues.

Background

The incidence of infection in critically ill patients, suffered before or following admission to ICU, is increasing. In Australia and New Zealand, 12% of admissions to intensive care units (ICU's) are for severe sepsis [1]. Despite advances in critical care medicine, 27% of these patients will die [1]. Improved antibiotic therapy has been proposed as a mechanism to improve outcome for septic patients [2,3], although the achievement of this depends on both the timely selection of an appropriate antibiotic and on using an appropriate dose so as to obtain appropriate antibiotic concentrations at the site of infection.

Data describing the likely benefits of appropriate dosing of antibiotics remains sparse [4-7]. The antibiotic dosing schedule for a trauma patient admitted to ICU is presently poorly defined and largely empiric. Dosing schedules rely largely on data obtained in non-critically ill patients and there is increasing evidence that describes how such an approach is likely to result in inadequate therapy [2,8].

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In trauma, tissue damage leads to activation of the innate immune system with the release of cytokines, interleukins and other mediators of inflammation [9]. This response may be localised or systemic; if systemic it is referred to as the systemic inflammatory response syndrome (SIRS). Sepsis is then defined as SIRS in the presence of a suspected or documented infection [10]. Many pathological processes (such as trauma, pancreatitis, burns and major surgery) can produce a SIRS response, leading to sepsis, if an infection is superimposed. The hemodynamic changes common to the SIRS response, regardless of the initiating insult, include a low systemic vascular resistance and a high cardiac output described as a hyperdynamic circulation [11].

This hyperdynamic circulatory SIRS response has been demonstrated to have an effect on the creatinine clearance (CL_{CR}) [12]. The magnitude of this effect is such that CL_{CR} can be increased by 50-100% [13]. This increase in CL_{CR} can occur in the presence of a normal serum creatinine concentration [14]. Identification of these patients based on laboratory creatinine concentrations is thus difficult. In fact, it has been demonstrated that an isolated serum creatinine concentration within the "normal" reference range is an insensitive indicator of the glomerular filtration rate in the critically ill [15]. The haemodynamic changes, induced by the SIRS response, may thus lead to altered pharmacokinetics (PK) through an augmented renal clearance in patients without significant renal dysfunction [16]. CL_{CR} is an important determinant in the pharmacokinetics of antibiotics in the critically ill [17,18].

A significant concern for clinicians is that the administration of standard antibiotic doses in such patients may result in a sub-therapeutic concentration, leading to suboptimal bacterial kill. In trauma patients receiving antibiotic prophylaxis, this may increase the risk of sepsis. In a patient with sepsis this may result in treatment failure with an increased mortality [2,3,19]. In addition, in both trauma and septic patients, failure to achieve adequate concentrations may result in the development of antibiotic resistance [20]. As such identification of the physiological characteristics of patients with a hyperdynamic circulation and thus an augmented renal clearance is poorly described and clinically important.

The optimal measurement of renal function in critically ill patients is still uncertain [16]. The Cockcroft-Gault equation is still widely utilized but its application in critically ill patients has been questioned [15,21-23]. Urinary creatinine collections of 8, 12 and 24 hrs have been used (with matched serum creatinine concentrations) although this will tend to overestimate GFR at lower filtration rates. Sinistrin clearance has also been used to measure GFR due to its unique properties of limited renal tubular secretion and reabsorption and

may provide insight into the accuracy of other approaches in critically ill patients [24].

In addition to changes in renal function, trauma and sepsis may also induce increased capillary leakage, microvascular stasis and the accumulation of peripheral fluid [11]. Previous studies evaluating antibiotic PK in the presence of sepsis or trauma have shown the volume of distribution of hydrophilic antibiotics to be significantly increased [24-26]. This capillary leak syndrome is well described in sepsis and to a lesser extent in patients with major trauma [27-29]. Trauma is further implicated in altered pharmacokinetics secondary to possible reduced intravascular volume, massive fluids shifts, and hypoproteinemia [3,30]. Hypoproteinemia is well described in sepsis and critical care [31]. These changes impact on antibiotic diffusion distance and delivery resulting in slow and possible incomplete antibiotic tissue penetration into infected tissues [3,16,32,33].

A consequence of the physiological changes, seen in both septic and trauma patients, is that these two subgroups of critically ill patients are at risk of significantly different pharmacokinetic (PK) profiles with respect to that of non-critically ill patients. As such standard treatment regimens are likely to be ineffective and result in sub-therapeutic target tissue concentrations.

Currently there is little data to guide the clinician to predict which patients may have different PKs in the acute phase of trauma or during sepsis. Furthermore most studies have examined the total drug concentrations in serum, rather than the pharmacologically active unbound drug in tissues where most infections occur [34]. This uncertainty of dosing requirements, in the presence of data that highlights the importance of appropriate antibiotic therapy, is of critical importance.

The identification of the physiological predictors of altered PK allows the development of dosing algorithms that can maximise the target site antibiotic concentration and reduce treatment failure.

As detailed above there are many causes for potential altered PK in patients both with sepsis or trauma. There is some overlap between the physiological pathways that cause these alterations in PK. However, we propose to study sepsis and trauma patients in separate groups, with the sepsis group receiving treatment with piperacillin-tazobactam and the trauma group receiving prophylaxis with cefazolin.

Piperacillin-tazobactam is a combination of a semisynthetic penicillin and β-lactamase inhibitor that is commonly used for empiric therapy of sepsis. Cefazolin is a narrower spectrum first generation cephalosporin antibiotic commonly used as prophylaxis in critically ill patients with traumatic injuries. Little data exists to confirm the appropriateness of dosing of these important antibiotics for critically ill patients. There is no data

describing potential interrelationships between the kinetics of these antibiotics and the physiological changes that occur in patients that have sepsis or significant traumatic injuries.

Aims

The first aim of this project is to identify the clinical characteristics of critically ill patients with significant trauma, that have been recently admitted to ICU, that may predict the dosing requirements for the antibiotic, cefazolin.

The second aim of this is to identify the clinical characteristics of critically ill patients with sepsis that may predict the dosing requirements for the combination antibiotic, piperacillin-tazobactam.

Our approach is to accurately describe the patient's altered physiology and develop physiologically-based pharmacokinetic (PBPK) models that may describe plasma and tissue cefazolin and piperacillin-tazobactam concentrations for each of these patient groups.

Methods/Design

Study design

This is an open-labelled pharmacokinetic study. Samples of blood, tissue microdialysate and urine will be collected from participants being treated in the ICU of the Royal Brisbane and Women's Hospital (RBWH), Queensland, Australia and the Princess Alexandra Hospital (PAH), Queensland, Australia for sepsis or major trauma.

Setting

The clinical study will be performed in the ICU at RBWH and the PAH, which have approximately 4000 patients admitted annually. This work will be done in collaboration with the Burns, Trauma and Critical Care Research Centre and the Therapeutics Research Centre, School of Medicine, The University of Queensland.

Identification of Eligible Patients

Participants would need to meet the inclusion and exclusion criteria to be enrolled. Informed consent will be obtained from each patient or a legally authorised representative to participate in the study.

Inclusion criteria

- Age of between 18 years and 80 years.
- Clinical indication for therapy with cefazolin for trauma patients or piperacillin-tazobactam after diagnosis of sepsis where sepsis is defined as:
    - Clinical suspicion of infection and/or positive culture results
    - SIRS as defined by two or more of the following [10]:

- Core temperature <36°C or >38°C
- Tachycardia as defined by a heart rate >90 beats per minute
- Tachypnoea as defined by a respiratory rate greater than 20 breaths per minute OR a $PaCO_2$ less than 32 mmHg during spontaneous breathing OR the requirement for mechanical ventilation.
- A white blood cell count >12 × 10^9/L or <4 × 10^9/L OR greater than 10% immature (band) forms.
- Renal function as defined by:
    - Serum creatinine concentration <170 μmol/L
- An arterial line in situ
- Written informed consent obtained

Exclusion criteria

Participants will be excluded if they have pre-existing renal impairment (serum creatinine concentration ≥171 μmol/L) or if they have a history of allergy to the study antibiotic or iodine.

Participants

Participants will be recruited into two separate groups:

1. Trauma patients (n = 30) receiving cefazolin; and
2. Sepsis patients (n = 50) receiving piperacillin-tazobactam.

Drug dosing

Antibiotic administration will only occur in patients where the treating clinician has deemed a clinical need for the study antibiotic. Administration will occur in line with the manufacturer's guidelines for each product. Cefazolin will be administered in 20 ml 0.9% sodium chloride by intravenous infusion via a central venous catheter over 5-minutes and piperacillin-tazobactam will be administered in 50 ml 0.9% sodium chloride by intravenous infusion via a central venous catheter over 20-minutes.

Other marker compounds will also be administered to assess the physiology of the patient at the time of antibiotic administration.

Indocyanine green (ICG) - Pulsion 0.5 mg/kg (maximum dose 50 mg) will be administered to provide a measure of plasma volume, an indication of hepatic function and the distribution kinetics of highly bound solutes. Plasma volume will be obtained from the final ICG concentration [35]. The ICG will be administered as a rapid bolus via central venous line 10 min prior to the start of the antibiotic infusion. ICG non-invasive oximetry measurements will be taken over a period of 7 min.

Sodium bromide (5% w/v solution; 1 ml/kg) will be administered intravenously to measure extracellular fluid fluctuations [36]. It will be administered as a slow bolus over 3 min. For cefazolin, sodium bromide will be administered starting 2 min after the initiation of the antibiotic infusion and for piperacillin-tazobactam, it will be administered for the final 3-minutes of the 20-minute antibiotic infusion [37].

Sinistrin 2500 mg (Inutest[R], Laevosan, Linz, Austria) will be given as a bolus over 30 seconds to help determine renal function (GFR). For cefazolin, sinistrin will be administered over the final 30-seconds of the antibiotic infusion and for piperacillin-tazobactam, it will be administered over the final 30-seconds of the 20-minute antibiotic infusion [38].

Sample collection
Sampling will occur during one 6-hour dosing interval for each patient.

Blood Samples
Six blood samples will be taken for each antibiotic.

Piperacillin-tazobactam (infused over 20 min) - the first sample will be taken 1 minute prior to start of the infusion and then at 20 min (end of infusion), 40 min, 60 min, 210 min and 360 min respectively post commencement of the infusion.

Cephazolin (infused over 5 min). The first sample will be taken 1 minute prior to the infusion of the antibiotic and then at 5 min (end of infusion), 20 min, 60 min, 210 min and 360 min respectively post commencement of the infusion.

Microdialysis Samples
Following insertion of a microdialysis catheter (CMA 60, 20 kDa dialysis window, Global Scientific, Sweden) subcutaneously by an experienced clinician, fourteen samples will be collected over the course of the antibiotic dosing interval. The catheter will be perfused with a solution of 0.9% sodium chloride and cefalotin (10 mg/L) which acts as a marker antibiotic of similar molecular size and physicochemical properties to the study antibiotics. Cefalotin will assist in the determination of the rate of movement of molecules across the dialysis membrane according to the retrodialysis method [39,40]. The first microdialysis sample is taken 1 min prior to the start of the antibiotic infusion with repeat measurements taken at 20 min, 40 min, 60 min, 90 min, 120 min, 150 min, 180 min, 210 min, 240 min, 270 min, 300 min, 330 min, and at 360 min respectively following which the microdialysis catheter will be removed.

Urine Samples
Urine samples for creatinine clearance will be collected as previously described according to the urinary collection clearance method [41]. Urine collection will start at the time of initiation of the antibiotic infusion. At 2 hours, 4 hours and 6 hours the urine will be collected with a 5 ml aliquot taken for quantification of the rate and amount of antibiotic excreted in that particular 2 hour time period. After the 6-hour sample, a subsequent 8-hour collection will commence providing four urinary creatinine clearance measures over a 14-hour period.

Tetrapolar Bioimpedance
An experienced clinician will perform tetrapolar bioimpedance on two occasions during the study. The first measurement occurring 20 minutes prior to the antibiotic dose and then repeated six and a half hours post initiation of the infusion. The results will be used for measuring the fat free mass [42] of the patient and detecting altered fluid status (e.g. variations in extracellular water) over the study period.

Cardiac Output
Pulse contour arterial waveform analysis will be used to measure cardiac output and other derived haemodynamic measurements utilizing the FloTrac/Vigileo™ system (Edwards Lifesciences, Irvine, CA, USA). Cardiac output results will be confirmed using an UltraSonic Cardiac Output Monitor (The USCOM ultrasonic CO monitor USCOM Pty, Coffs Harbour, NSW, Australia). These measurements will be made simultaneously at three times post the initiation of the antibiotic infusion (0 minutes, 180 minutes and 300 minutes).

Sample handling and storage
Blood samples that are collected will immediately be placed on ice and centrifuged within 60-minutes of sampling at 3000 rpm for 10-minutes and stored at -80°C until assay. Microdialysis and urine samples will be stored at -80°C until assay.

Sample analysis
Assays of all samples will occur, within 30-days of collection, at the Therapeutics Research Centre of The University of Queensland.

Blood, urine and microdialysis samples will be analysed using validated liquid chromatography-tandem-mass spectrometry (LC-MS/MS) analytical assays. Blood plasma protein and albumin concentrations will be measured. The unbound fraction of antibiotic in plasma will be determined using ultracentrifugation (12000 rpm for 20-minutes) through 3 kDa nominal cut-off membrane devices (Amicon[®] YM30, Millopore Corporation, Billerica, MA).

ICG, sodium bromide and sinistrin concentrations will all be measured using validated High-Performance-Liquid-Chromatography (HPLC) assays. ICG concentration clearance will also be assessed by non-invasive oximetry (LiMon - Pulsion Medical Systems) Non-invasive tetrapolar bioimpedance will be compared with measured sodium bromide concentrations.

Analysis of urine samples from the eight-hour urinary collection will be compared with other measures of renal function, including results from the sinistrin analysis (glomerular filtration) and creatinine clearance determination using the Cockroft-Gault formula [43].

Analysis of the 5 ml urine aliquots for antibiotic clearance will be performed using validated LC-MS/MS assays and will determine the rate and amount of antibiotic excreted in urine.

Data collection

Additional data will be obtained from the medical record and will include:

1. Participant demographics including age, gender, height, allergies, co-morbidities;

2. Clinical details (admission diagnosis, progress and outcome);

3. Measures of illness severity, including Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission [44];

4. A daily Sepsis Organ Failure Assessment (SOFA) score [45];

5. Revised Trauma Score (RTS) [46];

6. A tissue penetration and perfusion score consisting of oxygen saturation (%), serum lactate concentration (mmol/L) and noradrenaline dose (mcg/kg/min) will be taken at the time of the antibiotic infusion [47];

7. Microbiology results - Gram stain, culture and antimicrobial sensitivities of blood cultures or other culture sites following admission to hospital;

8. Laboratory investigations - full blood count, serum biochemistry, coagulation profile, liver function tests and arterial blood gas measurements.

Statistical considerations

It is anticipated that a minimum of 30 patients with data-rich sampling will be required to develop a pharmacokinetic model defining at least 3 predictors. The sample size is based on a power of 80%, a level of significance of 5%, multiple regression analysis with 3 predictor variables and a R-square (proportion of variation explained) of 30% [48].

Data analysis

Pharmacokinetic modelling of antibiotic distribution and clearances will be performed and compared, where possible, to previously published pharmacokinetic data from healthy volunteers and other non-critically ill patient groups. The results of sample analysis will be analysed using a non-linear mixed effects modelling approach (NONMEM, GloboMax LLC, Hanover, MD, USA). The aim of this process will be to develop a baseline population physiologically-based-pharmacokinetic (PBPK) model for each antibiotic assuming a re-circulatory PBPK-pharmacodynamic (PBPKPD) model [49,50]. NONMEM will mainly be used to model between subject variability and within subject variability in simultaneously modelling sparse data from multiple patients with a classical compartmental approach. Each of the factors that are identified to affect antibiotic pharmacokinetics will then be incorporated into the model to help describe the between subject variability and within subject variability, defining, where possible, the extent a patient's pharmacokinetics changes during critical illness. Incorporation of all variables will be used to develop a user-friendly antibiotic dosing algorithm.

The influence of demographic and clinical covariates will be tested in the model. The model will simulate antibiotic pharmacokinetics for different dosing schedules to predict the best dosing recommendations for sepsis patients receiving piperacillin-tazobactam and trauma patients receiving cefazolin.

Ethical considerations

The Human Research and Ethics Committee of the RBWH (2007/188). Princess Alexandra Hospital and the Medical Research Ethics Committee of the University of Queensland (2008000449) have approved this study.

Withdrawal from Study

Participants may withdraw from the study at anytime without prejudice, as documented and explained at the time of consenting.

Discussion

It is becoming increasingly evident that the dosing requirements for antibiotics in critically ill patients are different to non-critically ill patients. The pharmacokinetics in critically ill patients is affected by changes in haemodynamic parameters, hypoproteinemia, microvascular flow and capillary leak. This is due, in part, to the hyperdynamic circulation and augmented renal clearance induced by the SIRS response in both trauma and sepsis, resulting in increased GFR. The altered tissue physiology found in sepsis and trauma with increased capillary leakage and blood flow stasis may lead to altered volumes of distribution and slow antibiotic penetration. Trauma and sepsis are further implicated in altered pharmacokinetics secondary to possible reduced intravascular volume, massive fluids shifts, and hypoproteinemia. These two specific groups of patients are therefore at risk of altered pharmacokinetics and the potential for antibiotic underdosing demands further investigation.

Conclusions

Inappropriate antibiotic administration can lead to selection of resistant organisms and failure of therapy with increased mortality [2,3]. Identification of the physiological characteristics that may predict an altered pharmacokinetic profile will enable optimised dosing in these individuals. The proposed study will identify parameters instructive of the need for altered antibiotic doses to ensure therapeutic concentrations in both plasma and in the interstitial fluid of tissues.

Funding

Abbreviations

ICU: intensive care unit; PK: pharmacokinetic; RBWH: Royal Brisbane and Women's Hospital; PAH: Princess Alexandra Hospital; ICG: Indocyanine green; USCOM: UltraSonic Cardiac Output Monitor; LCMSMS: liquid chromatography-mass spectrometry; HPLC: High-Performance-Liquid-Chromatography; PBPKPD: PBPK-pharmacodynamic.

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Authors' contributions

JR, MSR, PK and JL designed the study and wrote the protocol. AS and MR assisted writing the protocol. AU, CMJ, and DLP provided advice and input into the protocol. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

References

1. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J: **Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units.** *Intensive Care Med* 2004, **30(4)**:589-96.
2. Kollef MH, Sherman G, Ward S, Fraser VJ: **Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients.** *Chest* 1999, **115(2)**:462-74.
3. Roberts JA, Lipman J: **Antibiotic dosing in intensive care: Pharmacokinetics, degree of disease and pharmacodynamics of sepsis.** *Clin Pharmacokinet* 2006, **45(8)**:755-773.
4. van Lent-Evers NA, Mathot RA, Geus WP, van Hout BA, Vinks A: **Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis.** *Ther Drug Monit* 1999, **21(1)**:63-73.
5. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ: **Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients.** *Antimicrob Agents Chemother* 1993, **37(5)**:1073-81.
6. Scaglione F, Esposito S, Leone S, Lucini V, Pannacci M, Ma L, Drusano GL: **Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia.** *Eur Respir J* 2009, **34(2)**:394-400.
7. Roberts JA, Ulldemolins M, Roberts MS, McWhinney BC, Ungerer JPJ, Paterson DL, Lipman J: **Therapeutic Drug Monitoring of Beta-lactams in Critically Ill Patients: Proof of concept.** *Int J Antimicrob Agents* 2010, **36(4)**:332-9.
8. Joukhadar C, Frossard M, Mayer BX, Brunner M, Klein N, Siostrzonek P, Eichler HG, Müller M: **Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock.** *Crit Care Med* 2001, **29**:385-391.
9. Khol BA, Deutschman CS: **The inflammatory response to surgery and trauma.** *Curr Opin Crit Care* 2006, **12(4)**:325-32.
10. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: **Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee, American College of Chest Physicians/Society of Critical Care Medicine.** *Chest* 1992, **101(6)**:1644-55.
11. Parillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP: **Septic shock in humans: advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy.** *Ann Int Med* 1990, **113(3)**:227-42.
12. Brown R, Babcock R, Talbert J, Greunenberg J, Czurak C, Cambell M: **Renal function in the critically ill pot-operative patients: sequential assessment of creatinine osmolar and free water clearance.** *Crit Care Med* 1980, **8(2)**:68-72.
13. Loirat P, Rohan J, Baillet A, Beaufils F, David R, Chapman A: **Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin.** *N Engl J Med* **299(17)**:915-9.
14. Martin JH, Fay MF, Udy A, Roberts J, Kirkpatrick C, Ungerer J, Lipman J: **Pitfalls of using estimations of glomerular filtration rate in an intensive care population.** *Intern Med J* 2010.
15. Hoste EA, Damen J, Vanholder RC, Norbert H, Lameire JR, Van den Hauwe KD, Colardyn FA: **Assessment of renal function in recently admitted critically ill patients with normal serum creatinine.** *Nephrol Dial Transplant* 2005, **20(4)**:747-53.
16. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J: **Augmented Renal Clearance: Implications for Antibacterial Dosing in the Critically Ill.** *Clin Pharmacokinet* 2010, **49(1)**:1-16.
17. Lipman J, Wallis SC, Rickard CM, Fraenkel D: **Low cefpirome levels during twice daily dosing in critically ill septic patients: pharmacokinetic modelling calls for more frequent dosing.** *Intensive Care Med* 2001, **27(2)**:363-70.
18. Young RJ, Lipman J, Gin T, C D Gomersall CD, Joynt GM, Oh TE: **Intermittent bolus dosing of ceftazidime in critically ill patients.** *J Antimicro Chemother* 1997, **40(2)**:269-73.
19. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, Barchuk W: **Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS Trial.** *Clin Infect Dis* 2004, **15(2)**:284-8.
20. Roberts JA, Kruger P, Paterson DL, Lipman J: **Antibiotic Resistance - What's dosing got to do with it?** *Crit Care Med* 2008, **36(8)**:2433-40.
21. Poggio ED, Nef PC, Wang X, Greene T, Van Lente F, Dennis VW, Ha PM: **Performance of the Cockcrof-Gault and modification of diet in renal disease equations in estimating GFR in ill hospitalized patients.** *Am J Kidney Dis* 2005, **46(2)**:242-52.
22. Snider RD, Kruse JA, Bander JJ, Dunn GH: **Accuracy of estimated creatinine clearance in obese patients with stable renal function in the intensive care unit.** *Pharmacotherapy* 1995, **15(6)**:747-53.
23. Buclin T, Pechere-Bertschi A, Sechaud R, Decosterd LA, Munafo A, Burnier M, Biollaz J: **Sinistrin clearance for determination of glomerular filtration rate: a reappraisal of various approaches using a new analytical method.** *J Clin Pharmacol* 1997, **37(8)**:679-92.
24. Triginer C, Izquierdo I, Fernandez R, Rello J, Torrent J, Benito S, Net A: **Gentamicin volume of distribution in critically ill septic patients.** *Intensive Care Med* 1990, **16(5)**:303-6.

25. Gosling P, Sanghera K, Dickson G: **Generalized vascular permeability and pulmonary function in patients following serious trauma.** *J Trauma* 1994, **36**:477-81.

26. Marik PE, Havlik I, Monteagudo FSE, Lipman J: **The pharmacokinetics of amikacin in critically ill adult and paediatric patients: comparison of once- versus twice-daily dosing regimens.** *J Antimicrob Chemother* 1991, **27(suppl C)**:81-89.

27. Plank LD, Monk DN, Woollard GA, Hill GL: **Evaluation of multifrequency bioimpedance spectroscopy for measurement of the extracellular water space in critically ill patients.** *Appl Radiat Isot* 1998, **49(5-6)**:481-3.

28. Cheng AT, Plank LD, Hill GL: **Prolonged overexpansion of extracellular water in elderly patients with sepsis.** *Arch Surg* 1998, **133(7)**:745-51.

29. Plank LD, Hill GL: **Similarity of changes in body composition in intensive care patients following severe sepsis or major blunt injury.** *Ann NY Acad Sci* 2000, **904**:592-602.

30. Jaehde U, Sorgel F: **Clinical pharmacokinetics in patients with burns.** *Clin Pharmacokinet* 1995, **29(1)**:15-28.

31. Finfer S, Bellomo R, Boyce N, French J, Myburg J, Norton R, SAFE study investigators: **A comparison of albumin and saline for fluid resuscitation in the intensive care unit.** *N Engl J Med* 2004, **350(22)**:2247-2256.

32. Lipman J, Wallis SC, Rickard C: **Low plasma cefepime levels in critically ill septic patients: pharmacokinetic modeling indicates improved troughs with revised dosing.** *Antimicrob Agents Chemother* 1999, **43(10)**:2559-61.

33. Roberts JA, Paratz JD, Paratz E, Krueger WA, Lipman J: **Continuous infusion of beta-lactam antibiotics in severe infections - a review of its role.** *Int J Antimicrob Agents* 2007, **30(1)**:11-8.

34. Ryan DM: **Pharmacokinetics of antibiotics in natural and experimental superficial compartments in animals and humans.** *J Antimicrob Chemother* 1993, **31(Suppl D)**:1-16.

35. Busse MW, Zisowshy S, Henschen S, Panning B, Piepenbrock B: **Plasma volume estimation using indocyanine green. A single intravenous injection method.** *Anaesthesia* 1993, **48(1)**:41-3.

36. Wong WW, Sheng HP, Morkeberg JC, Kosanovich JL, Clarke LL, Klein PD: **Measurement of extracellular water volume by bromide ion chromatography.** *Am J Clin Nutr* 1989, **50**:1290-1294.

37. Monk DN, Plank LD, Franch-Arcas G, Finn PJ, Streat SJ, Hill GL: **Sequential changes in the metabolic response in critically injured patients during the first 25 days after blunt trauma.** *Ann Surg* 1996, **223**:395-405.

38. Buclin T, Sechaud R, Bertschi AP, Decosterd LA, Belaz N, Appenzeller M, Burnier M, Biollaz J: **Estimation of glomerular filtration rate by sinistrin clearance using various approaches.** *Ren Fail* 1998, **20(2)**:267-76.

39. Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J: **Piperacillin penetration into tissue of critically ill patients with sepsis-Bolus versus continuous administration.** *Crit Care Med* 2009, **37(3)**:926-933.

40. Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J: **Meropenem dosing in critically ill patients with sepsis and without renal dysfunction - intermittent bolus vs continuous administration? Monte-Carlo dosing simulations and subcutaneous tissue distribution.** *J Antimicrob Chemother* 2009, **64**:142-50.

41. Cherry RA, Eachempati SR, Hydo L, Barie PS: **Accuracy of short-duration creatinine clearance determinations in predicting 24-hour creatinine clearance in critically ill and injured patients.** *J Trauma* 2002, **53(2)**:267-71.

42. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B: **Quantification of Lean Bodyweight.** *Clinical Pharmacokinetics* 2005, **44(10)**:1051-1065.

43. Cockroft DW, Gault MH: **Prediction of creatinine clearance from serum creatinine.** *Nephron* 1976, **16**:31-41.

44. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system.** *Crit Care Med* 1985, **13**:818-829.

45. Antonelli M, Moreno R, Vincent JL: **Application of SOFA score to trauma patients. Sequential Organ Failure Assessment.** *Intensive Care Med* 1999, **25**:389-394.

46. Champion HR, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Flanagan ME: **A revision of the Trauma Score.** *J Trauma* 1989, **29(5)**:623-629.

47. Zeitlinger BS, Zeitlinger M, Leitner I, Müller M, Joukhadar C: **Clinical Scoring System for the Prediction of Target Site Penetration of Antimicrobials in Patients with Sepsis.** *Clinical Pharmacokinetics* 2007, **46(1)**:75-83.

48. Faul F, Erdfelder E, Lang A, Buchner A: **G*power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences.** *Behav Res Methods* 2007, **39**:175-19.

49. Roos JF, Lipman J, Kirkpatrick CM: **Population pharmacokinetics and pharmacodynamics of cefpirome in critically ill patients against Gram-negative bacteria.** *Intensive Care Med* 2007, **33(5)**:781-8.

50. Roos JF, Bulitta J, Lipman J, Kirkpatrick CM: **Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units.** *J Antimicrob Chemother* 2006, **58(5)**:987-93.