PK/PD IN THE CRITICALLY ILL

ANTIBIOTICS - A REVIEW OF 2010-2018

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TITLE	JOURNAL	PMID	AUTHOR		AUTHORS SAY
Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients.	Crit Care	30244674	Veiga RP	2018 Sep 24	Although no studies have assessed clinical outcome, **we recommend using higher than standard dosing,** preferably with continuous or prolonged infusions, especially when treating less susceptible bacterial strains at these sites, as the pharmacodynamics profile may improve with no apparent increase in toxicity.A therapeutic drug monitoring-guided approach could be particularly useful in critically ill patients in whom achieving target concentrations is more difficult, such as obese patients, immunocompromised patients, those infected by highly resistant bacterial strains, patients with augmented renal clearance, and those undergoing extracorporeal support techniques.
Covariate determinants of effective dosing regimens for time-dependent beta-lactam antibiotics for critically ill patients.	Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub	29582860	Kaska M	2018 Sep	RESULTS: The treatment of both 8 septic patients with IV extended ME dosing 2 g/3 h q8 h and 10 polytraumatized patients with IV intermittent PIP/TZB dosing 4.0/0.5 g q8 h was monitored. 8/18 patients (44%) manifested augmented renal clearence (ARC) where Clcr >/=130 mL/min/1.73 m(2). Maximum changes were reported on days 2-3: the median positive CFB followed by the large median volume of distribution: Vdme=70.3 L (41.9-101.5), Vdpip = 46.8 L (39.7-60.0). 100%fTme>MIC was achieved in all patients on ME (aged >/=60 years), and only in two patients (non-ARC, aged >/=65 years) out of 10 on PIP/TZB. A mixed model analysis revealed positive relationship of CFBpip with Vdpip (P=0.021). **CONCLUSION: Assuming that the positive correlation between CFB and Vd exists for piperacillin in the setting of the pathological state, then CFB should predict Vdpip across subjects at each and every time point.**
Pharmacokinetic/Pharmacodynamic Considerations of Beta-Lactam Antibiotics in Adult Critically Ill Patients.	Curr Infect Dis Rep	29619607	Masich AM;	2018 Apr 4	PURPOSE OF REVIEW: Beta-lactam antibiotics are commonly prescribed in critically ill patients for a variety of infectious conditions. Our understanding of how critical illness alters beta-lactam pharmacokinetics/pharmacodynamics (PK/PD) is rapidly evolving. RECENT FINDINGS: There is a growing body of literature in adult patients demonstrating that physiological alterations occurring in critically ill patients may limit our ability to optimally dose beta-lactam antibiotics to reach these PK/PD targets. These alterations include changes in volume of distribution and renal clearance with multiple, often overlapping causative pathways, including hypoalbuminemia, renal replacement therapy, and extracorporeal membrane oxygenation. Strategies to overcome these PK alterations include extended infusions and therapeutic drug monitoring. **Combined data has demonstrated a possible survival benefit associated with extending beta-lactam infusions in critically ill adult patients. This review highlights research on physiological derangements affecting beta-lactam concentrations and strategies to optimize beta-lactam PK/PD in critically ill adults.**
Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: a prospective observational study.	Crit Care	29058601	Ehmann L	2017 Oct 21	RESULTS: Large inter- and intra-patient variability in meropenem concentrations was observed in the critically ill population (n = 48). Attainment of the target 100%T>MIC was merely 48.4% and 20.6%, given MIC values of 2 mg/L and 8 mg/L, respectively, and similar for the target 50%T>4xMIC. A hyperbolic relationship between CLCRCG (25-255 ml/minute) and meropenem serum concentrations at the end of the dosing interval (C8h) was derived. For infections with pathogens of MIC 2 mg/L, mild renal impairment up to augmented renal function was identified as a risk factor for target non-attainment (for MIC 8 mg/L, additionally, moderate renal impairment). CONCLUSIONS: **The investigated standard meropenem dosing regimen appeared to result in insufficient meropenem exposure in a considerable fraction of critically ill patients**. An easy- and free-to-use tool (the MeroRisk Calculator) for assessing the risk of target non-attainment for a given renal function and MIC value was developed.
Optimizing beta-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective?	Expert Rev Anti Infect Ther	28571493	Delattre IK	2017 Jul	Expert commentary: Considering that critically-ill patients are highly vulnerable and likely to experience antibiotic underexposure, and because effective initial treatment is a key determinant of clinical outcome, **we support the use of a target of 100%T > 4xMIC,** which could not only maximize efficacy but also minimize emergence of resistance. Clinical and microbiological studies are needed to test for the feasibility and effectiveness of reaching such a demanding target.
Aminoglycosides against carbapenem-resistant Enterobacteriaceae in the critically ill: the pitfalls of aminoglycoside susceptibility.	Expert Rev Anti Infect Ther	28375030	Zavascki AP	2017 Jun	Expert commentary: While new antimicrobials are not widely available, the authors forecast an increasing use of aminoglycosides as backbone antibiotics against CRE isolates. **However, the altered PK of aminoglycosides in critically ill patients severely impairs their predicted efficacy in these patients**. Aminoglycoside breakpoints may hide 'aminoglycoside-susceptible' CRE isolates for that aminoglycosides will unlikely be effective if used in monotherapy. Therefore, these breakpoints may need to be revised due to the increasing use of aminoglycosides as backbone antibiotics to treat severe infections by CRE isolates in critically ill patients.
Pharmacokinetic and Pharmacodynamic Evaluation of Doripenem in Critically Ill Trauma Patients with Sepsis.	Surg Infect (Larchmt)	27841954	Rahbar AJ	2016 Dec	RESULTS: Overall, the model fit the data well, and mean (standard deviation) clearance and volume of the central compartment were 16.9 (11.4) L/h and 28.5 (16.0) L, respectively. In the MCS analyses, doripenem 1 g, infused over 4 hours, administered every 8 hours, conferred >90% probabilities of achieving 30-50% time greater than the minimum inhibitory concentration (30-50% T>MIC) for MICs </=2 mg/L after infusion of both the first and fourth doses. The MCS indicated that more intensive doripenem dosing schemes should be considered for organisms with MIC values in excess of 2 mg/L. **CONCLUSIONS: This is the first study to describe the doripenem PK/PD in critically ill patients with trauma. Among these patients, the MCS analyses suggest that current dosing strategies may be ineffective when the MIC value for the infecting pathogen is expected to be above 2 mg/L.**
Optimizing intravenous fosfomycin dosing in combination with carbapenems for treatment of Pseudomonas aeruginosa infections in critically ill patients based on pharmacokinetic/pharmacodynamic (PK/PD) simulation.	Int J Infect Dis	27418581	Asuphon O	2016 Sep	RESULTS: MIC90 of fosfomycin alone, fosfomycin in combination with carbapenem, carbapenems alone and carbapenems in combination with fosfomycin were >1,024, 1,024, >32 and 32mug/ml, for multidrug resistant (MDR)-PA and 512, 128, 8 and 3mug/ml respectively, for non-MDR PA. Approximately 40% of the non-MDR PA were carbapenem-resistant strains. For non-MDR PA with CRPA, fosfomycin 16g continuous infusion in combination with carbapenems provided %PTA of approximately 80 and %CFR of > 88. While, %PTA and %CFR > 90 were achieved with fosfomycin 24g/day prolonged infusion in combination with carbapenem. **CONCLUSIONS: Prolonged infusion of fosfomycin 16 - 24g combined with extended carbapenem infusion could be used in non-MDR PA treatment with CRPA.**
Can we transfer pharmacokinetics/pharmacodynamics of antimicrobials into clinical practice?	Int J Antimicrob Agents	26607342	Scaglione	2015 Dec	In critically ill patients there is extensive evidence of subtherapeutic antibiotic exposure from standard doses across different antibiotic classes. This can be a direct consequence of pharmacokinetic alterations emanating from the complex pathophysiological processes associated with severe infection. Therapeutic drug monitoring (TDM) is being increasingly used for antibiotic dose optimisation in an attempt to improve the attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets and the outcomes of severe infection in critically ill patients. In clinical practice, it is necessary to reduce the number of blood samples collected from the patient to a minimum because of the cost (personnel, devises and analysis). **TDM to calculate PK/PD indices is easily feasible only when a single blood sample is adequate to perform the analysis.**
Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill.	Curr Opin Crit Care	26348420	Tsai D;	2015 Oct	**SUMMARY: Optimization of antimicrobial dosing in accordance with pharmacokinetics/pharmacodynamics targets can improve survival and clinical cure. Dosing regimens for critically ill patients should aim for pharmacokinetics/pharmacodynamics target attainment by utilizing altered dosing strategies including adaptive feedback using therapeutic drug monitoring.**
Extended versus bolus infusion of meropenem and piperacillin: a pharmacokinetic analysis.	Minerva Anestesiol	24762706	De Waele J	2014 Dec	RESULTS: Twenty extended infusion patients (15 piperacillin, 5 meropenem) were compared with 13 bolus infusion patients (8 piperacillin, 5 meropenem). The demographic and clinical characteristics between both groups were not statistically different. Significant pharmacokinetic differences were observed in median (interquartile range) Cmax for both meropenem (extended infusion 17 [12.6-21.9] vs. bolus 85.2 [66.7-140.3]; P=0.01) and piperacillin (extended infusion 76.2 [57.7-92.6] vs. bolus 240.2 [168.5-275.4]; P=0.001). Considerable pharmacokinetic variability existed in each group for both drugs. Compared to bolus infusion, fT>MIC using extended infusion was higher for both drugs: 96% (IQR 71-100%) compared to 77% (IQR 41-93%) for piperacillin (P=0.05) and 82% (IQR 63-89%) compared to 51% (IQR 48-63%) for meropenem (P=0.095); assuming a MIC of 16 mg/L and 2 mg/L respectively. **CONCLUSION: This study confirms that extended infusion in critically ill patients result in advantageous pharmacokinetic profiles by increasing the fT>MIC for piperacillin and meropenem. In a significant subpopulation of critically ill patients with normal renal function, a 100% fT>MIC target is not reached, even with 3-hour extended infusions.**
Doripenem population pharmacokinetics and dosing requirements for critically ill patients receiving continuous venovenous haemodiafiltration.	J Antimicrob Chemother	24879665	Roberts JA	2014 Sep	RESULTS: The median (IQR) age was 62 (53-71) years, the median (IQR) weight was 77 (67-96) kg and the median (IQR) APACHE II score was 29 (19-32). The median blood, dialysate and replacement fluid rates were 200, 1000 and 1000 mL/h, respectively. A two-compartment linear model with doripenem clearance described by CVVHDF, renal or non-renal mechanisms was most appropriate. The mean value for total doripenem clearance was 4.46 L/h and volume of distribution was 38.0 L. Doripenem clearance by CVVHDF was significantly correlated with the replacement fluid flow rate and accounted for approximately 30%-37% of total clearance. A dose of 500 mg intravenously every 8 h achieved favourable pharmacokinetic/pharmacodynamics for all patients up to an MIC of 4 mg/L. **CONCLUSIONS: This is the first paper describing the pharmacokinetics/pharmacodynamics of doripenem in critically ill patients with AKI receiving CVVHDF. A dose of 500 mg intravenously every 8 h was appropriate for our CVVHDF settings for infections caused by susceptible bacteria.**
Clinical implications of antibiotic pharmacokinetic principles in the critically ill.	Intensive Care Med	24045886	Udy AA	2013 Dec	Successful antibiotic therapy in the critically ill requires sufficient drug concentrations at the site of infection that kill or suppress bacterial growth. The relationship between antibiotic exposure and achieving the above effects is referred to as pharmacokinetics/pharmacodynamics (PK/PD). The associated indices therefore provide logical targets for optimal antibiotic therapy. While dosing regimens to achieve such targets have largely been established from studies in animals and non-critically ill patients, they are often poorly validated in the ICU. **Endothelial dysfunction, capillary leak, altered major organ blood flow, deranged plasma protein concentrations, extremes of body habitus, the application of extracorporeal support modalities, and a higher prevalence of intermediate susceptibility, independently, and in combination, significantly confound successful antibiotic treatment in this setting. As such, the prescription of standard doses are likely to result in sub-therapeutic concentrations, which in turn may promote treatment failure or the selection of resistant pathogens. (Further Review in Article)**
Can changes in renal function predict variations in beta-lactam concentrations in septic patients?	Int J Antimicrob Agents	23993066	Casu GS	2013 Nov	**Although CLCr was significantly correlated with concentrations and clearance of broad-spectrum beta-lactams, changes in CLCr did not reliably predict variations in drug pharmacokinetics/pharmacodynamics. Routine TDM should be considered to adapt beta-lactam doses in this setting.**
Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility.	Crit Care Med	23263583	Roberts JA;	2013 Feb	MEASUREMENTS AND MAIN RESULTS: A two-compartment linear model was most appropriate. The mean values for doripenem clearance (20.4 +/- 14.2 L/hr) and volume of distribution (45.9 +/- 36.3 L) were larger than that observed in previous studies in noncritically ill patients. Doripenem clearance was correlated with creatinine clearance and peripheral volume of distribution with patient body weight. Administration by extended infusion negated much of the pharmacokinetic variability caused by different patient body weight and renal function and enabled achievement of concentrations associated with maximal bacterial killing. **CONCLUSION: : This is the first article describing the pharmacokinetics/pharmacodynamics of doripenem solely in critically ill patients and emphasizes the effect of patient weight and creatinine clearance on pharmacokinetics. Use of extended infusions with this antibiotic should be encouraged as it maximizes the likelihood of achieving target blood concentrations.**
Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a Pk/Pd based approach.	Antimicrob Agents Chemother	23045356	Pea F	2012 Dec	Dosing nomograms based on CL(Cr) were created to target the meropenem C(ss) at 8, 12, and 16 mg/liter in critically ill patients. These nomograms could be helpful in improving the treatment of severe Gram-negative infections with meropenem, especially in the presence of borderline susceptible pathogens or even of carbapenemase producers and/or of pathophysiological conditions which may enhance meropenem clearance.
The relevance of drug volume of distribution in antibiotic dosing.	Curr Pharm Biotechnol	21554218	Ulldemolins M	2011 Dec	Compelling evidence shows significant increases in the Vd of both hydrophilic and lipophilic drugs in critically ill patients as a consequence of patient pathology and from clinical interventions. These increases in the Vd can lead to lower than expected plasma concentrations during the first day of therapy, which may result in sub-optimal achievement of antibiotic pharmacokinetics/pharmacodynamic targets, resulting in inappropriate treatment. Therefore, loading doses of antibiotic during the first day of therapy that account for the predicted increase in the Vd are required. **Further research towards the establishment of new dosing regimens that use loading doses to satisfy such increased volumes of distribution is recommended.**
Some current issues in the pharmacokinetics/pharmacodynamics of antimicrobials in intensive care.	Minerva Anestesiol	20613692	Petrosillo N	2010 Jul	There is significant but inconclusive evidence that critically ill patients may benefit more when antibiotics with time-dependent action are administered in a continuous/prolonged infusion regimen. On the other hand, aminoglycosides exhibit a concentration-dependent pattern of killing and should be administered at high doses once daily or at extended intervals, and their levels in the plasma should by strictly monitored to avoid both underexposure and toxicity. The problem of antimicrobial resistance now involves agents traditionally considered reliable in that aspect, such as vancomycin. **Strict monitoring of vancomycin MIC for methicillin-resistant Staphylococcus aureus and the prudent use of the available alternative agents as well as de-escalation strategies might be reasonable strategies for dealing with this problem.**
Pharmacokinetic-pharmacodynamic-model-guided doripenem dosing in critically ill patients.	Antimicrob Agents Chemother	20385857	Samtani MN	2010 Jun	In patients with creatinine clearance of >50 ml/min, a 500-mg dose of doripenem infused over 1 h every 8 h is expected to be effective against bacilli with doripenem MICs of < or =1 microg/ml based on a T>MIC 35% target and MICs of < or =2 microg/ml based on lower targets. A longer, 4-hour infusion time improved target attainment in most cases, such that the T>MIC was adequate for pathogens with doripenem MICs as high as 4 microg/ml. Efficacy is expected for infections caused by pathogens with doripenem MICs of < or =2 microg/ml in patients with moderate renal impairment (creatinine clearance, 30 to 50 ml/min) who receive doripenem at 250 mg infused over 1 h every 8 h and in patients with severe impairment (creatinine clearance between 10 and 29 ml/min) who receive doripenem at 250 mg, infused over 1 h or 4 h, every 12 h. **Results of pharmacokinetics/pharmacodynamics (PK/PD) modeling can guide dose optimization, thereby potentially increasing the clinical efficacy of doripenem against serious Gram-negative bacterial infections.**
Pharmacokinetics of moxifloxacin in patients with severe sepsis or septic shock.	Intensive Care Med	20336279	Pletz MW	2010 Jun	RESULTS: Data for 400 mg moxifloxacin i.v. were as follows (geometric mean): C (max): 3.5 mg/l, t(1/2): 7.8 h and AUC (48-72 h): 25 mg h/l. In five individual patients AUC (48-72 h) was <20 mg h/l. CONCLUSION: The main pharmacokinetics/pharmacodynamics parameter predicting clinical efficacy of moxifloxacin is AUC/MIC. **The mean AUC of patients with severe sepsis or septic shock was lower compared to healthy volunteers (39 mg h/l). In 5 of 12 patients the AUC was halved compared to healthy volunteers.**

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