REVIEW ARTICLE

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

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Abstract

Low serum albumin levels are very common in critically ill patients, with reported incidences as high as 40–50%. This condition appears to be associated with alterations in the degree of protein binding of many highly protein-bound antibacterials, which lead to altered pharmacokinetics and pharmacodynamics, although this topic is infrequently considered in daily clinical practice. The effects of hypoalbuminaemia on pharmacokinetics are driven by the decrease in the extent of antibacterial bound to albumin, which increases the unbound fraction of the drug. Unlike the fraction bound to plasma proteins, the unbound fraction is the only fraction available for distribution and clearance from the plasma (central compartment). Hence, hypoalbuminaemia is likely to increase the apparent total volume of distribution (V_d) and clearance (CL) of a drug, which would translate to lower antibacterial exposures that might compromise the attainment of pharmacodynamic targets, especially for time-dependent antibacterials. The effect of hypoalbuminaemia on unbound concentrations is also likely to have an important impact on pharmacodynamics, but there is very little information available on this area.

The objectives of this review were to identify the original research papers that report variations in the highly protein-bound antibacterial pharmacokinetics (mainly V_d and CL) in critically ill patients with hypoalbuminaemia and without renal failure, and subsequently to interpret the consequences for antibacterial dosing. All relevant articles that described the pharmacokinetics and/or pharmacodynamics of highly protein-bound antibacterials in critically ill patients with hypoalbuminaemia and conserved renal function were reviewed.

We found that decreases in the protein binding of antibacterials in the presence of hypoalbuminaemia are frequently observed in critically ill patients. For example, the V_d and CL of ceftriaxone (85–95% protein binding) in hypoalbuminaemic critically ill patients were increased 2-fold. A similar phenomenon was reported with ertapenem (85–95% protein binding), which led to failure to attain pharmacodynamic targets (40% time for which the concentration of unbound [free] antibacterial was maintained above the minimal inhibitory concentration [*f*T>MIC] of the bacteria throughout the dosing interval). The V_d and CL of other highly protein-bound antibacterials such as teicoplanin, aztreonam, fusidic acid or daptomycin among others were significantly increased in critically ill patients with hypoalbuminaemia compared with healthy subjects.

Increased antibacterial V_d appeared to be the most significant pharmacokinetic effect of decreased albumin binding, together with increased CL. These pharmacokinetic changes may result in decreased achievement of pharmacodynamic targets especially for time-dependent antibacterials, resulting in suboptimal treatment. The effects on concentration-dependent antibacterial pharmacodynamics are more controversial due to the lack of data on this topic. In conclusion, altered antibacterial-albumin binding in the presence of hypoalbuminaemia is likely to produce significant variations in the pharmacokinetics of many highly protein-bound antibacterials. Dose adjustments of these antibacterials in critically ill patients with hypoalbuminaemia should be regarded as another step for antibacterial dosing optimization. Moreover, some of the new antibacterials in development exhibit a high level of protein binding although hypoalbuminaemia is rarely considered in clinical trials in critically ill patients. Further research that defines dosing regimens that account for such altered pharmacokinetics is recommended.

Antibacterial dosing in critically ill patients remains a complicated and unresolved issue confronting clinicians. The effects of disease and severity of illness on patient physiology are known to exert significant effects on pharmacokinetics.[1] However, dosing regimens rarely account for such variability, with the exception of impairments in renal function and, to a lesser extent, hepatic function. It is known that critical illness is associated with important variations in patient physiology that lead to significant variations in pharmacokinetics and consequently pharmacodynamics.[2] Multiple factors such as the systemic inflammatory response syndrome (SIRS), fluid resuscitation or the use of inotropes are the likely cause of these variations.[1] However, a largely underappreciated issue likely to be problematic in pharmacokinetics is altered protein binding. Administration of other highly protein-bound drugs, increased concentration of endogenous molecules with high affinity to albumin, e.g. in uraemia, free fatty acids or cirrhosis-associated high bilirubin levels and especially hypoalbuminaemia are clinical scenarios known to affect the percentage of protein binding of highly protein-bound drugs,[3-6] but the implication of this effect for antibacterial dosing is still poorly defined. As albumin is the serum protein responsible for most of the drug-protein binding, decreased protein binding of highly protein-bound drugs is likely to commonly occur in the presence of hypoalbuminaemia.

Pharmacologically, albumin significantly affects the pharmacokinetics of many drugs because of drug-albumin binding. In patients with hypoalbuminaemia the unbound proportion of highly protein-bound drugs will increase because of a decrease in available binding sites. Given that critically ill patients frequently present with low serum albumin levels,[7] potential altered pharmacokinetics of highly protein-bound antibacterials may be of significant clinical relevance because of reduced attainment of pharmacodynamic targets.

The aim of this structured review is to describe the effect of hypoalbuminaemia on the pharmacokinetics and pharmacodynamics of highly protein-bound antibacterials with specific focus directed at identifying variations in two independent pharmacokinetic parameters, apparent total volume of distribution (V_d) and clearance (CL).

1. Search Strategy and Selection Criteria

Data for this review were identified by systematic searches of PubMed (January 1966 to November 2010) and the Cochrane Controlled Trial Registry, as well as references cited by relevant articles. Search terms included 'antibiotic' or 'antibacterial', 'critical illness', 'intensive care units' or 'intensive care' or 'critical care', 'hypoalbuminaemia' or 'albumin' or 'protein binding', and 'pharmacokinetics' or 'pharmacology'. Twenty-five articles were identified through these systematic searches. However, some of the articles were related to non-antibacterial drugs. Only English-language papers that described the pharmacokinetics of highly protein-bound antibacterials in hypoalbuminaemia

were reviewed. Many articles were identified through searches of the extensive files of the authors. All relevant articles that described the pharmacokinetics and/or the pharmacokinetics-pharmacodynamics of highly protein-bound antibacterials in patients with conserved renal and hepatic function were reviewed. We elected to exclude all studies that were performed in patients with hepatic failure, renal failure or receiving renal replacement therapy because of the effects of this pathology on pharmacokinetics which are likely to mitigate the effects of hypoalbuminaemia on drug CL (depending on the elimination pathway of each particular antibacterial). Such patients are less likely to be 'at risk' of sub-therapeutic dosing compared with patients with conserved renal or hepatic function.

2. Albumin-Drug Binding

Many drugs have high affinities for 'binding sites' on the albumin molecule. Binding to form albumin-drug complexes is mostly a reversible equilibrium that is dependent on the concentration of drug and albumin, as well as on a binding constant determined by the physicochemical properties of the drug (see figure 1).

Pharmacologically, albumin binding has three important implications. Firstly, only the unbound drug is able to exert pharmacological effect.[8] Secondly, only the unbound drug is able to distribute into body tissues and may be a significant determinant of the extent of tissue distribution and therefore the drug's V_d. The bound fraction acts as a 'reservoir' within the vascular compartment where dissociation of the albumin-drug complex enables further distribution of the unbound drug.[9] Thirdly, only the unbound fraction of drug is available for elimination from the vascular compartment.[10] Therefore, serum albumin levels will have a prominent effect on the V_d and CL of highly albumin-bound drugs.

3. Clinical Presentations in Critically Ill Patients that May Decrease Albumin Levels

The interaction between the drug and albumin is an equilibrium that can be easily altered in the presence of pathologies other than hypoalbuminaemia. Figure 2 summarizes the main causes of albumin binding variations in critically ill patients.

There is currently no consensus for the specific albumin levels defining hypoalbuminaemia. The SAFE (Saline versus Albumin Fluid Evaluation) study defined it as serum albumin levels <25 g/L, and reported an incidence in critically ill patients of 40–50%.[7] In critically ill patients, hypoalbuminaemia is mainly caused by disease-driven physiological changes. In patients with sepsis, transcapillary escape of albumin is likely to result from increased capillary permeability mediated by the SIRS response. Fleck et al.[12] showed a 200% increased rate of transcapillary escape of albumin from intravascular to extravascular space during the first 2 days of admission in critically ill patients with shock and a mean serum albumin concentration of 25 g/L. This contrasts with 'normal' reference values for serum albumin (42 g/L ± 10%).[13] Moreover, as a negative acute-phase reactant, albumin has its hepatic synthesis down-regulated in patients that present with a stress response, which is also commonly observed in critically ill patients.[14] Malnutrition is another common cause of hypoalbuminaemia. Kirsch et al.[15] demonstrated that insufficient dietary amino acid intake causes a marked decrease in the hepatic synthesis of albumin. Critically ill patients are at high risk of malnutrition, because of impaired gastrointestinal function that may lead to

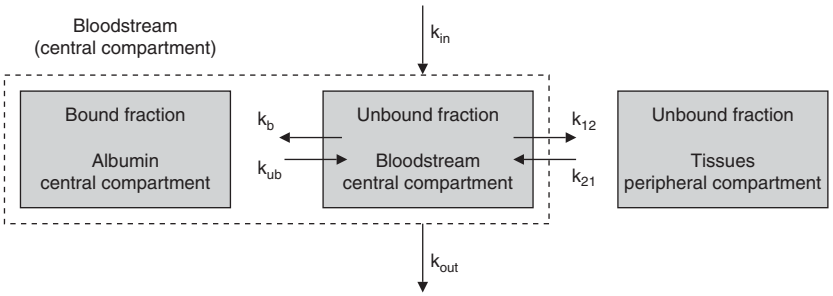

Fig. 1. Representation of the equilibrium between bound and unbound drug fraction in a two-compartment model. The central compartment is described as the intravascular blood volume. Peripheral compartments would correspond to the extravascular tissues where the drug distributes from the central compartment. k_{in} corresponds to the absorption constant (in oral administration) or the infusion rate (in intravenous infusion). k_{12} corresponds to the constant that describes the movement of drug from the central compartment (1) to the peripheral compartment (2). k_{21} describes the movement from the peripheral compartment(s) back to the central compartment. k_b and k_{ub} describe the equilibrium between bound and unbound drug and albumin. k_b and k_{ub} will depend on the binding affinity. The albumin-binding equilibrium will displace depending on the serum albumin concentration and the serum drug concentration. k_{out} corresponds to the elimination constant from the central compartment.

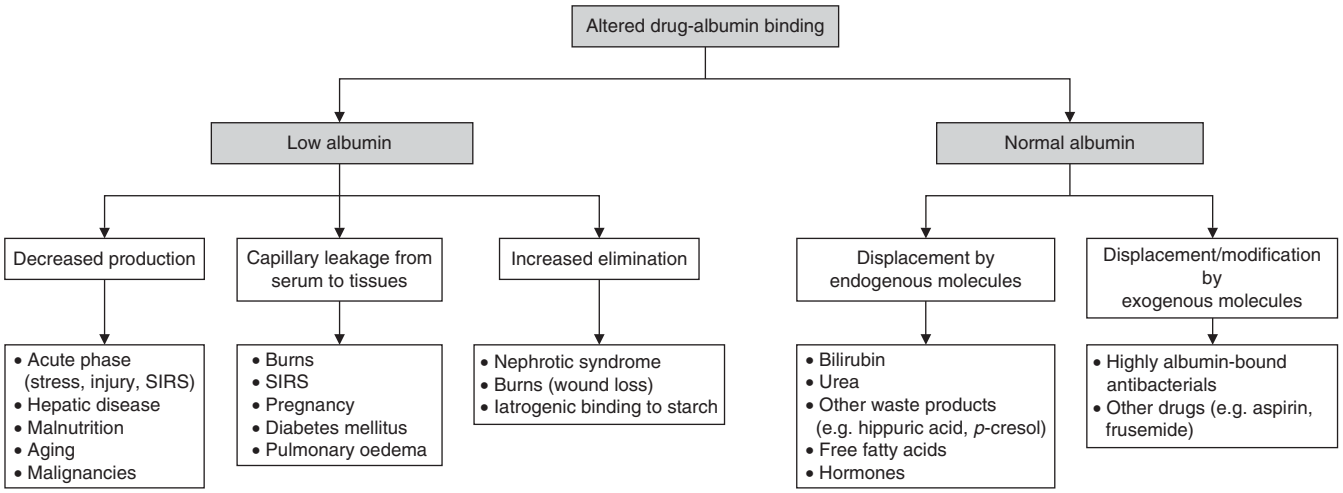

Fig. 2. Main factors responsible for alterations in drug-albumin binding.[11] **SIRS** = systemic inflammatory response syndrome.

malabsorption of nutrients.[16] Aging and malignancies also are associated with lower than usual serum albumin levels.[17,18]

4. Mechanisms of Altered Antibacterial Pharmacokinetics and Pharmacodynamics with Hypoalbuminaemia

The effects of hypoalbuminaemia on antibacterial pharmacokinetics are rarely considered, but may be clinically important. Mechanistically, hypoalbuminaemia leads to a larger amount of unbound drug molecules in the serum which are able to 'escape' from the bloodstream and distribute into tissues to a larger extent than when there is 'normal' albumin binding. Pharmacokinetically, this is translated into a larger V_d, because the higher initial unbound drug concentration distributes into the larger extravascular compartment faster, resulting in lower total concentrations in the intravascular compartment during the distribution phase. Given that critically ill patients frequently have larger than normal V_d *per se*,[2] the availability of more unbound molecules to distribute into the extravascular space is likely to further decrease the effective concentrations in serum over time.

In the particular case of V_d, hypoalbuminaemia is likely to affect this parameter most significantly for hydrophilic drugs in critically ill patients, as their V_d is lower *per se* and is influenced by extracellular water volume. Increases in the V_d are likely to decrease the maximum plasma/serum drug concentration (C_{max}) and total drug concentrations over time. This can lead to potential underdosing and sub-therapeutic concentrations. If pharmacokinetics are altered, that will have a subsequent effect on pharmacodynamics and therefore on the pharmacological effect.[19-21] This is of particular relevance for critically ill patients where early and appropriate therapy is a cornerstone in the treatment of severe infections.[22,23]

After the drug distribution phase, the drug elimination phase is driven by drug clearance from the intravascular compartment. As the kidneys and the liver can clear only unbound molecules, higher concentrations of unbound antibacterial appear to lead to increased total renal and/or hepatic clearance. Moreover, in the case of renal clearance, critically ill patients are likely to experience augmented glomerular filtration rates due to increased cardiac output[24] which, in concert with a higher unbound fraction of antibacterial from hypoalbuminaemia, will lead to enhanced CL and lower total concentrations during the elimination phase.

The relevance of hypoalbuminaemia in the absence of other physiological derangements was demonstrated by Mimoz et al.[25] in their study on ceftriaxone pharmacokinetics during iatrogenic hydroxyethyl starch-induced hypoalbuminaemia in post-surgical patients. The authors reported significant increases in the V_d and CL of ceftriaxone in these patients compared with healthy subjects. They also found a correlation between serum albumin levels and ceftriaxone CL ($p < 0.02$). Although these pharmacokinetics cannot be extrapolated to critically ill patients that may also have physiologically enhanced V_d and CL,[2] the data are instructive for describing the effect of hypoalbuminaemia, in the absence of other pathology, on the pharmacokinetics of highly protein-bound antibacterials.

The above variations in pharmacokinetics of highly protein-bound antibacterials have significant consequences for antibacterial pharmacodynamics (see table I for classification of various antibacterials according to published values for albumin

binding). For time-dependent antibacterials (e.g. β-lactams), increased clearances may lead to a reduced time for which the concentration of unbound (free) antibacterial is maintained above the minimal inhibitory concentration (MIC) of the bacteria throughout the dosing interval ($fT>MIC$) when treating less susceptible bacteria. For concentration-dependent antibacterials (e.g. daptomycin), the ratio of the C_{max} and the MIC of the bacteria (C_{max}/MIC) may be lower due to the increased V_d; although an increased unbound fraction in hypoalbuminaemia may mitigate this effect and maintain appropriate concentrations. For concentration-dependent antibacterials with time dependence (e.g. fluoroquinolones), the attainment of the target ratio between the area under the plasma/serum concentration-time curve (AUC) over 24 hours (AUC_{24}) and the MIC of the bacteria (AUC_{24}/MIC) can be also compromised, as AUC_{24} is a function of both CL and V_d.

It follows that hypoalbuminaemia is likely to contribute to the higher V_d and CL of highly protein-bound antibacterials in the critically ill patient, resulting in failure to attain pharmacodynamic targets associated with efficacy. Moreover, although the effect of hypoalbuminaemia on V_d and CL might be modest in some cases, where other physiological causes might be more prominent, consideration of hypoalbuminaemia in the context of concomitant pathology is necessary to optimize dosing.

It should be noted that of the available studies in this area, most report data in terms of total and not unbound antibacterial concentrations. Unfortunately, only a few of all the studies published thus far on this topic report pharmacokinetic variations related to unbound antibacterial concentrations rather than total concentrations.[28-31] Some other studies have measured unbound concentrations of some highly bound and

Table I. Protein binding of antibacterials commonly used in critically ill patients and of antibacterials in development (all protein binding data have been adapted from Donnelly et al.[26] and MIMS Australia[27]). We have also included data on antifungal agents for the reader's reference

Highly bound (>70%)	Moderately bound (70–30%)	Minimally bound (<30%)
Amphotericin B (90%)	Azithromycin (7–51%)	Amikacin (0–11%)
Anidulafungin (>99%)	Aztreonam (60%)	Amoxicillin (17–20%)
Caspofungin (97%)	Cefotaxime (40%)	Ampicillin (15–25%)
Cefazolin (75–85%)	Cefuroxime (33–50%)	Cefepime (16–19%)
Cefonicid (98%)	Cephalothin (55–75%)	Ceftazidime (17%)
Cefoperazone (90%)	Ciprofloxacin (20–40%)	Ceftobiprole (22%)
Cefoxitin (80–50%)	Clarithromycin (42–50%)	Cefpirome (9%)
Ceftriaxone (85–95%)	Chloramphenicol (60%)	Colistin (<10%)
Clindamycin (90% bound to α_1-acid glycoprotein)	Levofloxacin (50%)	Doripenem (8%)
Cloxacillin (94%)	Linezolid (31%)	Ethambutol (20–30%)
Dalbavancin (93%)	Moxifloxacin (30–50%)	Fluconazole (11–12%)
Daptomycin (90–93%, 30% to α_1-acid glycoprotein)	Nitrofurantoin (40%)	Fosfomycin (0%)
Dicloxacillin (97%)	Benzylpenicillin [penicillin-G] (65%)	Gentamycin (<30%)
Doxycycline (93%)	Piperacillin (30%)	Imipenem (20%)
Ertapenem (85–95%)	Sulfamethoxazole (68%)	Isoniazide (0–10%)
Erythromycin (73–81%)	Ticarcillin (55%)	Meropenem (2%)
Faropenem (96–99%)	Trimethoprim (45%)	Metronidazole (<20%)
Flucloxacillin (95%)	Vancomycin (30–60%)	Norfloxacin (10–15%)
Fusidic acid (95–97%)	Voriconazole (58%)	Polymyxin B (<10%)
Iclaprim (93%)		Quinupristin/dalfopristin (11–26%)
Itraconazole (99.8%)		Tobramycin (<30%)
Lincomycin (80–90%)		
Minocycline (75%)		
Nafcillin (90%)		
Oxacillin (93%)		
Posaconazole (>97%)		
Rifampicin [rifampin] (80%)		
Sulfisoxazole (92%)		
Teicoplanin (90–95%)		
Telavancin (92–94%)		
Tigecycline (71–89%)		

moderately bound antibacterials (e.g. daptomycin, teicoplanin and cefotaxime)[32-34] but do not provide pharmacokinetic analysis of unbound concentrations. As attainment of pharmacodynamic targets is dependent on the unbound concentration of the antibacterial, the results of the rest of the available studies should be considered in this context. Table II summarizes the results of the most relevant studies that report pharmacokinetics of the total concentration. Table III reports the published data available on pharmacokinetics of the unbound fraction of antibacterial.

5. β-Lactams

Penicillins, cephalosporins and monobactams belong to the β-lactam family of antibacterials and are categorized as 'time-dependent' antibacterials, where antibacterial activity is related to the *f*T>MIC.[50] Penicillins and monobactams are reported to require at least 50–60% *f*T>MIC for maximal bactericidal activity, while cephalosporins need a 60–70% *f*T>MIC.[50] Antibacterials in this class generally have low-to-moderate protein binding, although some agents exhibit high protein binding.

Ceftriaxone is a third-generation cephalosporin with 83–96% protein binding.[51] The protein binding of ceftriaxone has been shown to be dose dependent with saturation of binding sites at higher doses resulting in a higher unbound fraction in plasma. It follows that the CL of ceftriaxone is increased when higher doses are used.[38] More frequent dosing is therefore recommended when higher drug exposure is required. Data from Joynt et al.[20] (see table II) describe significantly increased V_d and CL in patients with hypoalbuminaemia, leading to failure to attain the pharmacodynamic targets for therapy in some of the patients. This is supported by data from other studies.[25,39,52]

The isoxazolil penicillin flucloxacillin is 95% bound to albumin. In hypoalbuminaemic critically ill patients, we have reported significant increases in the V_d of total drug compared with healthy subjects. With reference to unbound concentrations, we found that with a 2 g intravenous bolus dose, concentrations fell below 1 mg/L 4 hours after the end of the infusion, providing evidence that standard dosing would not achieve pharmacodynamic targets for the treatment of the most common wild-type methicillin (meticillin)-susceptible *Staphylococcus aureus* (MSSA) [MIC = 2 mg/L].[29] Furthermore, the results of Monte Carlo dosing simulations suggested that continuous infusion of high doses of flucloxacillin would be required for attainment of more aggressive pharmacodynamic targets or when treating intermediately susceptible MSSA in hypoalbuminaemic critically ill patients.[29]

The cephalosporin cephalothin is 55–75% bound to albumin. A study by Dalley et al.[28] in burns patients reported a 10% decrease in the protein binding of cephalothin in hypoalbuminaemic burns patients compared with healthy subjects. Surprisingly, V_d and CL of the unbound fraction were not affected significantly by this condition, even when burns patients presented a significantly higher creatinine clearance (CL_{CR}). This could be partially explained because the study was performed during the initial phase of burn injury, characterized by hypovolaemia and cardiac dysfunction, which are likely to affect drug distribution,[53] and because cephalothin is partially cleared by biliary excretion, therefore increases in CL_{CR} may not affect CL significantly.[54]

The monobactam aztreonam is only moderately bound to albumin (60%) but has also been shown to exhibit higher than expected V_d and/or CL in critically ill patients with hypoalbuminaemia. Janicke et al.[36] reported a significant decrease in the albumin binding of aztreonam in these patients compared with healthy subjects (30% vs 60%). The lower albumin binding was associated with a higher total aztreonam CL. Another study in burns patients described a significant increase in the V_d of aztreonam which was also inversely correlated with serum albumin concentrations ($p < 0.05$).[37] The high V_d and CL of these drugs in hypoalbuminaemic patients lead to low antibacterial concentrations, which may be below *f*T>MIC targets thereby compromising β-lactam's efficacy.

6. Carbapenems

Although belonging to the β-lactam family of antibacterials, carbapenems are often considered as a separate class because of a lower *f*T>MIC requirement (40%) for maximal bacterial killing activity.[55]

Ertapenem is highly albumin bound (85–95%), which considerably extends its elimination half-life ($t_{½}$; 4.5 hours[41]) compared with other carbapenems, such as meropenem (2% albumin binding, $t_{½}$ 1.2 hours[56]). As such the product information recommends that ertapenem should be administered once daily.[57] However, data from three studies suggest that hypoalbuminaemia may have a profound effect on ertapenem pharmacokinetics.

The first study by Burkhardt et al.[19] in critically ill patients with early-onset ventilator-associated pneumonia (VAP) found that V_d and CL were nearly doubled compared with healthy subjects, and AUC decreased to one-half (817 mg • h/L vs 419 mg • h/L). Unbound pharmacokinetics were also reported and showed contrasting results. The AUC of unbound ertapenem increased dramatically in hypaolbuminaemic patients

Table II. Variations in apparent total volume of distribution (V_d) and clearance (CL) of highly albumin-bound antibacterials in critically ill patients with hypoalbuminaemia compared with healthy subjects[a]

Drug	Study group	Subjects (n)	APACHE II score	CL_{CR} (mL/min)	Albumin (g/L)	CL (mL/min)		V_d (L/kg)	
						observed	%Δ[b]	observed	%Δ[b]
β-lactams									
Aztreonam	Healthy adults[35]	48	NA	NA (within ref. values)	NA (within ref. values)	88.7 ± 9.3[c]	0.0	0.16 ± 0.02	0.0
	Gram-negative infected patients[36]	7	NA	103 ± 21	24 ± 5	102 ± 12	14.5	0.16 ± 0.05	0.0
	Burns[37]	8	NA	90 ± 69	21 ± 2	81.7 ± 60.7[c]	–7.9	0.31 ± 0.08	93.8
Ceftriaxone	Healthy adults[38]	6	NA	NA (within ref. values)	NA (within ref. values)	13 ± 2.6	0	0.12 ± 0.01[c]	0
	Critically ill patients with severe sepsis[20]	11	21.7 ± 3.8	97.7 ± 49.6	22.2 ± 6.1	25.8 [19.0–59.3]	98.5	0.32 ± 0.05	166.7
	Critically ill patients[39]	18	NA	112 ± 29	NA	18 ± 5.5	38.5	0.17 ± 4	41.7
Flucloxacillin	Healthy subjects[40]	10	NA	NA (within ref. values)	NA (within ref. values)	136.3 ± 3.3	0	0.14 ± 0.24	0
	Critically ill patients with hypoalbuminaemia[29]	10	19.7 ± 4.4	62.5 [50.5–86.3]	20.7 [19.3–22.8]	150 [144.7–292.5]	10.1	0.22 [0.14–0.30]	57.1
Carbapenems									
Ertapenem	Healthy adults[41]	10	NA	NA (within ref. values)	NA (within ref. values)	20.2 ± 0.16	0.0	0.07 ± 0.003[c]	0.0
	Critically ill patients with VAP[19]	17	23.1 ± 4.2	93.8 ± 52.4	15.9 ± 5.7	43.2 ± 23.7	113.9	0.21 ± 0.05[c]	200.0
	Critically ill patients with severe sepsis[31]	8	8.9 ± 5.1	88.9 ± 36.3	26.9 ± 9	200.5 ± 306.9	892.6	0.98 ± 1.42	1300
Glycopeptides									
Teicoplanin	Healthy subjects[42]	6	NA	103.7 ± 22.9	NA (within ref. values)	13.4 ± 1.2	0.0	1.21 ± 0.56	0.0
	Critically ill patients without vasopressors[43]	12	NA (SAPS II score 26 [13–50])	184 [71–255]	19 [11–33]	18.2 [7.7–47.6]	35.8	NA	NA
Vancomycin	Healthy subjects[44]	11	NA	110 ± 19.3	NA	86.1 ± 8.9		0.59 ± 0.04	
	Critically ill patients[45]	46	18.9 ± 8.2	65.5 ± 48.1	23 ± 7	60.0 ± 39.7	–30.3	1.68 ± 2.19	184.7
Other drugs									
Daptomycin	Healthy adults[46]	24	NA	NA (within ref. values)	NA (within ref. values)	9.4 ± 1.2	0.00	0.10 ± 0.01	0.0
	Thermal burn injury[47]	9	NA (TBSAB 34 ± 12%)	132 ± 43	18 ± 4	23.6 ± 9.5	151.1	0.18 ± 0.05	80
Fusidic acid	Healthy subjects[48]	8	NA	NA	NA	11.1 ± 1.2	0	0.21 ± 0.02	
	Critically ill patients with normal hepatic function[49]	6	NA (SAPS score 10.2 ± 5.1)	NA	29.2 ± 3.7	21.5 ± 6.3	93.7	NA	

a Values are reported as median [range] or mean ± SD.

b %Δ = (Observed value – Reference value/Reference value) × 100.

c Data normalized to 70 kg if weight information was not provided in the original article.

APACHE II = Acute Physiology and Chronic Health Evaluation II; **CL_{CR}** = creatinine clearance; **NA** = not applicable/available; **ref.** = reference; **SAPS** = Simplified Acute Physiology Score; **TBSAB** = total body surface area burned; **VAP** = ventilator-associated pneumonia.

Table III. Variations in apparent unbound volume of distribution (V_d) and clearance (CL) of highly albumin-bound antibacterials in critically ill patients with hypoalbuminaemia compared with healthy subject data[a]

Drug	Patient group	APACHE II score	CL_{CR} (mL/min)	Albumin (g/L)	CL (mL/min)		V_d (L/kg)		$t_{½}$ (h)		AUC_{∞} (mg • h/L)	
					observed	%Δ[b]	observed	%Δ	observed	%Δ	observed	%Δ
β-lactams												
Cephalothin	Healthy adults	NA			1841 ± 175[c]	0	0.60 ± 0.09	0	0.26 ± 0.02	0	9.9 ± 2.8	
	Burns patients	14 ± 4	148 ± 75	25 ± 5	1584 ± 536	–14	0.63 ± 0.16	5	0.41 ± 0.18	57.7	12.1 ± 9.9	22.2
Flucloxacillin	No data available in healthy adults											
	Critically ill patients with hypoalbuminaemia[29]	19.7 ± 4.4	62.5 [50.5–86.3]	20.7 [19.3–22.8]	1623.3 [765–2473.3]		1.9 [0.9–4]		1.2			
Carbapenems												
Ertapenem	Healthy adults[41]	NA	NA (within ref. values)	NA (within ref. values)	513.6 ± 80.8	0	1.8 ± 0.5[c]	0	2.8	0	33.2 ± 5.5	
	Critically ill patients with VAP[30]	NA (SAPS II score 23 [18–28])	74 [66-109]	32.6 [28.1–39.4]	73.3 [63.3–81.7]	–85.7	0.8 [0.6-0.9]	–55.6	3.3	17.9	226.7 [202.2–263.9]	582.8
	Critically ill patients with severe sepsis[31]	8.9 ± 5.1	88.9 ± 36.3	26.9 ± 9	316.2 ± 374.3	–38.4	1.5 ± 1.5	–16.7	8	185.7	180.6 ± 167.4	444

a Values are reported as median [range] or mean ± SD.

b %Δ = (Observed value – Reference value/Reference value) × 100.

c Data normalized to 70 kg if weight information was not provided in the original article.

APACHE II = Acute Physiology and Chronic Health Evaluation II; **AUC_{∞}** = area under the serum/plasma concentration-time curve from time zero to infinity; **CL_{CR}** = creatinine clearance; **NA** = not applicable/available; **ref.** = reference; **SAPS** = Simplified Acute Physiology Score; **$t_{½}$** = elimination half-life; **VAP** = ventilator-associated pneumonia.

compared with data from healthy adults and yet the unbound concentration did not achieve minimum pharmacodynamic targets in some patients. It is therefore difficult to interpret ramifications of the increases in AUC in terms of appropriateness of dosing (table III). The second study by Brink et al.[31] studied the ertapenem total and unbound pharmacokinetics in critically ill patients with severe sepsis, and reported results consistent with the study by Burkhardt et al.[19] and showed that unbound concentrations did not achieve the 40% *f*T>MIC pharmacodynamic target in half of the patients. In line with those two studies, the results of the third study by Boselli et al.[30] showed important increases in both V_d and CL of total ertapenem. Similar results may be expected with the oral carbapenem faropenem, which exhibits an *in vitro* albumin binding of 96–99%.[58] However, there are no pharmacokinetic studies in hypoalbuminaemic patients available at this time to determine this.

7. Glycopeptides

Glycopeptides are still widely used for the treatment of methicillin-resistant *Staphyloccocus aureus* (MRSA) and include vancomycin and teicoplanin. Vancomycin is bound to albumin between 30% and 60% depending on serum albumin levels whilst teicoplanin has much more significant binding (90–95%). Soy et al.[59] performed a population pharmacokinetic analysis of teicoplanin in hospitalized patients and found a trend towards higher V_d and CL as serum albumin concentrations decreased. However, the patients in this study were not severely hypoalbuminaemic (all had serum albumin levels >23 g/L), which might be the reason for the failure to detect significant influences of serum albumin levels on these parameters. Additionally, a study by Mimoz et al.[34] described the effect of hypoalbuminaemia on the proportion of unbound fraction of teicoplanin. The authors measured the total and unbound steady-state trough concentrations of teicoplanin in patients with VAP and severe hypoalbuminaemia (median albumin concentration 16.1 g/L, range 14.2–28.4 g/L) and observed variations in the unbound fraction of the drug, ranging from 8% to 42% (median 22%). This significant variability may result from the variability in serum albumin levels although unfortunately the authors did not attempt to identify the presence of any correlation.

8. Other Highly Albumin-Bound Antibacterials

As described in table I, there are many more antibacterials that exhibit high rates of albumin binding used in the treatment of critically ill patients.

Daptomycin (protein binding 90–93%, 60% to albumin) pharmacokinetics were studied in a cohort of patients with thermal burn injury.[47] The authors compared data from burns patients with data from healthy subjects[46] and noted C_{max} and AUC_{24} values in the burns patients that were nearly half those observed in the healthy subjects. For a concentration-dependent antibacterial, such pharmacokinetic outcomes can gravely compromise antibacterial efficacy.

Another highly bound antibacterial is fusidic acid (albumin binding 95–97%). Fusidic acid is cleared by hepatic metabolism and biliary elimination, with the rate of the metabolism dependent on the unbound drug fraction available for the liver.[60] High CL of fusidic acid was described by Peter et al.[49] in hypoalbuminaemic critically ill patients.

Newer antibacterials such as tigecycline (protein binding 71–89%), dalbavancin (protein binding 93%), telavancin (protein binding 92–94%) and iclaprim (protein binding 93%) all exhibit high protein binding. Data from other highly protein-bound antibacterials suggest that the pharmacokinetics of the aforementioned antibacterials are likely to be affected by hypoalbuminaemia, and deserve further study.

9. Relevance of Altered Pharmacokinetics in Hypoalbuminaemia to Dosing Regimens and Clinical Trials

Empirical dosing regimens are usually derived from pharmacokinetic data from healthy subjects and from non-critically ill patients. However, critically ill patients are a special cohort of patients that exhibit great disease-driven modifications in their pharmacokinetics, likely to significantly change dose requirements. Lower albumin binding which results from hypoalbuminaemia has been demonstrated to result in increases in the total V_d and CL of highly bound drugs and also affects other pharmacokinetic parameters (e.g. AUC_{24}). The increased total V_d appears to be the most significant effect of decreased albumin binding and also serves to increase $t_{½}$ of the drug because of redistribution of the drug from the tissues back into blood. The effect of the extended $t_{½}$ on the attainment of pharmacodynamic targets is heavily dependent on the value of the MIC of the pathogen. Longer $t_{½}$ values for the treatment of low MIC values may result in increased achievement of pharmacodynamic targets for time-dependent antibacterials ($fT>MIC$). However, for organisms with higher MIC values, the extended $t_{½}$ may result in decreased achievement of pharmacodynamic targets such as a decreased percentage of $fT>MIC$ for time-dependent antibacterials and lower C_{max}/MIC and AUC_{24}/MIC ratios for concentration-dependent antibacterials. However, most of the presently available data only describe total antibacterial concentrations and, except for sparse data on flucloxacillin, cephalothin and ertapenem,[28-31] we are unaware of any published studies that described the pharmacokinetics and pharmacodynamics of the unbound fraction of the drug. This makes interpretation of the clinical implications of these results very complex. Future studies should focus on unbound, and not total, concentrations of antibacterials.

The precise strategy for optimizing antibacterial dosing in hypoalbuminaemic patients remains elusive, but increased doses, at least in the initial phase of treatment, seem to be necessary for achieving optimal antibacterial concentrations. This is because the predominant effect of hypoalbuminaemia appears to be an increased V_d. From a dosing perspective, this may mean that loading doses for at least the first 24 hours of treatment should be considered to ensure appropriate antibacterial exposure at the target site of infection. At present, teicoplanin is the only highly protein-bound antibacterial for which loading doses are recommended in the product information.[61] However, it has been demonstrated that the recommended loading doses of 6 mg/kg 12-hourly for three doses are not sufficient for achieving therapeutic serum concentrations in critically ill patients.[62] Moreover, there are no data available on the effect of hypoalbuminaemia on the antibacterial pharmacokinetics in tissues. This is problematic because tissues are the site of most infections,[9] and variations in unbound pharmacokinetics in serum are likely to affect the concentrations achieved in tissues.

At our institution, given the absence of validated pharmacokinetic data on unbound concentrations in serum and tissues, we commonly prescribe doses that are 50–100% higher than standard doses as a loading dose for highly bound drugs in cases of moderate-to-severe hypoalbuminaemia, in order to compensate for the increased V_d and to enable rapid achievement of therapeutic concentrations during the initial phase of therapy. Thereafter, dose adjustments must be driven by the predicted CL considering albumin levels and other factors that may determine CL, such as renal function, hepatic function and the use of inotropes or fluid resuscitation among others. Table IV provides some recommendations for dose adjustment of highly protein-bound antibacterials in critically ill patients with hypoalbuminaemia and conserved organ function. The applicability of these recommendations, however, is restricted to patients whose renal or hepatic function is conserved.

Given the evidence of low antibacterial concentrations in these clinical scenarios, use of loading doses could be

Table IV. Empirical recommendations for dosing highly protein-bound antibacterials in critically ill patients with hypoalbuminaemia based on available data and authors' own experience

Antibacterial	Standard ICU dosing	Recommended LD in hypoalbuminaemia	Recommended MD in hypoalbuminaemia
β-lactams and carbapenems			
Aztreonam	1 g q8h	2 g q8h for 3 doses	Increase frequency of administration (e.g. 1 g q6h)
Ceftriaxone	1 g q12h	2 g for initial dose	Increase frequency of administration (e.g. 1 g q8h)
Cephalothin			
Flucloxacillin, dicloxacillin, cloxacillin	2 g q6h	2 g	Consider continuous infusion (e.g. 8–12 g q24h)
Ertapenem	1 g q24h	2 g for initial dose	Increase frequency of administration (e.g. 1 g q12h)
Glycopeptides			
Vancomycin	1 g q12h	20–30 mg/kg for initial dose	Increase dosing (e.g. 1.5 g q12h) or consider continuous infusion (e.g. 3 g q24h); monitor trough concentrations to target concentrations of 15–25 mg/L
Teicoplanin	6 mg/kg q12h for 3 doses (LD) and 6 mg/kg q24h (MD)	6 mg/kg q12h for 3 doses	3–6 mg/kg q12h; monitor trough concentrations to target concentrations >15 mg/L
Other highly protein-bound drugs			
Daptomycin	4–6 mg/kg q24h	6–8 mg/kg	6 mg/kg q24h

LD = loading dose; **MD** = maintenance dose; **q*x*h** = every *x* hours.

considered safe for many antibacterials such as β-lactams given they have a wide therapeutic range and are therefore unlikely to result in concentration-related toxicity. In the case of glycopeptides, the use of therapeutic drug monitoring for titrating dosing, after initial loading doses, is the most appropriate approach to aggressively target therapeutic concentrations and minimize the likelihood of antibacterial toxicity.[63]

Many of the new antibacterials that are in development exhibit a high level of albumin binding although the relevance of altered albumin binding is rarely considered in clinical trials in critically ill patients. Pharmaceutical companies should be aware of the possible alterations in pharmacokinetics caused by low albumin levels, and consider implementing albumin-driven dose adjustments as is current practice for renal dysfunction where appropriate. For these studies, use of unbound antibacterial concentrations for pharmacokinetic modelling and dose simulations is essential to provide more clinically relevant results.

Efforts for improving the use of highly protein-bound antibacterials in hypoalbuminaemia should be seen as another step of the antibacterial optimization process. Undoubtedly, further research is recommended for designing dose algorithms for highly albumin-bound antibacterials in hypoalbuminaemia.

10. Conclusions

Outcomes of antibacterial therapy are heavily dependent on achieving therapeutic concentrations of unbound antibacterial at the target site of infection. Effectiveness of empiric dosing is contingent on assumptions that the actual unbound concentrations and antibacterial pharmacokinetics are consistent with those from dose-finding studies. There are emerging data that demonstrate significant pharmacokinetic changes for the total fraction of highly bound antibacterials in patients with hypoalbuminaemia. In the presence of increased CL, the increased V_d appears to still cause a significant prolongation of $t_{½}$ of the drug, which may be therapeutically advantageous for sustaining antibacterial concentrations throughout the dosing interval for highly susceptible pathogens. However, the decreased concentrations resulting from the increased V_d will affect the likelihood of therapeutic success against pathogens with higher MICs and therefore higher doses may be required in such situations. Compounding the sparse level of data available on the serum pharmacokinetics of highly protein-bound antibacterials is the absence of data describing unbound serum pharmacokinetics and tissue (the site of many infections) pharmacokinetics for these drugs in patients with hypoalbuminaemia. Further research on this topic is urgently required.

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References

1. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet 2006; 45 (8): 755-73
2. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009; 37 (3): 840-51
3. Craig WA, Suh B. Changes in protein binding during disease. Scand J Infect Dis Suppl 1978; (14): 239-44
4. Suh B, Craig WA, England AC, et al. Effect of free fatty acids on protein binding of antimicrobial agents. J Infect Dis 1981; 143 (4): 609-16
5. Friend R, Hatchett L, Wadhwa NK, et al. Serum albumin and depression in end-stage renal disease. Adv Perit Dial 1997; 13: 155-7
6. Novak M, Polacek K, Melichar V. Competition between bilirubin and nonesterified fatty acids for binding to albumin. Biol Neonat 1962; 4: 310-5
7. Finfer S, Bellomo R, McEvoy S, et al. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the Saline versus Albumin Fluid Evaluation (SAFE) study. BMJ 2006; 333 (7577): 1044
8. Merrikin DJ, Briant J, Rolinson GN. Effect of protein binding on antibiotic activity in vivo. J Antimicrob Chemother 1983; 11 (3): 233-8
9. Liu P, Derendorf H. Antimicrobial tissue concentrations. Infect Dis Clin North Am 2003; 17 (3): 599-613
10. Goldstein A. The interactions of drugs and plasma proteins. J Pharmacol Exp Ther 1949; 95 Pt. 2 (4): 102-65
11. Tillement JP, Lhoste F, Giudicelli JF. Diseases and drug protein binding. Clin Pharmacokinet 1978; 3 (2): 144-54
12. Fleck A, Raines G, Hawker F, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1985; 1 (8432): 781-4
13. Jarnum S. Turnover of plasma proteins. J Clin Pathol Suppl (Assoc Clin Pathol) 1975; 6: 13-21
14. Kushner I. The phenomenon of the acute phase response. Ann N Y Acad Sci 1982; 389: 39-48
15. Kirsch R, Frith L, Black E, et al. Regulation of albumin synthesis and catabolism by alteration of dietary protein. Nature 1968; 217 (5128): 578-9
16. Heyland DK, Tougas G, King D, et al. Impaired gastric emptying in mechanically ventilated, critically ill patients. Intensive Care Med 1996; 22 (12): 1339-44
17. Cooper JK, Gardner C. Effect of aging on serum albumin. J Am Geriatr Soc 1989; 37 (11): 1039-42
18. Mariani G, Strober W, Keiser H, et al. Pathophysiology of hypoalbuminemia associated with carcinoid tumor. Cancer 1976; 38 (2): 854-60
19. Burkhardt O, Kumar V, Katterwe D, et al. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother 2007; 59 (2): 277-84
20. Joynt GM, Lipman J, Gomersall CD, et al. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 2001; 47 (4): 421-9
21. Lindow J, Wijdicks EF. Phenytoin toxicity associated with hypoalbuminemia in critically ill patients. Chest 1994; 105 (2): 602-4
22. Rello J, Gallego M, Mariscal D, et al. The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 1997; 156 (1): 196-200
23. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34 (6): 1589-96
24. Udy AA, Roberts JA, Boots RJ, et al. Augmented renal clearance: implications for antibiotic dosing in the critically ill. Clin Pharmacokinet 2009; 49 (1): 1-16
25. Mimoz O, Soreda S, Padoin C, et al. Ceftriaxone pharmacokinetics during iatrogenic hydroxyethyl starch-induced hypoalbuminemia: a model to explore the effects of decreased protein binding capacity on highly bound drugs. Anesthesiology 2000; 93 (3): 735-43
26. Donnelly AJ, Baughman VL, Gonzales JP, et al. Anesthesiology & critical care drug handbook. 8th ed. Hudson (OH): Lexi-Comp, 2008
27. MIMS Australia [online]. Available from URL: http://www.mims.com.au/ [Accessed 2009 Dec]
28. Dalley AJ, Deans R, Lipman J, et al. Unbound cephalothin pharmacokinetics in adult burn patients are related to the elapsed time after injury. Antimicrob Agents Chemother 2009; 53 (12): 5303-5
29. Ulldemolins M, Roberts J, Wallis S, et al. Flucloxacillin dosing in critically ill patients with hypoalbuminemia: special emphasis on unbound pharmacokinetics. J Antimicrob Chemother 2010; 65 (8): 1771-8
30. Boselli E, Breilh D, Saux MC, et al. Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia. Intensive Care Med 2006; 32 (12): 2059-62
31. Brink AJ, Richards GA, Schillack V, et al. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. Int J Antimicrob Agents 2009; 33 (5): 432-6
32. Seguin P, Verdier MC, Chanavaz C, et al. Plasma and peritoneal concentration following continuous infusion of cefotaxime in patients with secondary peritonitis. J Antimicrob Chemother 2009; 63 (3): 564-7
33. Bubalo JS, Munar MY, Cherala G, et al. Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. Antimicrob Agents Chemother 2009; 53 (2): 428-34
34. Mimoz O, Rolland D, Adoun M, et al. Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia. Intensive Care Med 2006; 32 (5): 775-9
35. Swabb EA, Leitz MA, Pilkiewicz FG, et al. Pharmacokinetics of the monobactam SQ 26,776 after single intravenous doses in healthy subjects. J Antimicrob Chemother 1981; 8 Suppl. E: 131-40
36. Janicke DM, Cafarell RF, Parker SW, et al. Pharmacokinetics of aztreonam in patients with Gram-negative infections. Antimicrob Agents Chemother 1985; 27 (1): 16-20
37. Friedrich LV, White RL, Kays MB, et al. Aztreonam pharmacokinetics in burn patients. Antimicrob Agents Chemother 1991; 35 (1): 57-61
38. Stoeckel K, McNamara PJ, Brandt R, et al. Effects of concentration-dependent plasma protein binding on ceftriaxone kinetics. Clin Pharmacol Ther 1981; 29 (5): 650-7
39. Van Dalen R, Vree TB, Baars IM. Influence of protein binding and severity of illness on renal elimination of four cephalosporin drugs in intensive-care patients. Pharm Weekbl Sci 1987; 9 (2): 98-103
40. Landersdorfer CB, Kirkpatrick CM, Kinzig-Schippers M, et al. Population pharmacokinetics at two dose levels and pharmacodynamic profiling of flucloxacillin. Antimicrob Agents Chemother 2007; 51 (9): 3290-7

41. Pletz MW, Rau M, Bulitta J, et al. Ertapenem pharmacokinetics and impact on intestinal microflora, in comparison to those of ceftriaxone, after multiple dosing in male and female volunteers. Antimicrob Agents Chemother 2004; 48 (10): 3765-72

42. Outman WR, Nightingale CH, Sweeney KR, et al. Teicoplanin pharmacokinetics in healthy volunteers after administration of intravenous loading and maintenance doses. Antimicrob Agents Chemother 1990; 34 (11): 2114-7

43. Barbot A, Venisse N, Rayeh F, et al. Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med 2003; 29 (9): 1528-34

44. Healy DP, Polk RE, Garson ML, et al. Comparison of steady-state pharmacokinetics of two dosage regimens of vancomycin in normal volunteers. Antimicrob Agents Chemother 1987 Mar; 31 (3): 393-7

45. Fernandez de Gatta Garcia M, Revilla N, Calvo MV, et al. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 2007; 33 (2): 279-85

46. Dvorchik BH, Brazier D, DeBruin MF, et al. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. Antimicrob Agents Chemother 2003; 47 (4): 1318-23

47. Mohr 3rd JF, Ostrosky-Zeichner L, Wainright DJ, et al. Pharmacokinetic evaluation of single-dose intravenous daptomycin in patients with thermal burn injury. Antimicrob Agents Chemother 2008; 52 (5): 1891-3

48. Taburet AM, Guibert J, Kitzis MD, et al. Pharmacokinetics of sodium fusidate after single and repeated infusions and oral administration of a new formulation. J Antimicrob Chemother 1990; 25 Suppl. B: 23-31

49. Peter JD, Jehl F, Pottecher T, et al. Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. Antimicrob Agents Chemother 1993; 37 (3): 501-6

50. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998; 26 (1): 1-10

51. Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. Clin Pharmacokinet 2001; 40 (9): 685-94

52. Jungbluth GL, Pasko MT, Beam TR, et al. Ceftriaxone disposition in open-heart surgery patients. Antimicrob Agents Chemother 1989; 33 (6): 850-6

53. Bonate PL. Pathophysiology and pharmacokinetics following burn injury. Clin Pharmacokinet 1990; 18 (2): 118-30

54. Brogard JM, Haegele P, Kohler JJ, et al. The biliary excretion of cephalothin. Chemotherapy 1973; 18 (4): 212-21

55. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev 2004; 2 (4): 289-300

56. Leroy A, Fillastre JP, Borsa-Lebas F, et al. Pharmacokinetics of meropenem (ICI 194,660) and its metabolite (ICI 213,689) in healthy subjects and in patients with renal impairment. Antimicrob Agents Chemother 1992; 36 (12): 2794-8

57. INVANZ® [ertapenem for injection]: US prescribing information. Whitehouse Station (NJ): Merck Sharp & Dohme Corp., 2010 Mar [online]. Available from URL: http://www.merck.com/product/usa/pi_circulars/i/invanz/invanz_pi.pdf [Accessed 2010 Nov 16]

58. Boswell FJ, Ashby JP, Andrews JM, et al. Effect of protein binding on the in vitro activity and pharmacodynamics of faropenem. J Antimicrob Chemother 2002; 50 (4): 525-32

59. Soy D, Lopez E, Ribas J. Teicoplanin population pharmacokinetic analysis in hospitalized patients. Ther Drug Monit 2006; 28 (6): 737-43

60. Godtfredsen WO, Vangedal S. On the metabolism of fusidic acid in man. Acta Chem Scand 1966; 20 (6): 1599-607

61. Targocid (teicoplanin): Australian product information. Macquarie (NSW): Sanofi-Aventis Australia Pty Ltd, 2009 Jul 6 [online]. Available from URL: http://www.sanofi-aventis.com.au/products/aus_pi_targocid.pdf [Accessed 2010 Nov 12]

62. Brink AJ, Richards GA, Cummins RR, et al. Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. Int J Antimicrob Agents 2008; 32 (5): 455-8

63. MacGowan AP. Pharmacodynamics, pharmacokinetics, and therapeutic drug monitoring of glycopeptides. Ther Drug Monit 1998; 20 (5): 473-7

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