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ORIGINAL RESEARCH ARTICLE

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

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

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**Abstract**

*Introduction* In hypo-albuminemia, the extent of albumin binding of a drug decreases. The resulting change in plasma protein binding only rarely leads to clinically relevant changes in unbound drug exposure. Nevertheless, in the critically ill, a tendency to increase dosing of anti-infective therapy is seen in patients experiencing hypo-albuminemia. To reconcile basic pharmacological principles with current clinical practice, this work presents a pharmacologically-based pharmacokinetic simulation study to emphasize the (lack of) effect of altered plasma protein binding on a drug's concentration–time profile and associated pharmacokinetic parameters.

*Methods* Four virtual compounds, representing a broad chemical space (low/high clearance/volume of distribution), were created and administered to a virtual population of normal patients and three types of hypo-albuminemic patients in Simcyp®. The influence of decreased plasma protein binding in hypoalbuminemia on the pharmacokinetic parameters and profiles of these four compounds was investigated.

*Results* Simulation results showed that while high-clearance compounds suffer from increased unbound exposure with decreased plasma protein binding, the unbound exposure of low-clearance compounds was unaffected. However, for the subset of low-clearance compounds with a small volume of distribution, it appeared that there were still alterations in their plasma concentration-time profiles. Since this may lead to different times above a minimum inhibitory concentration value, this might affect the bacterial killing for some anti-infective drugs. Overall, for any compound involved in the simulations, the unbound exposure did not decrease in plasma protein binding subjects relative to normal plasma protein binding subjects.

*Discussion* This finding is in line with the few case-controlled studies in the literature. Hence, increasing the dose/dosing frequency seems futile and might reduce the benefit-risk ratio for narrow therapeutic index drugs. Moreover, these simulations indicate that when only total plasma concentrations and derived pharmacokinetic parameters are considered, incorrect conclusions will be drawn.

**Key Points**

Physiologically based pharmacokinetic simulations may be used to simulate the time course of plasma concentration in situations of changed plasma protein binding.

The reduction in plasma protein binding did not result in a decreased unbound drug exposure in any of the simulations.

Biased conclusions and inappropriate dosing may result from the measurement of total plasma concentrations in situations of reduced plasma protein binding.

**Electronic supplementary material** The online version of this article (doi:10.1007/s40262-017-0549-x) contains supplementary material, which is available to authorized users.

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## 1 Introduction

According to pharmacological principles, it is typically assumed that a drug's effects are linked to unbound drug concentrations at the site of action ($PK_{Unbound}$) (free drug hypothesis) [1]. An on-going discussion in the literature is whether alterations in plasma protein levels can result in changes in a drug's $PK_{Unbound}$ and hence treatment effects. Decreased plasma protein levels, more specifically hypo-albuminemia, are observed in different patient subpopulations [2, 3] including pregnant women, burn patients, and the critically ill (intensive care) patients.

Hence, the extent of plasma protein binding (PPB) of a drug is expected to be lower in this case if the drug is bound to albumin [4, 5]. In the literature, several authors reviewed the possible influence of alterations in PPB on unbound drug exposure [unbound area under the concentration–time curve ($AUC_u$)] [6–8]. Overall, it is thought that alterations in PPB will only rarely lead to clinically relevant changes in $AUC_u$. Based on theoretical considerations, the only 'class' of drugs where $AUC_u$ is expected to change significantly with altered PPB is intravenously administered high-clearance (CL) drugs (>0.3 $Q_{organ}$) showing high PPB (>70%) [6].

However, concerns regarding the need for changes in drug dosing continue to exist for those drugs whose effects are related to unbound concentrations ($C_u$) over time, rather than to the unbound total exposure ($AUC_u$). The β-lactam antibiotics are one of the classes of drugs where the pharmacological effect is related to $C_u$ [time above the minimum inhibitory concentration (MIC) of the invading pathogen] rather than to $AUC_u$ [9–11]. For this class of drugs to demonstrate an adequate effect, the $C_u$ should remain above a pre-defined target value (MIC) for a certain fraction of the dosing interval.

Ulldemolins et al. [3] studied the effects of hypo-albuminemia on β-lactam antibacterial dosing in critically ill patients by reviewing all published pharmacokinetic (PK) studies in populations with low albumin levels. They found that the incidence of low serum albumin levels is very common in critically ill patients (40–50%) and might impact drug pharmacokinetics in such a way that antibacterial dosing modifications are required. In their conclusions, these authors underline the importance of their findings by stating that "Pharmaceutical companies should […] consider implementing albumin-driven dose adjustments as is current practice for renal dysfunction where appropriate" [3]. Roberts et al. [12] further expanded on this topic. In their paper, more theoretical considerations were presented to stress the relevance of altered PPB for antibacterial dosing regimens. According to these authors, caution is advised, especially in the case of high-CL antibacterial drugs when hypo-albuminemia is expected.

In this debate, although the $AUC_u$ is not expected to change for β-lactam antibiotics, clinicians recommend dose adjustments in patients with hypo-albuminemia because of a potential change in unbound plasma concentrations as a function of time. The missing link in this instance is the availability of $C_u$ in well-designed case-controlled studies. Therefore, a case-controlled simulation study was undertaken using the physiologically based PK (PBPK) modeling and simulation platform, Simcyp® (a Certara Company, Princeton, NJ, USA). The impact of changes in PPB on the total and unbound plasma concentrations of a test set of virtual drugs was assessed. Not only the total exposure (AUC), but also the tissue distribution and plasma concentration–time profiles for the total and unbound drug are considered. Simcyp® is a well-known modeling and simulation platform, used to build customized whole-body PBPK models [13]. In these models, information that is drug specific (physicochemical and in vitro metabolism) and system specific (physiological) is clearly distinguished. Therefore, changes in a specific system parameter (e.g., circulating plasma albumin levels) can be studied without altering the intrinsic interaction behavior of the drug and the system components. In addition, variability can be incorporated into the simulations by creating virtual populations, which are based on genetic, physiological, and demographic information, available from population databases obtained from the literature. For general information regarding the Simcyp® platform and technical aspects regarding bottom-up PK predictions, the reader is referred to the following review articles [14, 15].

In the current simulation study, a PBPK modeling and simulation approach is applied to elucidate the role of changes in PPB on drug pharmacokinetics in normal and hypo-albuminemic populations. Subsequently, conclusions are drawn by comparing the results from the simulations to reported results from properly designed case-controlled studies from the literature.

## 2 Methods

### 2.1 Structural Pharmacologically Based Pharmacokinetic Model

In this simulation exercise, an intravenous whole body-PBPK model was constructed. The Rodgers and Rowland equations were used for predicting the compound's distribution [16]. Unbound unionized drug is assumed in equilibrium between plasma, interstitial, and intracellular space. The bound and ionized drug concentrations present

in each compartment are calculated by accounting for the binding proteins and the pH specific per space, respectively. Drug binding to proteins (albumin) is described by the association constant $Ka_{PR}$. More details on the workflow and the different equations used in describing the drug-binding behavior are provided in the Electronic Supplementary Material (ESM).

Liver CL is described by the dynamic well-stirred liver model, which assumes that drug concentration is homogenous throughout the liver and in equilibrium with that in the hepatic vein. Equations 1 and 2 provide static and dynamic forms of this liver model. Although the dynamic form is used in the simulations, the static form is provided as well, as it may help the reader in Sect. 3 to relate changes in PK parameters to changes in the unbound drug fraction. Renal CL is assumed to be governed by glomerular filtration only (Eq. 3), representing 12% of renal blood flow. Throughout this simulation study, metabolism kinetics and protein binding were assumed to be linear.

$$\mathrm{CL_H} = \frac{Q_\mathrm{H} * \mathrm{fu_p} * \mathrm{CLint_H}}{Q_\mathrm{H} + \mathrm{fu_p} * \mathrm{CLint_H}}, \quad (1)$$

where $Q_H$ is hepatic blood flow, $\mathrm{fu_p}$ is the drug fraction unbound in plasma, and $\mathrm{CLint}_H$ is intrinsic hepatic CL.

$$\mathrm{dC_{liver}} = \frac{1}{V_\mathrm{liver}}\left[Q_\mathrm{PV} * C_\mathrm{pv} + Q_\mathrm{HA} * C_\mathrm{sys} - (\mathrm{fu_P}/\mathrm{BP} * \mathrm{CLint_H} + Q_\mathrm{PV} + Q_\mathrm{HA}) * C_\mathrm{liver}\right], \quad (2)$$

where $Q_\mathrm{PV}$, $Q_\mathrm{HA}$ is hepatic blood from the portal vein and hepatic artery, respectively, *BP* is the blood-to-plasma ratio, $\mathrm{CLint_H}$ is hepatic intrinsic CL, and $C_\mathrm{pv}$, $C_\mathrm{sys}$, and $C_\mathrm{liver}$ are portal vein, systemic, and liver concentrations, respectively.

$$\mathrm{CL_R} = \mathrm{fu_P} * \mathrm{GFR} \quad (3)$$

## 2.2 Study Compounds

A matrix of four hypothetical compounds was created that represents low/high steady-state volume of distribution ($V_\mathrm{ss}$) and low/high CL. Details on the physicochemical properties, blood, PPB, and elimination pathways can be found in Table 1. The prediction of the $V_\mathrm{ss}$ depends on the compound's physicochemical properties: pKa, blood-to-plasma ratio, and the dissociation constant (Kd) of the drug-albumin complex [16]. These parameters were kept constant across simulations, such that the only factor affecting $V_\mathrm{ss}$ would be the lipophilicity (logP) of the compound. A monoprotic acid with a pKa of 12 was chosen for the simulations, as such a compound would be un-ionized across the whole physiological pH range (see ESM for more information). LogP values of 0.5 and 3 represent a hydrophilic compound with a low $V_\mathrm{ss}$ and a lipophilic compound with a high $V_\mathrm{ss}$, respectively (Table 1). Although the logP is different for both compounds, their Kd is the same, yielding the same extent of PPB. The blood-to-plasma ratio is 1, indicating passive permeation to blood cells without accumulation in erythrocytes. The hepatic extraction per compound was varied by selecting a low and a high hepatic intrinsic CL ($\mathrm{CLint_H}$) value. Renal CL was predicted based on the unbound fraction in plasma and the glomerular filtration rate.

**Table 1** Drug-specific inputs used for the virtual drugs in the physiologically based pharmacokinetic modeling and simulation platform

| | Low $V_\mathrm{ss}$ | | High $V_\mathrm{ss}$ | |
|---|---|---|---|---|
| | Low CL | High CL | Low CL | High CL |
| Drug-specific input parameters | | | | |
| Compound type | Monoprotic acid | | Monoprotic acid | |
| pKa | 12 | | 12 | |
| B/P ratio | 1 | | 1 | |
| $\mathrm{Kd_{PR}}$ (μM) | 7.18 | | 7.18 | |
| logP | 0.5 | | 3 | |
| $\mathrm{CLint_H}$ (μL/min/mg MP) | 50 | 20,000 | 50 | 20,000 |
| $\mathrm{CL_R}$ (L/h) | $\mathrm{fu_p}$ * GFR | | $\mathrm{fu_p}$ * GFR | |
| Trial design parameters | | | | |
| Dose | 100 mg iv bolus | | 100 mg iv bolus | |
| Study duration time (h) | 24 | 5 | 96 | 24 |

*B/P ratio* blood-to-plasma ratio, *CL* clearance, $CLint_H$ hepatic intrinsic clearance, $CL_R$ renal clearance, $fu_p$ drug fraction unbound in plasma, *GFR* glomerular filtration rate, *iv* intravenous, $Kd_{PR}$ dissociation constant of the protein-drug complex, *MP* microsomal protein, $V_\mathrm{ss}$ steady-state volume of distribution

## 2.3 Study Populations

In a normal albuminemic situation ('NORMO', Fig. 1), 60% of albumin is situated in the extravascular space, while 40% is situated intravascularly. The albumin level in tissue water depends on the tissue itself, with most of the albumin residing in muscle tissue [17]. In Simcyp®, the healthy volunteer North Caucasian population was selected as the normo-albuminemic population, with a typical albumin plasma concentration of 47.28 g/L or 705.67 μM.

In all three hypo-albuminemic ('HYPO') scenarios investigated, intravascular albumin levels were assumed to drop by 50%. HYPO1 represents the 'capillary leakage' scenario, encountered in patients undergoing cardiac surgery or with sepsis [18, 19]. In this case, 50% of the intravascular albumin mass was assumed to distribute into the extravascular tissue water, according to the different perfusion rates to the corresponding tissues (see ESM). HYPO2 represents the case where a 50% drop in the intravascular albumin level is achieved without a change in

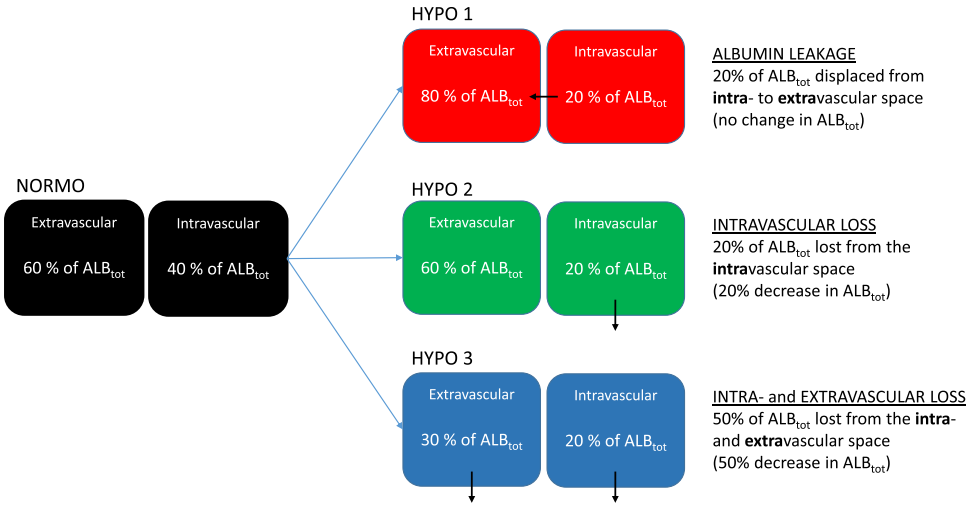


**Fig. 1** Overview of the normo- and hypo-albuminemic populations used in this simulation study. The *black* scenario represents the normal albuminemic situation (NORMO). *Red*, *green*, and *blue* scenarios represent different hypo-albuminemic situations, in which leakage/removal of albumin is indicated with the *black arrows*. HYPO1 (*red*) represents the albumin leakage case, HYPO2 (*green*) represents intravascular loss, and HYPO3 (*blue*) represents intra- and extravascular loss. $ALB_{tot}$ total albumin

the extravascular levels (intravascular loss). This may be the case in e.g., burns, dermatitis, and open wounds [20]. Hence, the ratio of tissue-to-plasma albumin levels is doubled, compared with the normal situation (see ESM). HYPO3 represents a situation in which 50% of the total albumin mass in the intra- and extravascular space is removed. This scenario may happen in situations of hepatic impairment where the total production of albumin is impaired and eventually the same steady-state distribution of albumin between the intra- and extravascular space may be maintained, albeit with lower plasma albumin levels. As a consequence, in this scenario, the ratio of tissue-to-plasma albumin levels for every tissue remains unchanged compared with the normal situation (see ESM). To focus specifically on the influence of PPB on unbound and total pharmacokinetics, we did not assume any fluid extravasation from the intravascular to the extravascular space (third spacing).

### 2.4 Virtual Clinical Trial Design

Simulations were performed in a typical individual of a normo-albuminemic population and three different hypo-albuminemic populations. Each compound was administered as a 100-mg intravenously administered bolus dose. For the low-CL low-volume virtual drug, an infusion design was also implemented by infusing 100 mg over 32 h. The PK parameters of CL (calculated from D/AUC), $V_{ss}$, and $fu_p$ that corresponded with total plasma concentrations were collected from the Simcyp® output. The unbound PK parameters of CL ($CL_u$) and volume of distribution ($V_{ss,u}$) were obtained by dividing the PK parameters with the $fu_p$. For every compound, the PK parameters for total concentrations and $C_u$ were compared per scenario. To capture the complete plasma concentration–time curve, the virtual study duration times were different per compound and are indicated in Table 1.

## 3 Results

### 3.1 Effect of Plasma Protein Binding on Pharmacokinetic Parameters

Table 2 displays the impact of changed PPB as a consequence of altered albumin distributions on the prediction of $fu_p$, CL, and $CL_u$. The $fu_p$ value in the hypo-albuminemic scenarios increased twofold vs. the baseline value in the normal situation. The CL or $CL_u$ prediction in the normal albuminemic population ('NORMO') is considered the baseline value to compare with the different hypo-albuminemic scenarios ('HYPO1', 'HYPO2', and 'HYPO3'). For low-CL drugs, the CL is doubled in every hypo-albuminemic scenario, independent of the extent of distribution (logP), and is linearly correlated with the increase in $fu_p$. For high-CL drugs, CL remains unchanged (5% change is considered negligible). For low-CL drugs, $CL_u$ is unchanged, although for high-CL drugs it is decreased by half. Table 3 displays the impact of changed PPB on the prediction of $V_{ss}$ and $V_{ss,u}$. Although the $fu_p$ is the same for every hypo-albuminemic scenario, the prediction of $V_{ss}$ and

**Table 2** Effect of plasma protein binding on drug fraction unbound in plasma ($fu_p$), clearance (CL), and unbound clearance ($CL_u$) for different albumin distribution scenarios: NORMO, HYPO1, HYPO2, and HYPO3

| % Change from baseline | | Low/high logP | | |
|---|---|---|---|---|
| | | $fu_p$ | CL | $CL_u$ |
| Low CLint | NORMO | Baseline (0.01) | Baseline (2.07 L/h) | Baseline (207 L/h) |
| | HYPO1 | +98% | +93% | −3% |
| | HYPO2 | +98% | +93% | −3% |
| | HYPO3 | +98% | +93% | −3% |
| High CLint | NORMO | Baseline (0.01) | Baseline (79.45 L/h) | Baseline (7945 L/h) |
| | HYPO1 | +98% | +5% | −47% |
| | HYPO2 | +98% | +5% | −47% |
| | HYPO3 | +98% | +5% | −47% |

*CLint* intrinsic clearance, *HYPO1* represents the albumin leakage case, *HYPO2* represents intravascular loss, *HYPO3* represents intra- and extravascular loss, *NORMO* represents the normal albuminemic situation

**Table 3** Effect of plasma protein binding on steady-state volume of distribution ($V_{ss}$) and unbound steady-state volume of distribution ($V_{ss,u}$) for different albumin distribution scenarios: NORMO, HYPO1, HYPO2, and HYPO3

| % change from baseline | | Low logP | | High logP | |
|---|---|---|---|---|---|
| | | $V_{ss}$ | $V_{ss,u}$ | $V_{ss}$ | $V_{ss,u}$ |
| Low/high CLint | NORMO | Baseline (10 L) | Baseline (995 L) | Baseline (42 L) | Baseline (4200 L) |
| | HYPO1 | +76% | −12% | +91% | −4% |
| | HYPO2 | +41% | −29% | +84% | −8% |
| | HYPO3 | +4% | −48% | +76% | −12% |

*CLint* intrinsic clearance, *HYPO1* represents the albumin leakage case, *HYPO2* represents intravascular loss, *HYPO3* represents intra- and extravascular loss, *NORMO* represents the normal albuminemic situation

$V_{ss,u}$ changes per scenario. The $V_{ss}$ displays the greatest change for compounds with a relatively high lipophilicity. The changes in $V_{ss,u}$ are highest for low logP compounds, i.e., in the HYPO2 and HYPO3 situations.

### 3.2 Effect of Plasma Protein Binding on Plasma Concentration–Time Profiles

The plasma concentration–time profiles for each compound are provided in the multi-panel plot below (Fig. 2). Solid lines represent total concentrations, while $C_u$ are represented by dashed lines. The normal albuminemic scenario is indicated in black (reference situation), while HYPO1, HYPO2, and HYPO3 are colored (red, green, and blue) in the graph. The first row represents PK profiles for low-CL compounds with a low (left) and a high volume of distribution [Vd] (right). The second row represents PK profiles for high-CL compounds with a low (left) and a high Vd (right). For low-CL compounds, the recorded time after a single bolus dose is longer than for the high-CL counterparts (Fig. 2a, b) because we need at least five recorded half-lives. Compounds exhibiting a high Vd (high logP) may be distinguished from the low-distribution compounds, in that the concentrations from all hypo-albuminemic simulations overlap. For low-distribution compounds, the total concentrations and $C_u$ are different for every simulation.

In addition, Table 4 provides data on the comparison of $AUC_u$ values and the time above MIC and how these change across the different scenarios. An arbitrary MIC value was chosen for the low- and high-CL situations as is indicated in the plots in Fig. 2.

For the sake of clarity, Fig. 3 represents an additional infusion design for low-CL low-distribution drugs in normal and hypo-albuminemic situations. From this figure, it can be derived that both $CL_u$ and $C_{ss,u}$ are unchanged (the small difference of +3%, also observed for the $CL_u$ in Table 2, is considered to be negligible). However, hypo-albuminemia does impact the time to reach the steady state in this case.

## 4 Discussion

### 4.1 Simulation Study

This simulation study investigates the effect of altered PPB on the total exposure and plasma concentration–time profiles of a set of four virtual compounds. The Simcyp®

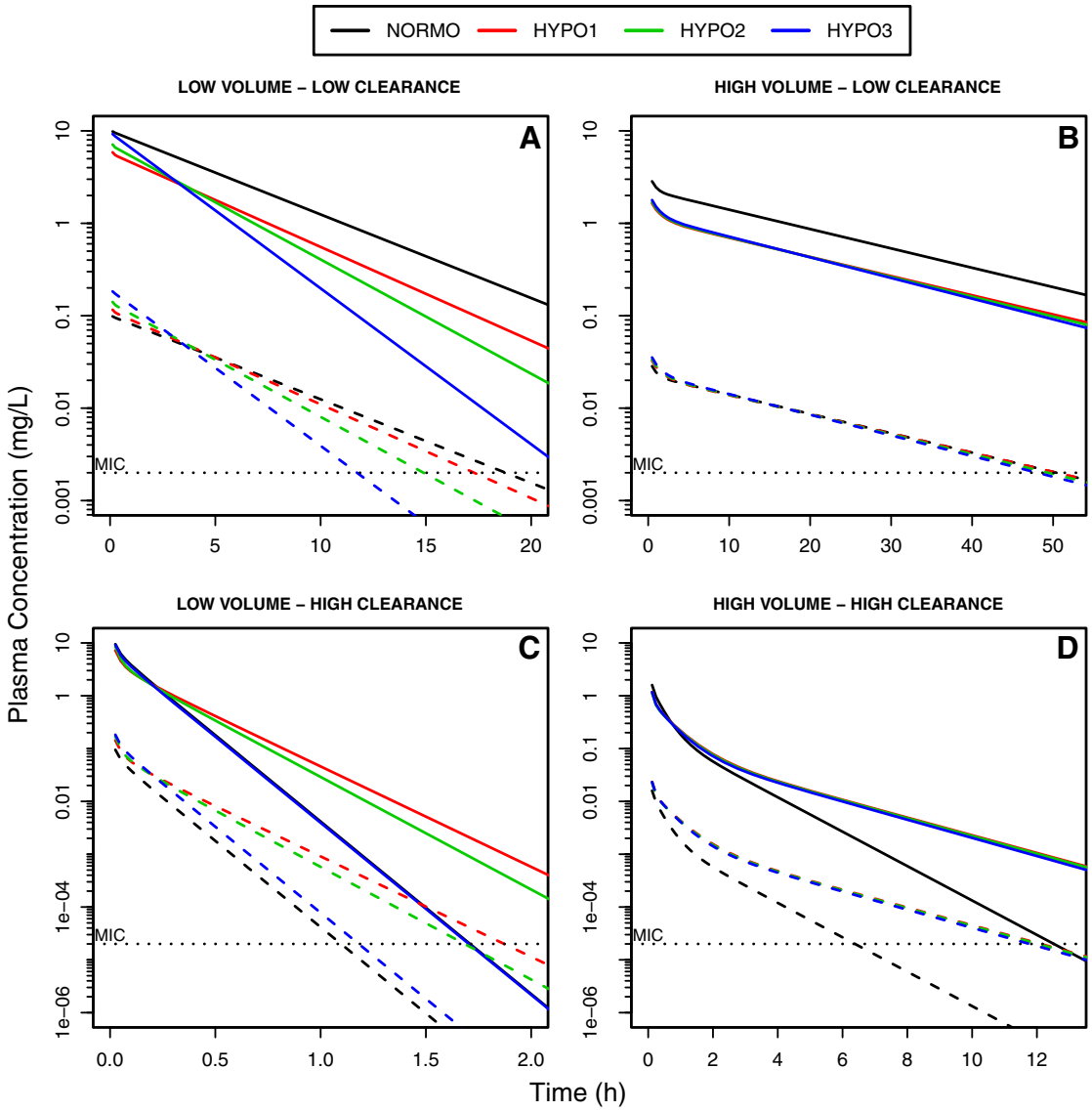


**Fig. 2** Multi-panel plot with plasma concentration–time profiles for total (*solid*) and unbound (*dashed*) concentrations. The legends indicate the different colors used to distinguish normal from hypoalbuminemic scenarios. Every panel illustrates one virtual compound: low distribution/low clearance (**a**), high distribution/low clearance (**b**), low distribution/high clearance (**c**), and high distribution/high clearance (**d**). The *dotted line* represents a hypothetical minimal inhibitory concentration of 0.002 mg/L for low-clearance drugs and 0.0002 mg/L for high-clearance drugs. The significance is further discussed in Table 4. *HYPO1* represents the albumin leakage case, *HYPO2* represents intravascular loss, *HYPO3* represents intra- and extravascular loss, *NORMO* represents the normal albuminemic situation

physiologically based modeling and simulation platform was used to gain mechanistic insights into the clinically observed association between altered plasma protein levels and altered drug pharmacokinetics. It is important to stress that in a clinical setting it is often impossible to reliably study the causal relationship between a particular patient covariate (in this case, plasma albumin levels) and alterations in drug pharmacokinetics. However, using in silico PK prediction tools, the possibility exists to alter one specific covariate of the virtual population at a time and assess its impact on predicted drug behavior (case-controlled study design). Four virtual compounds were designed to represent a broad physicochemical space (low-to-high lipophilicity), with low-to-high intrinsic CL. The value of $CLint_H$ determines the extent of predicted hepatic CL (range 2–80 L/h), whereas the lipophilicity (logP) determines the distribution characteristics of the virtual compounds (range 10–42 L) (Tables 2, 4). Accordingly,

**Table 4** Changes in unbound area under the concentration–time curve ($AUC_u$) and time above minimum inhibitory concentration (MIC) for the different simulated scenarios and compounds

| | $AUC_u$ | Time above MIC |
|---|---|---|
| Low volume, low clearance | | |
| NORMO | Baseline (0.483 mg*h/L) | Baseline (18.8 h) |
| HYPO1 | +3% | −7% |
| HYPO2 | +3% | −20% |
| HYPO3 | +3% | −37% |
| High volume, low clearance | | |
| NORMO | Baseline (0.483 mg*h/L) | Baseline (50 h) |
| HYPO1 | +3% | +0% |
| HYPO2 | +3% | −1% |
| HYPO3 | +3% | −3% |
| Low volume, high clearance | | |
| NORMO | Baseline (0.0126 mg*h/L) | Baseline (1.1 h) |
| HYPO1 | +89% | +71% |
| HYPO2 | +89% | +53% |
| HYPO3 | +89% | +7% |
| High volume, high clearance | | |
| NORMO | Baseline (0.0126 mg*h/L) | Baseline (6.3 h) |
| HYPO1 | +89% | +90% |
| HYPO2 | +89% | +90% |
| HYPO3 | +89% | +85% |

*HYPO1* represents the albumin leakage case, *HYPO2* represents intravascular loss, *HYPO3* represents intra- and extravascular loss, *NORMO* represents the normal albuminemic situation

the effects of altered PPB could be investigated for compounds that undergo low or extensive hepatic elimination in combination with a limited or an extensive distribution.

#### 4.1.1 *Effect of Plasma Protein Binding on Total and Unbound Exposure*

First, the total and unbound exposure results of our simulation study were checked with concepts put forward in the paper by Benet and Hoener [6]. For low-CL drugs, $AUC_u$ and hence $CL_u$ should not change when PPB alterations occur ($CL_u = D/AUC_u$). For these compounds, $CL_u$ is indeed unchanged in our simulations (a change of 3% is considered negligible) for every hypo-albuminemic scenario (Table 2). Because in the well-stirred liver model (Eq. 1) $CL_u$ represents the intrinsic CL, and it is unchanged, this correctly indicates that there is no change in intrinsic elimination properties of the organism. The opposite is true for high-CL drugs. As was also indicated by Benet and Hoener [6], the CL of compounds with a high CLint is limited by the blood flow to the eliminating organ. For these compounds, the $CL_u$ is dependent on the unbound fraction in plasma ($CL_u = Q_H/fu_p$), which is confirmed in our simulations: $CL_u$ is halved for every hypo-albuminemic scenario (Table 2).

Our simulation results regarding total/unbound exposure (or CL) are hence fully aligned to the ones from the Benet and Hoener article [6]: "High extraction ratio drugs (either orally or intravenously administered) eliminated by a high extraction process (hepatic–nonhepatic) will exhibit changes in unbound drug exposure when protein binding changes."

#### 4.1.2 *Effect of Plasma Protein Binding on Tissue Distribution*

To quantify the presumed effect of PPB on tissue distribution, the total $V_{ss}$ and $V_{ss,u}$ are evaluated. Compounds with a high logP value display a more extensive tissue distribution. For these compounds, an increase in the unbound fraction in plasma is expected to result in a proportional increase in $V_{ss}$ [21]. As a consequence, the $V_{ss,u}$ should remain constant. This can only be the case if there is no change in tissue binding. This makes perfect physiological sense because compounds with a high Vd that bind to tissue components have a large number of binding options. Therefore, a change in $fu_p$ would not necessarily result in a change in $fu_t$. The opposite is true for compounds with a small Vd, displaying high protein (albumin) binding. In this case, the Vd is much more dependent on the distribution of albumin itself. Indeed, albumin is not retained intravascularly, but escapes the capillaries through wide-open sinusoids and fenestrated capillaries. As a consequence, the distribution of albumin in healthy subjects is 7.5 L, which is indicative of distribution across the capillary wall [17, 21]. For low-distribution highly bound compounds, albumin determines the binding capacity in intravascular and extravascular spaces, implying that the albumin distribution becomes the sole determinant of plasma ($fu_p$) and tissue ($fu_t$) binding. The advantage of our applied PBPK approach is that it accounts for differences in drug binding across tissues (tissue-specific $Kp_u$), instead of assuming a similar binding in one 'lumped' tissue compartment only ($fu_t$ in $V_d = V_p + fu_p/fu_t * V_t$).

Our results indicate that the $V_{ss}$ and $V_{ss,u}$ values in Table 3 differ between the normal and each of the hypo-albuminemic scenarios, for low as well as high lipophilic compounds. As pointed out earlier, the $fu_p$ from the normal ($fu_p = 0.01$) to the hypo-albuminemic ($fu_p = 0.0198$) situation almost doubled and is identical for every hypo-albuminemic situation. For compounds with a high lipophilicity, it is expected that $V_{ss}$ would increase linearly with $fu_p$ and that $V_{ss,u}$ would remain constant. In our study, however, the increase in $V_{ss}$ is less than proportional with $fu_p$ and the $V_{ss,u}$ is decreased, depending on the hypo-

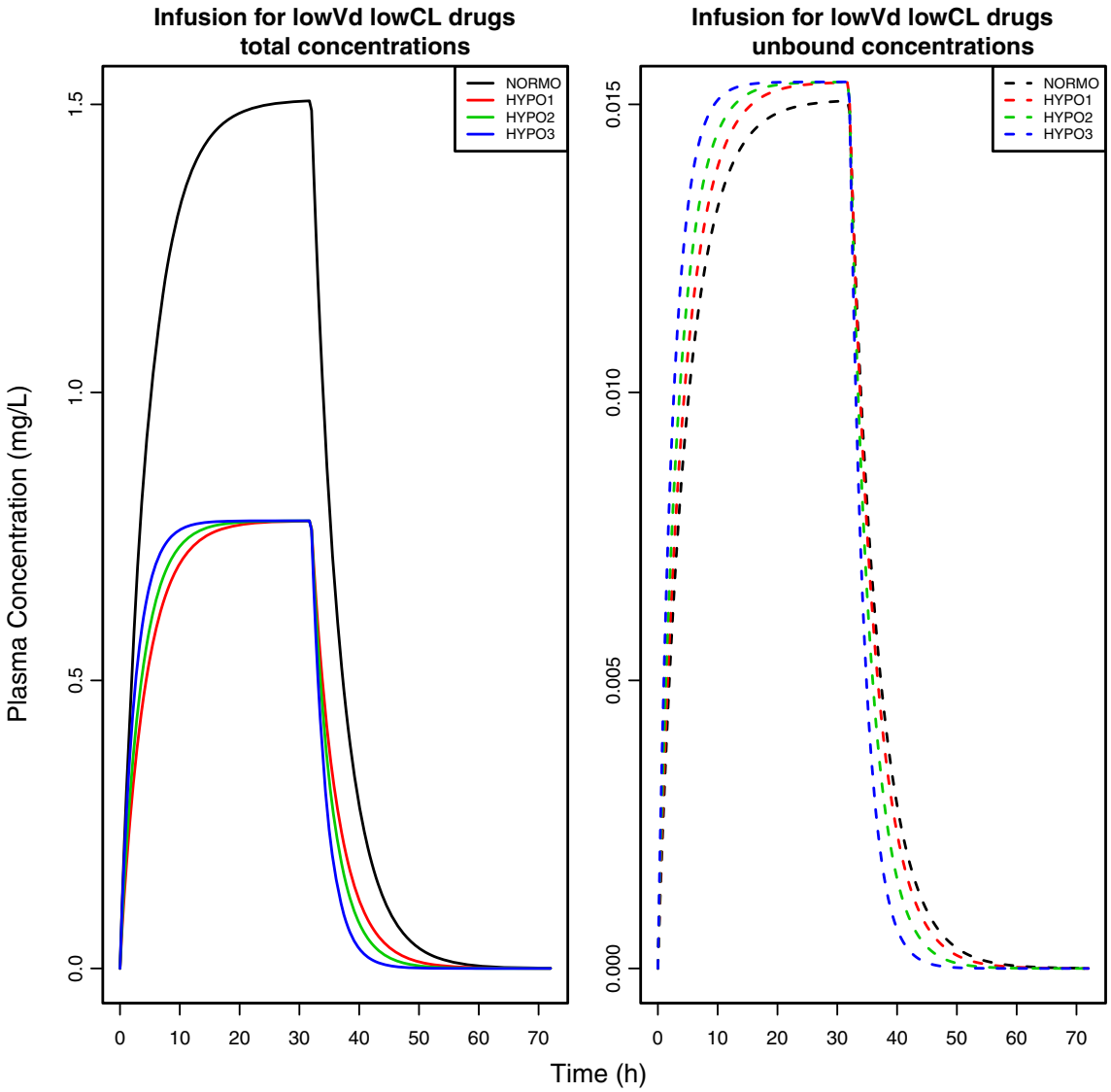


**Fig. 3** Infusion simulation for the normal and hypo-albuminemic scenarios. While total steady-state concentrations differ twofold, the unbound steady-state concentration is nearly identical between normal and hypo-albuminemic scenarios. Total plasma concentrations on the *left*, unbound plasma concentrations on the *right*. *CL* clearance, *Vd* volume of distribution

albuminemic scenario (Table 3). This can be explained because the Vd for these high logP compounds still is not very high, only 42 L. As a consequence, the influence of changed intravascular to extravascular ratios for albumin still impact the Vd to a minor extent. For compounds with a low lipophilicity and hence a small Vd, changes in $V_{ss}$ and $V_{ss,u}$ are harder to anticipate. $V_{ss}$ increases by 76%, 41%, and 4%, while the $V_{ss,u}$ decreases by 12%, 29%, and 48% for HYPO scenarios 1, 2, and 3, respectively.

#### *4.1.3 Time-Dependent Effects of Altered Plasma Protein Binding*

Plasma concentration–time profiles were simulated to investigate the effects of altered albumin distributions for the four hypothetical compounds. These profiles over time are especially relevant to study those drugs that are administered in hypo-albuminemic cases, and whose effects are linked to the time their effective concentration is higher than a certain minimal level (e.g., MIC), such as some anti-infective agents [22]. For high-CL compounds, when plasma albumin levels are halved, total drug concentrations in plasma are decreased (in line with an elevated $V_{ss}$) and $AUC_u$ increased, indicative of a decreased elimination capacity of the biological system. This can also be observed in the plasma concentration–time plots (Fig. 2c, d) where $C_u$ for high-CL drugs in every hypo-albuminemic situation are higher compared with a normal situation. For low-CL drugs, the $AUC_u$ does not change for the different hypo-albuminemic situations. If they have a

high Vd, their unbound plasma concentration–time profiles for different hypo-albuminemic scenarios overlap (Fig. 2b). In contrast, these unbound plasma concentration–time profiles are distinct in every scenario if compounds have a low Vd (Fig. 2a). This means that for low-distribution low-CL, although the $AUC_u$ is the same, differences in the duration of effect after a single dose might be observed. It seems that unbound concentration–time profiles are steeper compared with normal, and the half-life of the unbound drug is shorter. In the clinical setting, patients experiencing hypo-albuminemia are typically hospitalized and therapeutically monitored. Infusion will be the preferred route of drug administration. In this context, we have simulated an infusion design, illustrated in Fig. 3. In hypo-albuminemia, the time to reach the steady state is shorter, but the unbound steady-state plasma concentration is the same as in a normal situation.

Based on these simulation results, when PPB is altered, unbound exposure is increased for high-CL compounds only, independent of the distributional behavior of the compound. Identical unbound AUC values do not necessarily imply overlapping unbound plasma concentration–time profiles, as can be concluded from the behavior of low-distribution compounds.

Depending on the mechanism of action of the antibacterial compound, differences in either unbound exposure or the time above MIC will be indicative of the therapeutic effect. Table 4 summarizes the results of our simulations in terms of $AUC_u$ and time above MIC. The results for the $AUC_u$ follow the same trend as the $CL_u$ because they are inversely proportional. For low-CL compounds, the unbound exposure hardly changes, while for high-CL compounds it almost doubles. Considering time above MIC, an arbitrary MIC value for low- and high-CL drugs was chosen to describe the effects of altered PPB for different HYPO scenarios. Although the choice of MIC value will influence the magnitude of the effect, some obvious trends may be discerned. For compounds with a high Vd (low and high CL), there is no difference between the different hypo-albuminemic scenarios. In the case of low-CL compounds, there is not even a difference between the normal and hypo-albuminemic situation. In the case of low-volume compounds, the effect on time above MIC differs with every hypo-albuminemic situation. For high-CL compounds, the time above MIC is extended, while for low-CL compounds it is shortened. However, in the latter case, if the MIC is equal to the point where all unbound curves intersect, there would be no difference in time above MIC. It is now clear that the outcome of this metric relies on the compound's pharmacokinetics and MIC value. An interesting aspect of this study is that similar $AUC_u$ values may have significant differences in time above MIC values. Knowledge on the mechanism of action should hence drive possible dose adaptions.

#### 4.1.4 *Comparing Simulations with Case-Controlled Observations and Implications for Anti-Infective Dosing*

Most anti-infective drugs are classified as low-CL drugs, with small Vd. In Table 5, some case-controlled observation results from a number of clinical studies with anti-infective drugs are summarized that can be compared with our simulation outcomes. These studies (albeit with different experimental setups) report on a change in exposure of unbound drug of three different compounds (one β-lactam antibiotic, and two anti-inflammatory agents), which have a low intrinsic CL and small Vd. They report on a 10–75% lower $CL_u$ value in hypo-albuminemia (Table 5).

Why is the outcome different between the PBPK simulations (unchanged $CL_u$) and case-controlled in vivo data (decreased $CL_u$)? The reason is that the current PBPK model is designed to only predict differences in PK parameters that are related to a shift in PPB. In the case–controlled studies, secondary effects on elimination (provoked by the hypo-albuminemia) might also contribute. These effects may include, but are not restricted to: (1) the saturation of PPB, or of an elimination process [23]; (2) a

**Table 5** Three in vivo case-controlled studies on the effect of hypoalbuminemia on unbound pharmacokinetic ($PK_{Unbound}$) parameters

| Study | %Δ[a] $PK_{Unbound}$ in hypo-albuminemia subjects vs. matched controls | | | |
|---|---|---|---|---|
| | $CL_u$ | $V_u$ | $T_{1/2u}$ | $AUC_u$ |
| Mimoz et al. [23] | −35% | −27% | −15% | +57% |
| Pérez-Urizar et al. [30] | −75%[b] | −82%[b] | −28%[b] | +300%[b] |
| Troconiz et al. [31] | −10% | | | |

*$AUC_u$* unbound area under the concentration–time curve, *$CL_u$* unbound clearance, *$T_{1/2u}$* unbound half-life, *$V_u$* unbound volume of distribution

[a] $\%\Delta$ = (observed value—reference value (controls)/reference value) × 100

[b] Pharmacokinetic parameters were estimated using the pharmacokinetic package in R® (R, Foundation for Statistical Computing, Vienna, Austria) after digitization of the data in [30]

build-up of 'anti-substrates' competing for hepatic elimination of the drug; or (3) the extravasation of intravascular fluid causing the organ blood flow to drop, decreasing the elimination of renally cleared drugs. Additionally, other clinical manifestations in critically ill patients mean the constructed PBPK model will fail to predict the real in vivo situation. In severe infections, the systemic circulation decreases as a result of disseminated intravascular coagulation. In parallel, inflammation would increase the migration of the drug to the tissues. Although the influence of decreased systemic circulation and increased drug penetration may be investigated in a PBPK model, they are not factored in in the current simulations. In adjusting the drug dose for critically ill patients, these factors should also be accounted for. However, the aim of this article was not to provide new dosing guidelines for the critically ill patient, but to critically evaluate currently available dosing guidelines and provide mechanistic insights into the association of drug and albumin levels.

The PBPK simulations (unchanged $CL_u$) as well as the case-controlled in vivo studies (decreased $CL_u$) indicate that unbound CL is never higher in cases of hypoalbuminemia. This implies that unbound drug concentrations will be equal or even higher in hypo-albuminemic patients than in healthy volunteers. Given that the case-controlled in vivo studies show a decrease in $CL_{u,}$ the clinical implication is that dosing regimens should not be increased but rather decreased in hypo-albuminemic patients. This fact is in contrast with dosing guidelines currently applied in this field, describing higher doses/dosing frequency in patients experiencing hypo-albuminemia [3, 24, 25]. Not changing the dose in these cases is of particular importance if the drug has proven side effects, e.g., vancomycin-related nephrotoxicity [26], cefipime-related neurotoxicity [27], and the narrow therapeutic index of amiglycosides [28]. Thus, if albumin-based dosing is to be considered in the clinic, it should be based on the correct principles. However, as pointed out earlier, a reduction in plasma protein levels is typically not the only factor that should be accounted for when administering drugs to critically ill patients. Given the current uncertainties associated with factors determining the dose in this population, therapeutic drug monitoring is still the most appropriate way to guide therapy. In addition, in the case of subtherapeutic (unbound) concentrations or resistance to antibiotics [29] observed in vivo, this is likely owing to impaired target tissue penetration, e.g., microvascular dysfunction, use of vasoactive medications, or pressure exhibited by tissue edema.

Where does the misconception that hypo-albuminemia necessitates higher/more frequent dosing find its origin? This is the result of inference made using total plasma concentrations. Whether compartmental or non-compartmental approaches are used to derive the parameters 'CL' and '$V_{ss}$' in these populations, wrong conclusions will always be drawn whenever total concentrations are used. This is because they are confounded with the unbound fraction in plasma. Because the free drug hypothesis dictates that only the unbound concentration has an anti-bacterial effect, this concentration should be used to construct dosing guidelines.

A limitation of this study is that the PBPK model, developed for this study purpose, is not able to predict a change in elimination capacity, as is observed in case-controlled in vivo studies. As a consequence, the results from the simulations should be transferred with caution to a real-life setting. However, the PBPK model was never designed to make inference on dose adjustments, only to investigate the mechanistic nature of the effect of changing albumin levels on the pharmacokinetics of drugs. In addition, although many highly protein-bound drugs display concentration-dependent binding, this was not investigated in the current study. More research is needed to investigate such effects.

## 5 Conclusion

A test set of drugs representing low/high CL and low/high Vd was used to compare different total and unbound PK parameters and profiles. Simulations allowed the prediction of the theoretical effect of protein (albumin) distribution on PK parameters. The results show that for high-CL compounds, unbound exposure increases with decreased PPB. Moreover, for these compounds, unbound plasma concentrations for all of the simulated hypo-albuminemic situations are above the unbound plasma concentrations for the normo-albuminemic situation. For low-CL compounds, the unbound exposure was unaffected. However, the unbound plasma concentration–time profiles were different from the normo-albuminemic situation. Bolus administration resulted in higher, equal, or lower unbound plasma concentrations depending on the time after dosing, together with implications on a given time above the MIC value. Additionally, continuous infusion of low-Vd low-CL drugs resulted in a faster achievement of the same (comparable) steady-state plasma concentration. Overall, when considering continuous infusion, for none of the simulated situations did the unbound exposure decrease when albumin levels decreased. Hence, properly designed PK-pharmacodynamic studies are the only studies that should be used to link effective (unbound) drug concentrations to

antimicrobial effects. This should enable more appropriate drug dosing recommendations to achieve better clinical outcomes.

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**Compliance with Ethical Standards**

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**Conflict of interest** An Vermeulen is an 80% employee of Johnson and Johnson and owns J&J stock/stock options. She is also a visiting Professor at Ghent University. Huybrecht T'jollyn, Pieter Colin, and Jan Van Bocxlaer declare have no conflicts of interest that are directly relevant to the contents of this manuscript.

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