



HAL
open science

Hypoalbuminemia and Pharmacokinetics: When the Misunderstanding of a Fundamental Concept Leads to Repeated Errors over Decades

Peggy Gandia, Sarah Decheiver, Manon Picard, Romain Guilhaumou, Sarah Baklouti, Didier Concordet

► To cite this version:

Peggy Gandia, Sarah Decheiver, Manon Picard, Romain Guilhaumou, Sarah Baklouti, et al.. Hypoalbuminemia and Pharmacokinetics: When the Misunderstanding of a Fundamental Concept Leads to Repeated Errors over Decades. *Antibiotics*, 2023, 12 (3), pp.515. <10.3390/antibiotics12030515>. <hal-04061765>

HAL Id: hal-04061765

<https://hal.science/hal-04061765v1>

Submitted on 11 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License

Review

Hypoalbuminemia and Pharmacokinetics: When the Misunderstanding of a Fundamental Concept Leads to Repeated Errors over Decades

Peggy Gandia ^{1,2,*} , Sarah Decheiver ¹, Manon Picard ¹, Romain Guilhaumou ³, Sarah Baklouti ^{1,2} and Didier Concordet ² 

¹ Laboratoire de Pharmacocinétique et Toxicologie Clinique, Institut Fédératif de Biologie, CHU de Toulouse, 330 avenue de Grande-Bretagne, CEDEX 9, 31059 Toulouse, France

² INTHERES, Université de Toulouse, UMR 1436, INRAE, ENVT, 23 Chemin des Capelles, CEDEX 3, 31076 Toulouse, France

³ AP-HM Hôpital de la Timone, Service de Pharmacologie Clinique et Pharmacovigilance, 264 rue Saint Pierre, 13005 Marseille, France

* Correspondence: gandia.p@chu-toulouse.fr

Abstract: Surprisingly, misinterpretation of the influence of hypoalbuminemia on pharmacokinetics and the clinical effects of drugs seems to be a current problem, even though hypoalbuminemia has no impact on the pharmacologically active exposure. Exceptions to this fact are highly protein-bound anaesthetics with high elimination capacity (i.e., <5 drugs on the market). To assess the frequency of misinterpretation of the influence of hypoalbuminemia on pharmacokinetics and the clinical effects of drugs between 1975 and 2021, a PubMed literature review was conducted. Each paragraph on albumin binding was classified as correct, ambiguous or incorrect, creating two acceptable categories: (1) content without any errors, and (2) content containing some incorrect and/or ambiguous statements. The analyses of these articles showed that fewer than 11% of articles contained no interpretation errors. In order to contain this misinterpretation, several measures are proposed: (1) Make the message accessible to a wide audience by offering a simplified and didactic video representation of the lack of impact of albumin binding to drugs. (2) Precise terminology (unbound/free form/concentration) should be used for highly bound drugs. (3) Unbound/free forms should be systematically quantified for highly plasma protein bound drugs for clinical trials as well as for therapeutic drug monitoring.

Keywords: hypoalbuminemia; unbound/free concentration; misinterpretation; therapeutic drug monitoring



Citation: Gandia, P.; Decheiver, S.; Picard, M.; Guilhaumou, R.; Baklouti, S.; Concordet, D. Hypoalbuminemia and Pharmacokinetics: When the Misunderstanding of a Fundamental Concept Leads to Repeated Errors over Decades. *Antibiotics* **2023**, *12*, 515. <https://doi.org/10.3390/antibiotics12030515>

Academic Editor: Aaron J. Oakley

Received: 9 January 2023

Revised: 17 February 2023

Accepted: 2 March 2023

Published: 4 March 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Take-home message:

- The misinterpretation of the influence of hypoalbuminemia on drug pharmacokinetics and clinical effects is still a problem in 2022.
- Two major levers can be used to reduce this endemic error: (i) improve the way in which the protein-binding concept is taught to medical/pharmacy students; and (ii) systematically quantify the unbound/free form for drugs highly bound to plasma proteins for clinical trials as well as for therapeutic drug monitoring.

1. Introduction

Moderate and severe hypoalbuminemia is frequently reported in malnourished patients and in individuals presenting systemic inflammatory syndrome, chronic gut disease or nephrotic syndrome [1–3]. In these cases, and given that albumin is a key drug binding protein, some pharmacists and clinicians have questioned the impact of variations in albuminemia on circulating drug concentrations and thus on drug efficacy, with a particular focus on highly bound drugs (i.e., >90%).

Indeed, in their minds and rather confusedly, hypoalbuminemia tends to vary the “effective” concentration requiring dose adjustments in order to maintain efficacy and avoid toxicity. For many healthcare professionals, the underlying mechanism is the detachment of the drug from its albumin-binding sites, thus leading to an increase in the unbound/free form. This conjures up the mental image of the body operating as a tank filled with stagnant water. The detached drug remains in the tank, thus leading to increased unbound/free concentration without any variation in the total concentration, similar to the *in vitro* investigation of hypoalbuminemia. However, this mental image is incorrect and, consequently, leads to misinterpretation of the impact of hypoalbuminemia on pharmacokinetics. Indeed, when a patient presents hypoalbuminemia, the bound concentration decreases while the unbound/free concentration remains unchanged [4–11]. This reduces the measured concentration (i.e., sum of unbound/free and bound forms). As a consequence, the unbound/free fraction (i.e., ratio of the unbound/free concentration on the total concentration) increases due to a decreased total concentration, while the unbound/free concentration remains unchanged.

From a mathematical point of view, this is described explicitly by the following equations that are also reported in Toutain et al. [4]. To facilitate comprehension, we consider all concentrations at the steady state:

$$C_{tot} = C_{free} + C_{bound} \quad (1)$$

where C_{free} and C_{bound} are the free/unbound and bound concentrations, respectively. For a drug with a single family of binding sites (binding sites characterized by the same affinity constant k_a), C_{bound} is given by the general equation:

$$C_{bound} = \frac{B_{max} \times C_{free}}{K_D + C_{free}} \quad (2)$$

where B_{max} is the maximal binding capacity (related to the molar concentration of the binding protein), and K_D is the equilibrium dissociation constant. Incorporating Equation (2) into Equation (1) gives:

$$C_{tot} = C_{free} + \frac{B_{max} \times C_{free}}{K_D + C_{free}} \quad (3)$$

Thus, when hypoalbuminemia occurs, one can see that: $C_{bound} = \frac{B_{max} \times C_{free}}{K_D + C_{free}}$ decreases because B_{max} decreases without affecting C_{free} .

For the same reason, hypoalbuminemia causes $C_{tot} = C_{free} + \frac{B_{max} \times C_{free}}{K_D + C_{free}}$ to decrease because B_{max} decreases without affecting C_{free} .

In the same way, the impact of hypoalbuminemia on $f_u = \frac{C_{free}}{C_{tot}} = \frac{C_{free}}{C_{bound} + C_{free}}$ can be deduced from the previous remarks: in the case of hypoalbuminemia, C_{bound} (and consequently C_{tot}) decreases, which increases f_u , while the unbound/free concentration remains unchanged.

In summary, because the free fraction (f_u) changes with B_{max} , its interpretation is misleading.

More recently, T’Jollyn et al. [12] published the kinetic profile of unbound/free and total concentrations when hypoalbuminemia occurs. Their simulations once again confirm the explanations presented above.

Even if there are few (i.e., less than 5 marketed drugs) exceptions to the rule (i.e., highly bound drugs with high elimination capacities) [13,14], there is no room to generalize these exceptions. Thus, the selection criterion applied in our study excluded drugs with a high elimination capacity. In this way, all the included drugs had only a low elimination capacity as there were no anti-infectious drugs with medium elimination capacity. Elimination capacity is characterized by the extraction ratio (ER) determined by the ratio of

hepatic/renal clearance to hepatic/renal blood flow. For a low elimination capacity, the ER is considered to be <0.3 , whereas for high elimination capacity, $ER > 0.7$.

A common source of confusion, which will not be discussed in this article, is the change in glomerular filtration rate (GFR), which controls the unbound/free concentration of renally eliminated drugs. When the GFR decreases (e.g., in renal failure) or conversely increases (e.g., in a hyperfiltrating patient), the concentration increases or decreases, respectively. Thus, a change in GFR concomitant with hypoalbuminemia leads to the mistaken belief that hypoalbuminemia is the cause of the change in unbound/free drug concentration.

Misunderstanding the protein-binding concept provides one explanation for incorrect and sometimes dangerous drug dosage adjustments.

In the 2000s, our colleagues [4,7,9], some of whom are the founders of modern pharmacology, wrote didactic research papers to explain protein binding and dispel misconceptions. The understanding of the impact of plasma protein binding in the 2020s seems still very unclear. The purpose of this paper is to assess the prevalence of this error in medical literature from the 1970s to the present day, focusing on dosing adjustments for patients presenting hypoalbuminemia. This work was focused on anti-infective drugs. Indeed, anti-infective drugs are widely prescribed and a drug dosage adjustment based on a therapeutic drug monitoring (TDM) is recommended for patients most at risk of therapeutic failure or toxicity.

2. Results

Flowchart in Figure 1 shows the methodology used to select PubMed articles. This methodology follows the recommendations given in [15].

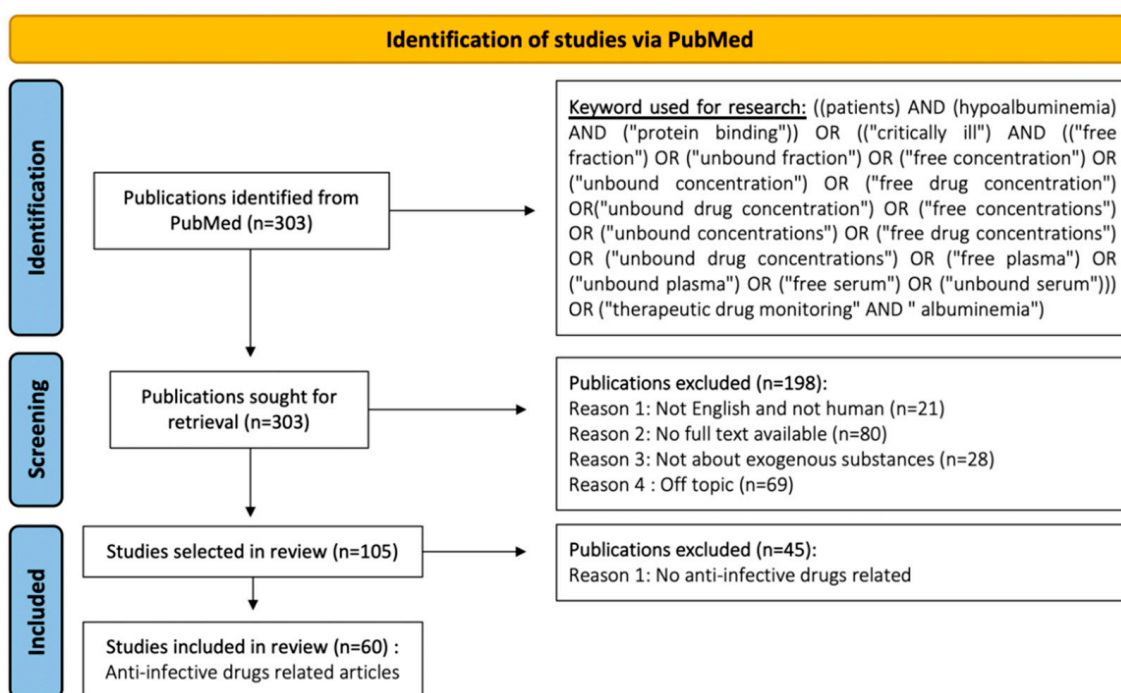


Figure 1. Flowchart describing PubMed review regarding unbound/free fractions/concentrations. This flowchart has been produced using the guidelines provided in [15].

Three hundred and three articles were identified from 1975 to 2021 (Figure 2) and screened.

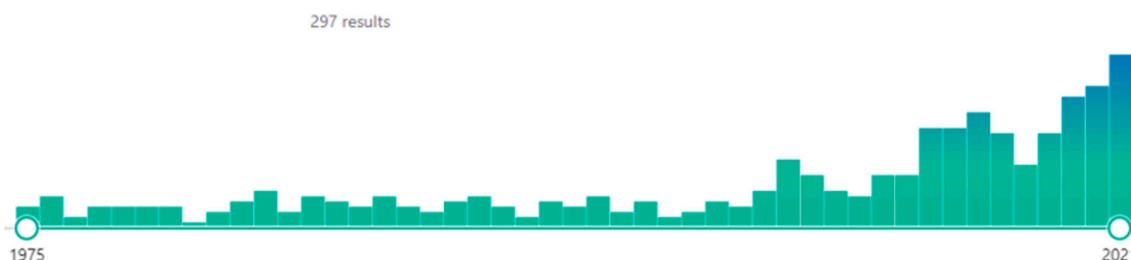


Figure 2. Diagram showing the articles available on PubMed when we reviewed the literature.

One hundred and five articles were first selected for our global analysis. Then, only articles referring to anti-infective drugs were included (Table 1).

Table 1. Number of screened articles and articles with no incorrect sentences over the timeline.

Period	Screening		Analysis		
	Number of Articles Using Keywords	Number of Included	Category 1 ¹	Category 2 ² (True + Ambiguous)	At Least One False Assertion
1975–1980	18	1	0	1 (0 + 1)	0
1981–1985	15	0	0	0	0
1986–1990	19	0	0	0	0
1991–1995	17	0	0	0	0
1996–2000	15	1	0	0	1
2001–2005	16	0	0	0	0
2006–2010	32	8	1	4 (1 + 3)	4
2011–2015	61	19	2	6 (2 + 4)	13
2016–2020	81	21	3	11 (3 + 8)	10
2021	29	11	1	4 (1 + 3)	7
Total	303	61	7	26 (7 + 19)	35
%	-	-	11	43	57

¹ Category 1—article makes no ambiguous or incorrect assertions; ² Category 2—article contains ambiguous and correct assertions; %—percentages of articles in each category.

The list of anti-infective drug related articles and an analysis of their contents (regarding the interpretation of hypoalbuminemia on unbound/free exposure) is provided in Table S1 [16–76]. Thorough reading of its contents is beneficial.

An increasing number of manuscripts have been published on this topic over the last fifty years. Regardless of the period in question, fewer than 11% articles did not contain any errors in interpreting the impact of hypoalbuminemia on unbound/free drug exposure (category 1). Similarly, fewer than 43% articles did not contain entirely false statements on the impact of hypoalbuminemia on unbound/free drug exposure despite containing ambiguous statements (category 2).

All the results are contained in the supplemental data, which is over 30 pages long. Due to the length of the supplemental data, a selection of the most representative examples is presented below (Tables 2 and 3):

- **The correct explanations:**

“A previous study indicated that although clearance of total daptomycin (CL) was affected by alterations in fu, CLu did not get affected. In our study, fu ranged from 0.05 to 0.14 depending on the influence of serum albumin, BUN, and FBG. Regarding factors affecting fu and CL, reports on teicoplanin, which is an antimicrobial agent with a high protein binding rate, identified serum albumin and FBG. In our study, the results were similar to those of teicoplanin, and, to the best of our knowledge, this is the first report on factors that affected fu in daptomycin. Moreover, our results suggested that because

CL varies with the influence of fu, establishing the dose using total concentrations may result in an under- or overestimation.” [17]

- *The ambiguous explanations reported in five different cases:*

Table 2. Examples of ambiguous explanations found in the literature.

Cases	Ambiguous Sentences	Explanations
A	<p>“Calculation of the unbound concentrations, assuming 95% protein binding, may therefore result in considerable overdosing, in particular in critically ill patients with hypoalbuminaemia and renal impairment. In the present study, the inter-individual unbound plasma fraction of flucloxacillin varied widely from 1.1% to 64.7%, showing a substantially higher median value (11%) than reported for healthy individuals (5%).” [32]</p>	<p>Combining the impact of hypoalbuminemia and a change in kidney/liver and drug-drug interactions in the same sentence makes it difficult to identify clinical repercussions. Indeed, hypoalbuminemia does not alter unbound/free concentrations and cannot have any clinical impact. On the contrary, a defective excretory system reduces unbound/free/intrinsic clearance, leading to greater unbound/free exposure and, therefore, impacts the clinical effect of the drug. Moreover, when two drugs (A and B) are administered concomitantly, drug A can modify the protein-binding of drug B without altering the latter’s unbound/free concentration. However, it cannot be ruled out that drug A will also decrease the clearance of drug B, thereby potentially increasing the unbound/free exposure (i.e., concentrations) of drug B. Two mechanisms are, therefore, involved in the drug A–drug B interaction.</p>
B	<p>“The binding of beta-lactams to albumin and plasma proteins determines the free fraction, which is the biologically active fraction that diffuses across biological membranes to tissues. The free fraction is also the fraction that is eliminated by renal and liver clearance. When plasma protein amount decreases, the capacity of beta-lactams to bind to protein decreases and beta-lactam-free fraction increases. Previous studies have shown that the binding of beta-lactams to plasma proteins in ICU patients is highly variable and is more altered for antibiotics highly bound to plasma proteins in conditions of homeostasis (e.g., ceftriaxone, cefazolin, or ertapenem). As a result, plasma concentration of beta-lactam antibiotics may be lowered and more unpredictable in patients with severe hypoalbuminemia.” [38]</p>	<p>There is confusion of the terms, “unbound/free form” and “unbound/free fraction” as in the sentence “the unbound/free fraction is the pharmacologically active fraction”. A number (i.e., unbound/free fraction) cannot be pharmacologically active, unlike the drug form. Indeed, the unbound/free form of the drug is the pharmacologically active form regardless of the albuminemia and unbound/free fraction. Moreover, the value of the unbound/free fraction is misleading because it increases with the hypoalbuminemia and thus incorrectly suggests that the unbound/free concentration also rises, thereby suggesting an enhanced clinical effect with the drug in question.</p>

Table 2. Cont.

Cases	Ambiguous Sentences	Explanations
C	<p>“SAFE Study Investigator reported that approximately 40% of critically ill patients presented with hypoalbuminemia, because cefoperazone, meropenem, and imipenem are highly bound to albumin, which could increase the unbound fraction significantly. Therefore, various pathological characteristics in critically ill patients may induce a wide discrepancy in the unbound fraction concentrations.” [34]</p>	<p>Use of the term, “unbound/free fraction” instead of “unbound/free concentration” is confusing because the unbound/free fraction changes with hypoalbuminemia, while the unbound/free concentration is unchanged. Consequently, the variation in terms of the unbound/free fraction sheds no light on the clinical effect of the drug.</p>
D	<p>“Probably due to this dramatic increase in the fu, our patients exhibit a higher ceftriaxone CL than healthy volunteers or critically ill patients with sepsis, septic shock, and different degrees of renal function, a CL that is dependent on albumin concentration and weight based on the results of the population PK model. Surprisingly, in spite of the augmented CL, dosing simulations show that, for an MIC ≤ 2 mg/L (the clinical breakpoint for susceptibility to ceftriaxone), a dose of 1000 mg q24 h maintains unbound ceftriaxone concentrations for a 100% of the dosing interval above the MIC regardless of albumin concentration and body weight.” [31]</p>	<p>Using expressions such as “mostly, usually, often, almost, potentially, may, in several cases, surprisingly . . . ” suggests that the fact is only observed in specific cases, as indicated in the sentence, “Serum albumin concentrations may not affect unbound/free concentrations”, whereas this is always the case.</p>
E	<p>“In addition, low serum albumin concentration is frequently observed in ICU patients, leading to an increase in the free fraction of the beta-lactams highly bound to plasma proteins, such as cefazoline, ceftriaxone, or ertapenem. Thus, hypoalbuminemia may lead to increased Vd and tissue penetration, and also increased elimination, of beta-lactam antibiotics by glomerular filtration and/or metabolic clearance. This has been particularly observed for ceftriaxone or ertapenem.” [38]</p>	<p>The paper gives correct conclusions on total pharmacokinetic parameters of no clinical consequence. For example, hypoalbuminemia implies an increase in total clearance without affecting the unbound/free/intrinsic clearance that controls unbound/free exposure. This information misleadingly suggests to the reader that the unbound/free concentration is lower because of increased total clearance. In another example, hypoalbuminemia implies an increase in the total volume of distribution without affecting the unbound/free volume of distribution. This information incorrectly suggests to the reader that the kinetic profile of the unbound/free concentration is modified because of the increase in the total volume of distribution.</p>

TZP: piperacillin/tazobactam; MER: meropenem; PK: pharmacokinetic; fu: unbound/free fraction; CL: clearance; MIC: minimum inhibitory concentration; ICU: intensive care unit; Vd: distribution volume.

- *The incorrect explanations:*

Table 3. Examples of incorrect explanations found in the literature.

Incorrect Sentences	Explanations
<p>“We recognise that our case series is limited and that the study design was retrospective and monocentric. Additionally, only total cefiderocol concentrations were measured, thus potential variability in protein binding commonly encountered in critically ill patients could impact on cefiderocol free levels.” [58]</p>	<p>Variation in unbound concentration occurs over a very short duration (probably seconds or minutes). However, unbound/free concentration returns to the baseline level, while unbound/free fraction (f_u) increases. This increase in f_u leads to an increase in the clearance and the volume of distribution for total concentration but not for unbound/free concentration.</p>

PK: pharmacokinetic.

Misunderstanding the protein-binding concept is also palpable when one examines the way in which this concept is discussed by the same research team through its various publications:

- None of the selected articles contained exclusively true assertions for a specific author;
- Some authors wrote both correct and ambiguous sentences in different articles ([20]/[27]; [22]/[47]; [23]/[41]);
- Some authors have remained consistent by repeating the same incorrect message over time, suggesting that this concept was not taught to them properly at medical school (references of two articles with wrong assertions: [64]/[74]; [66]/[67]; [72]/[73]).
- Some authors state in articles published a few months apart (or even in the same article), facts that contradict each other (references of two articles with correct and incorrect assertions, respectively: [21]/[59]; [20]/[59]; [19]/[41]; [19]/[39]; [22]/[25]; [23]/[66]; [21]/[66]; [21]/[21]; [25]/[25]).

3. Discussion and Conclusions

The impact of hypoalbuminemia on pharmacokinetics is largely misunderstood by healthcare professionals. This is an observation reflected in the increasing number of manuscripts published on this topic over the last fifty years that contain interpretation errors. Regardless of the period in question, around 89% of articles contain ambiguous and/or false ($(19 + 35/61 \text{ articles}) \times 100$) statements on the impact of hypoalbuminemia on unbound/free drug exposure. Surprisingly, and despite the fact that Benet’s, Rolan’s and Toutain’s articles [4,7,9] have been cited on numerous occasions (517, 310 and 110 times, respectively), the percentage of articles containing misleading or confusing information did not decrease following their publication in the early 2000’s. The reasons are not totally clear but some of them seem obvious: (i) some research units/laboratories do not technically have the possibility of determining the unbound/free form, whereas total concentration is easily accessible with current analytical tools; (ii) the level of pharmacokinetic knowledge is not harmonised between the different teams publishing on the impact of hypoalbuminemia on drug protein binding, leading to confusion between “unbound/free concentration” and “unbound/free fraction”; and (iii) the third argument is certainly linked to a lack of harmonisation of teaching on the influence of hypoalbuminemia on drug protein binding between different universities in the same country, or even between different specialisations (pharmacy, medicine, etc.). These accumulated reasons, combined with the need for research units to publish, lead to the publication of results that continue to perpetuate errors in the pharmacokinetic interpretation of hypoalbuminemia.

The main consequence of a poor understanding of drug binding to plasma proteins is the overexposure of patients with hypoalbuminemia. Indeed, in case of hypoalbuminemia, total concentration (i.e., concentration measured by the pharmacology-toxicology laboratories in hospital practices) decreases, while free/unbound concentration remains unchanged, leading clinicians to increase the patient dose in order to reach a target based on total concentration. This is typically the error encountered today with dalbavancin, ceftriaxone,

cefazolin, cloxacillin and ertapenem TDM, especially because a patient's hypoalbuminemia is not systematically examined when interpreting total concentration.

The concept of protein binding applies to all plasma proteins. Thus, a misunderstanding can lead to underexposure. For example, this kind of underexposure was observed with lopinavir used in the early weeks of the COVID-19 pandemic. As lopinavir is highly bound to alpha-1-acid glycoprotein (AAG), an increase in AAG induced by a cytokine storm resulted in an increase in bound and thus total concentrations without a change in free/unbound concentration [77]. This led medical teams to apply lower doses due to total concentrations four to five times those reported in HIV+ patients treated with lopinavir.

Overexposures are of no consequence for drugs with a wide therapeutic range (e.g., isavuconazole, posaconazole). On the other hand, they can induce toxicity for drugs with a narrow therapeutic range (e.g., valproic acid).

Conversely, the consequence of under-exposure is the lack of efficacy. However, this situation is not expected in cases of hypoalbuminemia.

A visual dynamic representation of the influence of hypoalbuminemia on bound and total concentrations is available in our sound video (<https://www.youtube.com/watch?v=4SXY8YyRbQo>).

As mentioned previously, there are few exceptions to the rule (i.e., bupivacaine, propofol, sufentanil). These drugs are highly bound drugs with high elimination capacities [13,14]. For these drugs, which are always administered intravenously, hypoalbuminemia leads to an increase in unbound/free concentrations, whereas the total concentrations remain unchanged. As there is no TDM for this kind of drugs (as it is not suitable), it is essential (i) not to generalize these exceptions and (ii) to keep in mind the correct interpretation (i.e., there is no impact of hypoalbuminemia on unbound concentrations).

In summary, the most important consequences of misinterpreting hypoalbuminemia are for drugs that are highly related and have a narrow therapeutic range. These drugs are mainly used in hospitals and, therefore, concern a limited number of patients; the consequences of an iatrogenic overexposure in general practice would probably be much more serious.

To conclude, it is possible that in the future, healthcare professionals may no longer confuse unbound/free drug fraction and unbound/free drug concentration to adapt the dosage of antibiotics in patients with hypoalbuminemia. With this aim, the solution is obvious and warrants a two-fold approach: (i) to improve the way in which the protein-binding concept is taught at medical school, in particular by prohibiting the use of the "unbound/free fraction" terminology for highly bound drugs and by using the "unbound/free concentration instead" terminology; and (ii) to systematically quantify the unbound/free form for drugs highly bound to plasma proteins in both clinical trials and TDM.

Advancements in technology, both in the analytical and pedagogical fields, (e.g., ChatGPT) should improve the situation.

4. Methods

We conducted a PubMed literature review from January 1st, 1975 to December 31st, 2021. We looked for all articles including an interpretation of free/unbound fraction by using the following key terms in our search: (patients) AND (hypoalbuminemia) AND ("protein binding") OR ("critically ill") AND ("free fraction") OR ("unbound fraction") OR ("free concentration") OR ("unbound concentration") OR ("free drug concentration") OR ("unbound drug concentration") OR ("free concentrations") OR ("unbound concentrations") OR ("free drug concentrations") OR ("unbound drug concentrations") OR ("free plasma") OR ("unbound plasma") OR ("free serum") OR ("unbound serum") OR ("therapeutic drug monitoring" AND "albuminemia").

Some articles did not fall into the scope of this study based on this initial sequence. We excluded (a) *in vitro* studies, (b) *in vivo* studies performed in animals, (c) articles on highly bound drugs with high elimination capacities, (d) articles on endogenous drugs and articles on endogenous substances with retrocontrols (e.g., hormones), (e) articles written in a

language other than English, (f) articles with no full text available, (g) duplicates/triplicates (i.e., articles with the same title by the same team published in different journals), and (h) articles not covering protein binding, even if the keywords highlighted them in PubMed. The remaining articles were those described as “global articles” in this review. Then, a last selection was made based on the mention of anti-infective drugs among the global articles. Indeed, anti-infective drugs are widely prescribed. In hospitals, for most of them, drug dosage adjustment is based on the therapeutic drug monitoring that implies an assay of total concentration.

For the evaluation process, we classified the contents of an article into three categories:

- *False*: The authors state that hypoalbuminemia leads to higher unbound/free concentrations and/or higher/lower unbound/free/intrinsic clearance and/or higher/lower unbound/free volume of distribution.
- *Ambiguous*: The paper suggests, without stating it explicitly, that hypoalbuminemia can impact unbound/free concentration. Various examples of ambiguous sentences are provided below:

Case A: Combining the impact of hypoalbuminemia and a change in kidney/liver and drug–drug interactions in the same sentence/section makes it difficult to identify clinical repercussions. Indeed, hypoalbuminemia does not alter unbound/free concentrations and cannot have any clinical impact. On the contrary, a defective excretory system reduces unbound/free/intrinsic clearance leading to greater unbound/free exposure and, therefore, impacts the clinical effect of the drug. Moreover, when two drugs (A and B) are administered concomitantly, drug A can modify the protein-binding of drug B without altering the latter’s unbound/free concentration. However, it cannot be ruled out that drug A will also decrease the clearance of drug B, thereby potentially increasing the unbound/free exposure (i.e., concentrations) of drug B. Two mechanisms are, therefore, involved in the drug A–drug B interaction.

Case B: Confusion of the terms, “unbound/free form” and “unbound/free fraction” as in the sentence “the unbound/free fraction is the pharmacologically active fraction”. A number (i.e., unbound/free fraction) cannot be pharmacologically active, unlike the drug form. Indeed, the unbound/free form of the drug is the pharmacologically active form regardless of the albuminemia and unbound/free fraction. Moreover, the value of the unbound/free fraction is misleading because it increases with the hypoalbuminemia and thus incorrectly suggests that the unbound/free concentration also rises, thereby suggesting an enhanced clinical effect with the drug in question.

Case C: Use of the term, “unbound/free fraction” instead of “unbound/free concentration” is confusing because the unbound/free fraction changes with hypoalbuminemia, whereas the unbound/free concentration is unchanged. Consequently, the variation in terms of the unbound/free fraction sheds no light on the clinical effect of the drug.

Case D: Using expressions such as “mostly, usually, often, almost, potentially, may, in several cases, surprisingly . . . ” suggests that the fact is only observed in specific cases as indicated in the sentence, “Serum albumin concentrations may not affect unbound/free concentrations”, whereas this is always the case.

Case E: Giving correct conclusions on total pharmacokinetic parameters is of no clinical consequence. For example, hypoalbuminemia implies an increase in total clearance without affecting the unbound/free/intrinsic clearance that controls unbound/free exposure. This information misleadingly suggests to the reader that the unbound/free concentration is lower because of increased total clearance. In another example, hypoalbuminemia implies an increase in the total volume of distribution without affecting the unbound/free volume of distribution. This information incorrectly suggests to the reader that the kinetic profile of the unbound/free concentration is modified because of the increase in the total volume of distribution.

- *True*: The sentence states explicitly that hypoalbuminemia has no impact on the unbound/free concentration.

Some articles make false and/or ambiguous and/or correct assertions relating to the impact of hypoalbuminemia on unbound/free drug concentrations. We consequently propose two classifications:

- **Category 1:** an article is retained when it contains only correct assertions; an article is deemed unacceptable when it contains ambiguous and/or false assertions.
- **Category 2:** an article is retained when it contains correct or ambiguous assertions; an article is deemed unacceptable when it contains only incorrect assertions.

To give a visual dynamic representation of the influence of hypoalbuminemia on bound and total concentrations, we created a sound video (<https://www.youtube.com/watch?v=4SXY8YyRbQo>). We used a single-compartment model and continuous infusion to simplify the image. However, the same mechanism applies for more complex models (n -compartments with $n > 1$) and intravenous/oral discontinuous drug administration. A description of the different periods of the movie is detailed below:

Period A: From drug administration to steady state

- The black squares represent albumin molecules (1 black square = 1 albumin molecule). These squares remained fixed to make this video watchable. The red dots appearing at the top of the figure represent the drug molecules (i.e., 1 red dot = 1 drug molecule) injected into the blood (central compartment) at a constant perfusion rate (i.e., X molecules per hour);
- When the drug (red dots) binds to albumin (black squares), the black squares turn green to illustrate the albumin-binding of the drug. In an attempt to simplify the presentation, we illustrated the drug bound to albumin as a static relationship throughout all of the simulation periods. There is actually a continuous “bond and detachment” process that would have been difficult to represent;
- All red dots travel from the top of the figure to the bottom at the same pace. This means that the drug molecules pass through the excretory organ at the same speed, thereby mimicking intrinsic clearance. This speed does not change over time (i.e., intrinsic clearance is constant and independent of time and dose/concentration);
- At the beginning of the drug perfusion stage, a few red dots reach the bottom of the figure. This shows that a few drug molecules are eliminated at the start of drug perfusion. Indeed, when the first drug molecules reach the blood, they immediately bind to albumin as the drug has a high affinity for albumin. More and more black squares gradually turn green as increasing numbers of drug molecules bind to albumin;
- Due to continuous perfusion, drug accumulation in the body simultaneously leads to an increase in the number of red dots in the figure (i.e., an increase in drug concentration) until a perfusion and a steady elimination rate is reached;
- Once the steady state has been reached, (i) the ratio of red dots (i.e., unbound drug molecules) to green squares (i.e., bound drug molecules) is constant, (ii) the number of red dots expelled at the bottom of the figure per unit of time is constant, and (iii) the number of red dots injected into the central compartment per unit of time is equal to the number of red dots expelled at the bottom of the figure per unit of time.

Period B: Severe hypoalbuminemia

- When severe hypoalbuminemia occurs (i.e., a marked decrease in albumin molecules, despite the fact that severe hypoalbuminemia takes many days to appear), a large number of green squares disappear and an equal number of red dots appear;
- This increase in red dots indicates an increase in unbound/free drug molecules as well as an increase in unbound/free drug concentrations;
- The excess red dots are channeled downwards at the same speed for all the dots. This means that the surplus unbound/free drug molecules are gradually eliminated by the body, with unbound/free drug concentrations being restored to the original steady state driven by both the perfusion rate and intrinsic clearance;
- Peak concentrations are transient and of short duration, as highlighted by the concentration-versus-time curve of the unbound/free drug.

Period C: New steady state with hypoalbuminemic status

- When the peak has been reached and the number of albumin molecules has decreased, the number of bound drug molecules falls along with the overall number (bound + unbound) of drug molecules. Consequently, bound and total concentrations are lower when comparing hypoalbuminemia to the values reported at steady state when the patient was not hypoalbuminemic;
- The new steady state shows the same unbound/free drug concentration with lower bound and total drug concentrations.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/antibiotics12030515/s1>. Movie S1 (<https://www.youtube.com/watch?v=4SXY8YyRbQo>): using a dynamic approach, this video covers various events from the initiation of drug perfusion to a patient without hypoalbuminemia who suddenly presents severe hypoalbuminemia. Table S1. The list of screened articles and an analysis of their contents (regarding the interpretation of hypoalbuminemia on unbound/free exposure).

Author Contributions: Conceptualization, P.G. and D.C.; methodology, P.G. and D.C.; bibliography review, M.P. and S.D.; writing—original draft preparation, S.D., P.G. and D.C.; review, S.B. and R.G.; supervision, P.G. and D.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article or supplementary material.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Haller, C. Hypoalbuminemia in Renal Failure: Pathogenesis and Therapeutic Considerations. *Kidney Blood Press. Res.* **2005**, *28*, 307–310. [[CrossRef](#)] [[PubMed](#)]
2. Gatta, A.; Verardo, A.; Bolognesi, M. Hypoalbuminemia. *Intern. Emerg. Med.* **2012**, *7*, 193–199. [[CrossRef](#)] [[PubMed](#)]
3. Soeters, P.B.; Wolfe, R.R.; Shenkin, A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *J. Parenter. Enter. Nutr.* **2019**, *43*, 181–193. [[CrossRef](#)] [[PubMed](#)]
4. Toutain, P.L.; Bousquet-Melou, A. Free drug fraction vs free drug concentration: A matter of frequent confusion. *J. Vet. Pharmacol. Ther.* **2002**, *25*, 460–463. [[CrossRef](#)]
5. Derendorf, H.; Schmidt, S. *Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*, 5th ed.; Wolters Kluwer: Philadelphia, PA, USA, 2020.
6. McElnay, J.C.; D'Arcy, P.F. Protein binding displacement interactions and their clinical importance. *Drugs* **1983**, *25*, 495–513. [[CrossRef](#)]
7. Rolan, P.E. Plasma protein binding displacement interactions—why are they still regarded as clinically important? *Br. J. Clin. Pharmacol.* **1994**, *37*, 125–128. [[CrossRef](#)]
8. Sansom, L.N.; Evans, A.M. What is the True Clinical Significance of Plasma Protein Binding Displacement Interactions? *Drug Saf.* **1995**, *12*, 227–233. [[CrossRef](#)]
9. Benet, L.Z.; Hoener, B.A. Changes in plasma protein binding have little clinical relevance. *Clin. Pharmacol. Ther.* **2002**, *71*, 115–121. [[CrossRef](#)]
10. Bjornsson, T.D.; Meffin, P.J.; Swezey, S.; Blaschke, T.F. Clofibrate displaces warfarin from plasma proteins in man: An example of a pure displacement interaction. *J. Pharmacol. Exp. Ther.* **1979**, *210*, 316–321.
11. Heuberger, J.; Schmidt, S.; Derendorf, H. When is Protein Binding Important? *J. Pharm. Sci.* **2013**, *102*, 3458–3467. [[CrossRef](#)]
12. T'jollyn, H.; Vermeulen, A.; Van Bocxlaer, J.; Colin, P. A Physiologically Based Pharmacokinetic Perspective on the Clinical Utility of Albumin-Based Dose Adjustments in Critically Ill Patients. *Clin. Pharmacokinet.* **2018**, *57*, 59–69. [[CrossRef](#)]
13. Hiraoka, H.; Yamamoto, K.; Okano, N.; Morita, T.; Goto, F.; Horiuchi, R. Changes in Drug Plasma Concentrations of an Extensively Bound and Highly Extracted Drug, Propofol, in Response to Altered Plasma Binding. *Clin. Pharmacol. Ther.* **2004**, *75*, 324–330. [[CrossRef](#)] [[PubMed](#)]
14. Takizawa, E.; Hiraoka, H.; Takizawa, D.; Goto, F. Changes in the effect of propofol in response to altered plasma protein binding during normothermic cardiopulmonary bypass. *Br. J. Anaesth.* **2006**, *96*, 179–185. [[CrossRef](#)]

15. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, 71. [[CrossRef](#)] [[PubMed](#)]
16. Lodise, T.P.; Van Wart, S.; Sund, Z.M.; Bressler, A.M.; Khan, A.; Makley, A.T.; Hamad, Y.; Salata, R.A.; Silveira, F.P.; Sims, M.D.; et al. Pharmacokinetic and Pharmacodynamic Profiling of Minocycline for Injection following a Single Infusion in Critically Ill Adults in a Phase IV Open-Label Multicenter Study (ACUMIN). *Antimicrob. Agents Chemother.* **2021**, *65*, e01809-20. [[CrossRef](#)]
17. Samura, M.; Takada, K.; Yamamoto, R.; Ito, H.; Nagumo, F.; Uchida, M.; Kurata, T.; Koshioka, S.; Enoki, Y.; Taguchi, K.; et al. Population Pharmacokinetic Analysis and Dosing Optimization Based on Unbound Daptomycin Concentration and Cystatin C in Nonobese Elderly Patients with Hypoalbuminemia and Chronic Kidney Disease. *Pharm. Res.* **2021**, *38*, 1041–1055. [[CrossRef](#)]
18. Leegwater, E.; Kraaijenbrink, B.V.C.; Moes, D.J.A.R.; Purmer, I.M.; Wilms, E.B. Population pharmacokinetics of ceftriaxone administered as continuous or intermittent infusion in critically ill patients. *J. Antimicrob. Chemother.* **2020**, *75*, 1554–1558. [[CrossRef](#)]
19. Sime, F.B.; Byrne, C.J.; Parker, S.; Stuart, J.; Butler, J.; Starr, T.; Pandey, S.; Wallis, S.C.; Lipman, J.; Roberts, J.A. Population pharmacokinetics of total and unbound concentrations of intravenous posaconazole in adult critically ill patients. *Crit. Care* **2019**, *23*, 205. [[CrossRef](#)]
20. Wasmann, R.E.; Muilwijk, E.W.; Burger, D.M.; Verweij, P.E.; Knibbe, C.A.; Brüggemann, R.J. Clinical Pharmacokinetics and Pharmacodynamics of Micafungin. *Clin. Pharmacokinet.* **2018**, *57*, 267–286. [[CrossRef](#)] [[PubMed](#)]
21. Wong, G.; Briscoe, S.; McWhinney, B.; Ally, M.; Ungerer, J.; Lipman, J.; Roberts, J.A. Therapeutic drug monitoring of β -lactam antibiotics in the critically ill: Direct measurement of unbound drug concentrations to achieve appropriate drug exposures. *J. Antimicrob. Chemother.* **2018**, *73*, 3087–3094. [[CrossRef](#)] [[PubMed](#)]
22. Schleibinger, M.; Steinbach, C.L.; Töpper, C.; Kratzer, A.; Liebchen, U.; Kees, F.; Salzberger, B.; Kees, M.G. Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients: Unbound ceftriaxone in ICU patients. *Br. J. Clin. Pharmacol.* **2015**, *80*, 525–533. [[CrossRef](#)] [[PubMed](#)]
23. Carlier, M.; Stove, V.; Wallis, S.C.; De Waele, J.J.; Verstraete, A.G.; Lipman, J.; Roberts, J.A. Assays for therapeutic drug monitoring of β -lactam antibiotics: A structured review. *Int. J. Antimicrob. Agents* **2015**, *46*, 367–375. [[CrossRef](#)]
24. Enokiya, T.; Muraki, Y.; Iwamoto, T.; Okuda, M. Changes in the pharmacokinetics of teicoplanin in patients with hyperglycaemic hypoalbuminaemia: Impact of albumin glycosylation on the binding of teicoplanin to albumin. *Int. J. Antimicrob. Agents* **2015**, *46*, 164–168. [[CrossRef](#)] [[PubMed](#)]
25. Kees, M.G.; Wicha, S.G.; Seefeld, A.; Kees, F.; Kloft, C. Unbound fraction of vancomycin in intensive care unit patients. *J. Clin. Pharmacol.* **2014**, *54*, 318–323. [[CrossRef](#)] [[PubMed](#)]
26. Dasgupta, A. Usefulness of monitoring free (unbound) concentrations of therapeutic drugs in patient management. *Clin. Chim. Acta* **2007**, *377*, 1–13. [[CrossRef](#)]
27. Wallenburg, E.; Ter Heine, R.; De Lange, D.W.; Van Leeuwen, H.; Schouten, J.A.; Ten Oever, J.; Kolwijck, E.; Burger, D.M.; Pickkers, P.; Gieling, E.M.; et al. High unbound flucloxacillin fraction in critically ill patients. *J. Antimicrob. Chemother.* **2021**, *76*, 3220–3228. [[CrossRef](#)]
28. Aulin, L.B.S.; De Paepe, P.; Dhont, E.; De Jaeger, A.; Vande Walle, J.; Vandenberghe, W.; McWhinney, B.C.; Ungerer, J.P.J.; Van Hasselt, J.G.C.; De Cock, P.A.J.G. Population Pharmacokinetics of Unbound and Total Teicoplanin in Critically Ill Pediatric Patients. *Clin. Pharmacokinet.* **2021**, *60*, 353–363. [[CrossRef](#)]
29. Gijzen, M.; Dreesen, E.; Van Daele, R.; Annaert, P.; Debaveye, Y.; Wauters, J.; Spriet, I. Pharmacokinetic/Pharmacodynamic Target Attainment Based on Measured versus Predicted Unbound Ceftriaxone Concentrations in Critically Ill Patients with Pneumonia: An Observational Cohort Study. *Antibiotics* **2021**, *11*, 557. [[CrossRef](#)] [[PubMed](#)]
30. Asada, M.; Nagata, M.; Mizuno, T.; Uchida, T.; Takahashi, H.; Makita, K.; Arai, H.; Kijima, S.; Echizen, H.; Yasuhara, M. Population pharmacokinetics of cefazolin before, during and after cardiopulmonary bypass in adult patients undergoing cardiac surgery. *Eur. J. Clin. Pharmacol.* **2021**, *77*, 735–745. [[CrossRef](#)]
31. Ulldemolins, M.; Bastida, C.; Llauradó-Serra, M.; Csajka, C.; Rodríguez, A.; Badia, J.R.; Martín-Loeches, I.; Soy, D. Once-daily 1 g ceftriaxone optimizes exposure in patients with septic shock and hypoalbuminemia receiving continuous veno-venous hemodiafiltration. *Eur. J. Clin. Pharmacol.* **2021**, *77*, 1169–1180. [[CrossRef](#)]
32. Moser, S.; Rehm, S.; Guertler, N.; Hinic, V.; Dräger, S.; Bassetti, S.; Rentsch, K.M.; Sendi, P.; Osthoff, M. Probability of pharmacological target attainment with flucloxacillin in *Staphylococcus aureus* bloodstream infection: A prospective cohort study of unbound plasma and individual MICs. *J. Antimicrob. Chemother.* **2021**, *76*, 1845–1854. [[CrossRef](#)] [[PubMed](#)]
33. Tang Girdwood, S.C.; Tang, P.H.; Murphy, M.E.; Chamberlain, A.R.; Benken, L.A.; Jones, R.L.; Stoneman, E.M.; Kaplan, J.M.; Vinks, A.A. Demonstrating Feasibility of an Opportunistic Sampling Approach for Pharmacokinetic Studies of β -Lactam Antibiotics in Critically Ill Children. *J. Clin. Pharmacol.* **2021**, *61*, 565–573. [[CrossRef](#)] [[PubMed](#)]
34. Rao, Z.; Dang, Z.L.; Li, B.; Zhu, L.; Qin, H.Y.; Wu, X.A.; Wei, Y.H. Determination of Total and Unbound Meropenem, Imipenem/Cilastatin, and Cefoperazone/Sulbactam in Human Plasma: Application for Therapeutic Drug Monitoring in Critically Ill Patients. *Ther. Drug Monit.* **2020**, *42*, 578–587. [[CrossRef](#)]
35. Wong, G.; Taccone, F.; Villois, P.; Scheetz, M.H.; Rhodes, N.J.; Briscoe, S.; McWhinney, B.; Nunez-Nunez, M.; Ungerer, J.; Lipman, J.; et al. β -Lactam pharmacodynamics in Gram-negative bloodstream infections in the critically ill. *J. Antimicrob. Chemother.* **2020**, *75*, 429–433. [[CrossRef](#)]

36. Abdulla, A.; Dijkstra, A.; Hunfeld, N.G.M.; Endeman, H.; Bahmany, S.; Ewoldt, T.M.J.; Muller, A.E.; Van Gelder, T.; Gommers, D.; Koch, B.C.P. Failure of target attainment of beta-lactam antibiotics in critically ill patients and associated risk factors: A two-center prospective study (EXPAT). *Crit. Care Lond. Engl.* **2020**, *24*, 558. [[CrossRef](#)]
37. Grégoire, N.; Marchand, S.; Ferrandière, M.; Lasocki, S.; Seguin, P.; Vourc'h, M.; Barbaz, M.; Gaillard, T.; Launey, Y.; Asehnoune, K.; et al. Population pharmacokinetics of daptomycin in critically ill patients with various degrees of renal impairment. *J. Antimicrob. Chemother.* **2019**, *74*, 117–125. [[CrossRef](#)]
38. Guilhaumou, R.; Benaboud, S.; Bennis, Y.; Dahyot-Fizelier, C.; Dailly, E.; Gandia, P.; Goutelle, S.; Lefeuvre, S.; Mongardon, N.; Roger, C.; et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics and the French Society of Anaesthesia and Intensive Care Medicine. *Crit. Care* **2019**, *23*, 104. [[CrossRef](#)] [[PubMed](#)]
39. Sime, F.B.; Lassig-Smith, M.; Starr, T.; Stuart, J.; Pandey, S.; Parker, S.L.; Wallis, S.C.; Lipman, J.; Jason, A.; Roberts, J.A. Population Pharmacokinetics of Unbound Ceftolozane and Tazobactam in Critically Ill Patients without Renal Dysfunction. *Antimicrob. Agents Chemother.* **2019**, *63*, e01265-19. [[CrossRef](#)] [[PubMed](#)]
40. Stein, G.E.; Smith, C.L.; Scharmen, A.; Kidd, J.M.; Cooper, C.; Kuti, J.; Mitra, S.; Nicolau, D.P.; Havlicek, D.H. Pharmacokinetic and Pharmacodynamic Analysis of Ceftazidime/Avibactam in Critically Ill Patients. *Surg. Infect.* **2019**, *20*, 55–61. [[CrossRef](#)]
41. Dhaese, S.A.M.; Thooff, A.D.J.; Farkas, A.; Lipman, J.; Verstraete, A.G.; Stove, V.; Roberts, J.A.; De Waele, J.J. Early target attainment of continuous infusion piperacillin/tazobactam and meropenem in critically ill patients: A prospective observational study. *J. Crit. Care* **2019**, *52*, 75–79. [[CrossRef](#)]
42. Alexandre, K.; Fantin, B. Pharmacokinetics and Pharmacodynamics of Temocillin. *Clin. Pharmacokinet.* **2018**, *57*, 287–296. [[CrossRef](#)] [[PubMed](#)]
43. Zheng, C.; Hu, X.; Zhao, L.; Hu, M.; Gao, F. Clinical and pharmacological hallmarks of rifapentine's use in diabetes patients with active and latent tuberculosis: Do we know enough? *Drug Des. Devel. Ther.* **2017**, *11*, 2957–2968. [[CrossRef](#)]
44. De Cock, P.A.; Desmet, S.; De Jaeger, A.; Biarent, D.; Dhont, E.; Herck, I.; Vens, D.; Colman, S.; Stove, V.; Commeyne, S.; et al. Impact of vancomycin protein binding on target attainment in critically ill children: Back to the drawing board? *J. Antimicrob. Chemother.* **2017**, *72*, 801–804. [[CrossRef](#)]
45. Tsai, D.; Stewart, P.; Goud, R.; Gourley, S.; Hewagama, S.; Krishnaswamy, S.; Wallis, S.C.; Lipman, J.; Roberts, J.A. Total and unbound ceftriaxone pharmacokinetics in critically ill Australian Indigenous patients with severe sepsis. *Int. J. Antimicrob. Agents.* **2016**, *48*, 748–752. [[CrossRef](#)]
46. Laterre, P.F.; Wittebole, X.; Van de Velde, S.; Muller, A.E.; Mouton, J.W.; Carryn, S.; Tulkens, P.M.; Dugernier, T. Temocillin (6 g daily) in critically ill patients: Continuous infusion versus three times daily administration. *J. Antimicrob. Chemother.* **2015**, *70*, 891–898. [[CrossRef](#)] [[PubMed](#)]
47. Liebchen, U.; Kratzer, A.; Wicha, S.G.; Kees, F.; Kloft, C.; Kees, M.G. Unbound fraction of ertapenem in intensive care unit patients. *J. Antimicrob. Chemother.* **2014**, *69*, 3108–3111. [[CrossRef](#)]
48. Vanstraelen, K.; Wauters, J.; Vercammen, I.; De Loo, H.; Maertens, J.; Lagrou, K.; Annaert, P.; Spriet, I. Impact of hypoalbuminemia on voriconazole pharmacokinetics in critically ill adult patients. *Antimicrob. Agents Chemother.* **2014**, *58*, 6782–6789. [[CrossRef](#)]
49. Wong, G.; Briscoe, S.; Adnan, S.; McWhinney, B.; Ungerer, J.; Lipman, J.; Roberts, J.A. Protein Binding of β -Lactam Antibiotics in Critically Ill Patients: Can We Successfully Predict Unbound Concentrations? *Antimicrob. Agents Chemother.* **2013**, *57*, 6165–6170. [[CrossRef](#)] [[PubMed](#)]
50. Hayashi, Y.; Lipman, J.; Udy, A.A.; Ng, M.; McWhinney, B.; Ungerer, J.; Lust, K.; Roberts, J.A. β -Lactam therapeutic drug monitoring in the critically ill: Optimising drug exposure in patients with fluctuating renal function and hypoalbuminaemia. *Int. J. Antimicrob. Agents* **2013**, *41*, 162–166. [[CrossRef](#)] [[PubMed](#)]
51. Vilay, A.M.; Griot, M.; Depestel, D.D.; Sowinski, K.M.; Gao, L.; Heung, M.; Salama, N.N.; Mueller, B.A. Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. *Crit. Care Med.* **2011**, *39*, 19–25. [[CrossRef](#)]
52. Benko, R.; Matuz, M.; Doro, P.; Peto, Z.; Molnar, A.; Hajdu, E.; Nagy, E.; Gardi, J.; Soos, G. Pharmacokinetics and pharmacodynamics of levofloxacin in critically ill patients with ventilator-associated pneumonia. *Int. J. Antimicrob. Agents* **2007**, *30*, 162–168. [[CrossRef](#)] [[PubMed](#)]
53. Burkhardt, O.; Kumar, V.; Katterwe, D.; Majcher-Peszynska, J.; Drewelow, B.; Derendorf, H.; Welte, T. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: Pharmacokinetics with special consideration of free-drug concentration. *J. Antimicrob. Chemother.* **2006**, *59*, 277–284. [[CrossRef](#)] [[PubMed](#)]
54. Mimoz, O.; Rolland, D.; Adoun, M.; Marchand, S.; Breilh, D.; Brumpt, I.; Debaene, B.; Couet, W. 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*, 775–779. [[CrossRef](#)]
55. Mimoz, O.; Soreda, S.; Padoin, C.; Tod, M.; Petitjean, O.; Benhamou, D. 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*, 735–743. [[CrossRef](#)]
56. Ochs, H.R.; Greenblatt, D.J.; Woo, E. Clinical pharmacokinetics of quinidine. *Clin. Pharmacokinet.* **1980**, *5*, 150–168. [[CrossRef](#)]
57. Booke, H.; Frey, O.R.; Röhr, A.C.; Chiriack, U.; Zacharowski, K.; Holubec, T.; Adam, E.H. Excessive unbound cefazolin concentrations in critically ill patients receiving veno-arterial extracorporeal membrane oxygenation (vaECMO): An observational study. *Sci. Rep.* **2021**, *20*, 16981. [[CrossRef](#)] [[PubMed](#)]

58. Gatti, M.; Bartoletti, M.; Cojutti, P.G.; Gaibani, P.; Conti, M.; Giannella, M.; Viale, P.; Pea, F. A descriptive case series of pharmacokinetic/pharmacodynamic target attainment and microbiological outcome in critically ill patients with documented severe extensively drug-resistant *Acinetobacter baumannii* bloodstream infection and/or ventilator-associated pneumonia treated with cefiderocol. *J. Glob. Antimicrob. Resist.* **2021**, *27*, 294–298. [[CrossRef](#)] [[PubMed](#)]
59. Jager, N.G.L.; van Hest, R.M.; Xie, J.; Wong, G.; Ulldemolins, M.; Brüggemann, R.J.M.; Lipman, J.; Roberts, J.A. Optimization of flucloxacillin dosing regimens in critically ill patients using population pharmacokinetic modelling of total and unbound concentrations. *J. Antimicrob. Chemother.* **2020**, *75*, 2641–2649. [[CrossRef](#)] [[PubMed](#)]
60. Van Raaij, J.J.; Mabelis, N.J.D.; Shudofsky, K.N.; Meenks, S.D.; Le Noble, J.L.M.L.; Janssen, P.K.C. Quantification of total and unbound cefuroxime in plasma by ultra-performance liquid chromatography tandem mass spectrometry in a cohort of critically ill patients with hypoalbuminemia and renal failure. *J. Clin. Lab. Anal.* **2020**, *34*, e23100. [[CrossRef](#)] [[PubMed](#)]
61. Kalaria, S.N.; Gopalakrishnan, M.; Heil, E.L. A Population Pharmacokinetics and Pharmacodynamic Approach To Optimize Tazobactam Activity in Critically Ill Patients. *Antimicrob. Agents Chemother.* **2020**, *64*, e02093-19. [[CrossRef](#)]
62. Wilkes, S.; van Berlo, I.; Ten Oever, J.; Jansman, F.; Ter Heine, R. Population pharmacokinetic modeling of total and unbound flucloxacillin in non-critically ill patients to devise a rational continuous dosing regimen. *Int. J. Antimicrob. Agents* **2019**, *53*, 310–317. [[CrossRef](#)]
63. Osthoff, M.; Siegemund, M.; Balestra, G.; Abdul-Aziz, M.H.; Roberts, J.A. Prolonged administration of β -lactam antibiotics—A comprehensive review and critical appraisal. *Swiss Med. Wkly.* **2016**, *146*, w14368. [[CrossRef](#)] [[PubMed](#)]
64. Brink, A.J.; Richards, G.A.; Lautenbach, E.E.G.; Rapeport, N.; Schillack, V.; Van Niekerk, L.; Lipman, J.; Roberts, J.A. Albumin concentration significantly impacts on free teicoplanin plasma concentrations in non-critically ill patients with chronic bone sepsis. *Int. J. Antimicrob. Agents* **2015**, *45*, 647–651. [[CrossRef](#)] [[PubMed](#)]
65. Roberts, J.A.; Udy, A.A.; Jarrett, P.; Wallis, S.C.; Hope, W.W.; Sharma, R.; Kirkpatrick, C.M.; Kruger, P.S.; Roberts, M.S.; Lipman, J. Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of ceftazidime in post-trauma critically ill patients. *J. Antimicrob. Chemother.* **2015**, *70*, 1495–1502. [[CrossRef](#)] [[PubMed](#)]
66. Roberts, J.A.; Stove, V.; De Waele, J.J.; Sipinkoski, B.; McWhinney, B.; Ungerer, P.J.P.; Akova, M.; Bassetti, M.; Dimopoulos, G.; Kaukonen, K.M.; et al. DALI Study Authors. Variability in protein binding of teicoplanin and achievement of therapeutic drug monitoring targets in critically ill patients: Lessons from the DALI Study. *Int. J. Antimicrob. Agents* **2014**, *43*, 423–430. [[CrossRef](#)]
67. Roberts, J.A.; Paul, S.K.; Akova, M.; Bassetti, M.; De Waele, J.J.; Dimopoulos, G.; Kaukonen, K.M.; Koulenti, D.; Martin, C.; Montravers, P.; et al. DALI Study. DALI: Defining antibiotic levels in intensive care unit patients: Are current β -lactam antibiotic doses sufficient for critically ill patients? *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2014**, *58*, 1072–1083. [[CrossRef](#)]
68. Eyler, R.F.; Vilay, A.M.; Nader, A.M.; Heung, M.; Pleva, M.; Sowinski, K.M.; DePestel, D.D.; Sörgel, F.; Kinzig, M.; Mueller, B.A. Pharmacokinetics of ertapenem in critically ill patients receiving continuous venovenous hemodialysis or hemodiafiltration. *Antimicrob. Agents Chemother.* **2014**, *58*, 1320–1326. [[CrossRef](#)]
69. Yagi, T.; Naito, T.; Doi, M.; Nagura, O.; Yamada, T.; Maekawa, M.; Sato, S.; Kawakami, J. Plasma exposure of free linezolid and its ratio to minimum inhibitory concentration varies in critically ill patients. *Int. J. Antimicrob. Agents* **2013**, *42*, 329–334. [[CrossRef](#)]
70. Roberts, J.A.; Pea, F.; Lipman, J. The clinical relevance of plasma protein binding changes. *Clin. Pharmacokinet.* **2013**, *52*, 1–8. [[CrossRef](#)]
71. Wenisch, J.M.; Meyer, B.; Fuhrmann, V.; Saria, K.; Zuba, C.; Dittrich, P.; Thalhammer, F. Multiple-dose pharmacokinetics of daptomycin during continuous venovenous haemodiafiltration. *J. Antimicrob. Chemother.* **2012**, *67*, 977–983. [[CrossRef](#)]
72. Ulldemolins, M.; Roberts, J.A.; Rello, J.; Paterson, D.L.; Lipman, J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. *Clin. Pharmacokinet.* **2011**, *50*, 99–110. [[CrossRef](#)]
73. Ulldemolins, M.; Roberts, J.A.; Wallis, S.C.; Rello, J.; Lipman, J. Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: Special emphasis on unbound pharmacokinetic. *J. Antimicrob. Chemother.* **2010**, *65*, 1771–1778. [[CrossRef](#)]
74. Brink, A.J.; Richards, G.A.; Schillack, V.; Kiem, S.; Schentag, J. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. *Int. J. Antimicrob. Agents* **2009**, *33*, 432–436. [[CrossRef](#)] [[PubMed](#)]
75. Pea, F.; Viale, P.; Pavan, F.; Furlanut, M. Pharmacokinetic Considerations for Antimicrobial Therapy in Patients Receiving Renal Replacement Therapy. *Clin. Pharmacokinet.* **2007**, *46*, 997–1038. [[CrossRef](#)] [[PubMed](#)]
76. Wolf, G.K.; McClain, C.D.; Zurakowski, D.; Dodson, B.; McManus, M.L. Total phenytoin concentrations do not accurately predict free phenytoin concentrations in critically ill children. *Pediatr. Crit. Care Med.* **2006**, *7*, 434–439. [[CrossRef](#)]
77. Stanke-Labesque, F.; Concordet, D.; Djerada, Z.; Bouchet, B.; Solas, C.; Mériçlier, E.; Bonnet, F.; Mourvillier, B.; Ruiz, S.; Martin-Blondel, G.; et al. Neglecting Plasma Protein Binding in COVID-19 Patients Leads to a Wrong Interpretation of Lopinavir Overexposure. *Clin. Pharmacol. Ther.* **2021**, *109*, 1030–1033. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.