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Title

Scaling beta-lactam antimicrobial pharmacokinetics from early life to old age

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Conflict of interest

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Abstract

Aims

Beta-lactam dose optimisation in critical care is a current priority. We aimed to review the PK of three commonly used beta-lactams (amoxicillin+/-clavulanate, piperacillin-tazobactam and meropenem) to compare PK parameters reported in critically and non-critically ill neonates, children and adults, and to investigate whether allometric and maturation scaling principles could be applied to describe changes in PK parameters through life.

Methods

A systematic review of PK studies of the three drugs was undertaken using MEDLINE and EMBASE. Pharmacokinetic parameters and summary statistics were extracted and scaled using allometric principles to 70 kg individual for comparison. Pooled data was used to model clearance maturation and decline using a sigmoidal (Hill) function.

Results

A total of 130 papers were identified. Age ranged from 29 weeks–82 years and weight from 0.9–200 kg. PK parameters from critically ill populations were reported with wider confidence intervals than those in healthy volunteers, indicating greater PK variability in critical illness. The standard allometric size and sigmoidal maturation model adequately described increasing clearance in neonates and a sigmoidal model was also used to describe decline in older age. Adult weight-adjusted clearance was achieved at approximately 2 years post menstrual age. Changes in volume of distribution were well described by the standard allometric model, although amoxicillin data suggested a relatively higher volume of distribution in neonates.

Conclusions

Critical illness is associated with greater PK variability than in healthy volunteers. The maturation models presented will be useful for optimising beta-lactam dosing, although a prospective, age-inclusive study is warranted for external validation.

Key words

Pharmacokinetics; pharmacometrics; antibiotics; critical care; paediatrics

What is already known on this subject:

- Antimicrobial resistance and high sepsis related mortality has led to increasing interest in dose optimisation of antibiotics
- Pharmacokinetic data from paediatric and neonatal critically ill populations is lacking
- Modern modelling approaches, using size and age maturation functions may allow extrapolation of PK data from adults to children

What this study adds:

- To our knowledge, this is the first review of the pharmacokinetics of amoxicillin, clavulanic acid, meropenem and piperacillin-tazobactam across all ages.
- The range of reported parameters has allowed comparison of values in critically ill and non-critically ill patients.
- For the first time parameters for a clearance maturation in young patients has been combined with a decline function in elderly patients, generating models that could be used for dose optimisation in patients of all ages.

1 Introduction

Infection is a common reason for admission to intensive care, accounting for 25-30% of admissions to adult units [1-3] and 8-12% of admissions to paediatric units [4, 5]. At any one time, half of the patients on an adult intensive care unit may be considered to have an infection [6] and up to 70% of intensive care patients will receive at least one course of antibiotics during their stay, regardless of age [6, 7]. Mortality for those with severe infection remains as high as 25-30% [8, 5] and infection remains one of the most common causes of death in neonates in the UK and worldwide [9-11]. Infection associated healthcare costs are considerable, with pneumonia and septicaemia accounting for over $30 billion (approximately 8%) of US healthcare spending [12].

Provision of prompt, targeted antimicrobial therapy is a key priority in the early stages of treatment of infection. While recent decades have seen the evolution of sepsis care bundles that tailor therapy for severe infection to the individual patient, antimicrobial dosing in critically ill patients remains largely identical to that in the non-critically ill [13]. This is despite the fact that pharmacokinetics in critical illness, particularly in patients at the extremes of the age spectrum, may be radically different from that in health or non-critical illness [14].

In adults, antimicrobial pharmacokinetics in critical illness is increasingly an area of interest for researchers. Population approaches to pharmacokinetic data modelling have afforded the opportunity for the investigation of pharmacokinetics in specific patient groups such as those with burns. However, studies are often small ($n<20$) and reported pharmacokinetic parameters vary considerably. For example, Bourget et al. reported piperacillin clearance of 6.8 L/hr/70kg whereas Jeon et al. reported 17.2 L/hr/70kg in critically ill patients with burns [15, 16].

Pharmacokinetic studies of antimicrobials in paediatric and neonatal populations are limited, with many dosing regimens still based on extrapolation from adults [17]. Anderson and Holford [18] argue that the scaling with size of the majority of biological systems can be described using an allometric power model with fixed exponents (for example 0.75 for clearance). This theory is supported by other work, for example by Calvier et al. [19], who showed that 0.75 as a fixed scaling exponent provided a good explanation to the clearance of 12,620 hypothetical drugs in older children, with maturation meaning this relationship breaks down with decreasing age. The age at which 0.75 scaling becomes inappropriate was drug-specific [19]. Holford et al. [20] separately argue that clearance maturation in intra-uterine, neonatal and early life can be described by a sigmoidal (E_{max} / Hill) function. Germovsek et al.

[21] recently showed that combining these methods describe pharmacokinetic maturation well in neonates and children in a review of midazolam and gentamicin pharmacokinetics. Other examples of the success of this combined allometric and maturation approach include the busulfan model by McCune et al. [22] and a comparison of morphine models by Holford et al. [23]. One criticism of the focus on paediatric patients in these studies is that a common standard adult mature value is assumed, whereas we know drug clearance declines with age [24]. To recommend beta-lactam dosing for patients of all ages, it would seem sensible to develop a model based on data from the whole population.

We therefore undertook a review of pharmacokinetic studies of three commonly used beta-lactam antibiotics: amoxicillin (+/- clavulanic acid), meropenem and piperacillin-tazobactam. Our aim was to compare pharmacokinetic parameters reported in critically ill and non-critically ill neonates, children and adults, and to investigate whether allometric and maturation scaling principles could be applied to describe changes in pharmacokinetic parameters through life.

2 Methods:

2.1 Data source and search strategy

The US national library of medicine PubMed search engine (including MEDLINE database) and EMBASE electronic database (using Wolters Kluwer OVID search engine) were used to search for human studies [25-27]. Drug name (e.g. 'amoxicillin') and 'pharmacokinetic*' were the key words searched for. Results were taken up to the 30th week of 2017.

2.2 Eligibility criteria

English-language studies were included that published pharmacokinetic parameters from original data or used data for which pharmacokinetic parameters had not been published previously, contained description of participant characteristics and the methods used for obtaining pharmacokinetic parameters, and included 8 or more subjects (in order to exclude small case series or case reports).

2.3 Data extraction

We extracted the following data: number of participants, patient population and clinical setting, methods for estimating pharmacokinetic parameters and final structural model used (where compartmental methods were used), summary statistics of the age and weight of the study group, and pharmacokinetic parameters (clearance and volume of distribution). 95%

confidence intervals for population mean values of pharmacokinetic parameters were recorded where published (including Bootstrap analyses) or were calculated, assuming a Student's t-distribution where standard deviation or standard error were published.

2.4 Scaling of parameters

Pharmacokinetic parameters were scaled to 70 kg, using mean participant weight (or median where mean not published). Volume of distribution was scaled linearly with weight and clearance was scaled with an allometric exponent of 0.75, as described previously [18] (equations 1). For parameters that were already allometrically scaled to 70 kg, the typical pharmacokinetic values were used directly from the source paper.

Equations 1 Allometric scaling of volume (top) and clearance (bottom) parameters

$$V_{D_{scaled}} = V_{D_{study}} \left(\frac{70}{Mean\ weight}\right)$$

$$CL_{scaled} = CL_{study} \left(\frac{70}{Mean\ weight}\right)^{0.75}$$

Where V and CL are volume of distribution and clearance values identified from the study scaled to a 70 kg individual using the mean weight from the study participants (median used where mean not presented).

2.5 Data summary measures

Population mean/median pharmacokinetic parameters with confidence intervals were plotted and compared in different populations using analysis of variance (ANOVA), where appropriate (adults/children/neonates, healthy/critically ill). Where comparisons between study groups were made (e.g. adult healthy and adult critically ill), unweighted mean parameter values were used. Unweighted means were used to avoid over-influence of one or two larger studies in specific populations groups e.g. Udy et al. study (n=48) of piperacillin in patients with augmented renal clearance [28]. Neonates were less than 28-days corrected age, children 28-days corrected age to 18 years and adults were aged over 18. Where corrected age in prematurely delivered neonates is chronological age from birth minus the number of days of prematurity. Prematurity is defined as birth earlier than 36 weeks gestation.

2.6 Modelling maturation-decline of pharmacokinetics through life

Pooled data (unweighted mean parameter estimates) were used to model the effect of ageing on pharmacokinetic parameters. A sigmoidal (Hill) function (Equation 2) was fitted to clearance values to model maturation of drug clearance with age [21]. Post-menstrual age was used (chronological age plus number of weeks gestation at birth) in these models. Similarly, a sigmoidal decline function was fitted to model decline in function in old age. An exponential error model was used as these parameters are commonly assumed to be log-normally distributed. Studies where a majority of participants were receiving some form of renal replacement therapy were excluded from this analysis. Parameters for these functions were estimated using NONMEM version 7.3 (ICON plc)[29]. Model fit was assessed using established statistical and graphical methods, including likelihood-based diagnostics (via the NONMEM objective function value) and assessment of model simulation properties (visual predictive check). Model plots and graphical analysis was undertaken using R language and environment for statistical computing, with the ggplot2 package [30, 31]

Equation 2 Clearance maturation decline function

$$CL = CL_{STD}.\left(\frac{WT}{70}\right)^{0.75}.\left(\frac{PMA^{\theta_1}}{PMA^{\theta_1} + PMA_{50}^{\theta_1}}\right).\left(1 - \frac{AGE^{\theta_2}}{AGE^{\theta_2} + AGE_{50}^{\theta_2}}\right).\exp(\varepsilon)$$

Where: CL is model predicted clearance, CL_{STD} is a standardised clearance, PMA is post menstrual age in weeks and PMA_{50} is the PMA age at which 50% of adult function is achieved; AGE is age in years and AGE_{50} is the AGE at which 50% of decline has occurred; θs are Hill coefficients. $CL_{STD}, PMA_{50}, AGE_{50}$ and θs are estimated in the model fitting process. Model is fitted to the observed (literature) values with parameters chosen to minimise ε.

3 Results

3.1 Study selection

A flow chart of study selection for each drug is provided in Figure 1. A total of 2082 articles were identified and screened, with 130 studies included in the final analysis [15, 16, 28, 32-158]. Some studies provided pharmacokinetic parameters for two drugs (e.g. piperacillin and tazobactam) or several discrete groups (e.g. 0-1, 1-2 years etc.), meaning 173 sets of pharmacokinetic parameters were available for analysis. A summary of the articles identified, the patient setting, number of participants and scaled pharmacokinetic parameters with calculated confidence intervals is presented in supplementary material - Appendix 1. The range of methods used to calculate pharmacokinetic parameters included non-compartmental analyses and population approaches using parametric and non-parametric methodology.

3.2 Pharmacokinetic parameters

Table 1 summarises the demographics and pharmacokinetic parameters from the identified studies including the range of values identified. Plots of weight-standardised clearance (Figure 2) and volume of distribution (Figure 3) with associated confidence intervals for population mean are shown. Clavulanic acid data are not presented as there were only a small number of studies (6) identified. There were more adult models identified (129) than paediatric (28) and neonatal (16). The range of ages was 25 weeks–82 years and weight 0.9–200 kg. Mean drug clearance and volume of distribution were similar for the 5 drugs, 8.9–13.9 L/h/70kg and 23.6–28.9 L/70kg. Mean clearance values for adults did not appear to differ between setting (healthy/hospital/critical illness), although confidence intervals (Figure 2) appeared greater for studies in critical illness compared with healthy volunteers, perhaps suggesting greater pharmacokinetic variability in critically ill populations. Volume of distribution was significantly greater in critically ill adults compared with healthy volunteers administered piperacillin (25.4 vs 13.4 L/70 kg, $p<0.001$) and meropenem (26.2 vs 16.1, $p=0.02$). Comparison between settings for children and neonates was not possible as healthy volunteer data was not available.

3.3 Maturation-decline functions

Parameters for the maturation-decline function for each drug are shown in Table 2. These were estimated using NONMEM from the pharmacokinetic parameters identified in the literature review. One study by Cohen-Wolkowiez et al. [132] was excluded from the piperacillin model fit as it used a scavenged sampling technique and the parameter estimates from this study were distinctly different from others in similar participants and uncertainty was large. Two ceftolozane-tazobactam studies [134, 135] were excluded from the tazobactam model fit as the clearance values from these studies deviated significantly from similar studies with piperacillin-tazobactam. Clavulanic acid was not modelled as the number of studies was small.

The pooled maturation model suggests that size standardised clearance approaches adult values at around 2 years post-menstrual age. Figure 4 shows a visual predictive check of the pooled model, it appears to describe age related changes at the extremes of life well. As the amoxicillin data suggested higher volume of distribution in neonates, a ‘hockey stick’ function was fitted to these data (Figure 5), with a pivot point at 34 years (relative standard error (RSE) 29%).

4 Discussion

We have, for the first time, presented a unified model to describe beta-lactam pharmacokinetics throughout life. This was achieved by describing the changes in beta-lactam pharmacokinetics in early life using the standard allometric scaling and organ maturation functions described by Holford et al. [20] and further extending this model by using a sigmoidal decline function to describe the decline in clearance associated with old age. Parameters from the pooled model suggest adult values of clearance are achieved at approximately two years post-menstrual age and at 87 years beta-lactam clearance is half of that found in young adults. This quantification of the effect of age on beta lactam pharmacokinetics could be used in dose-optimisation studies.

The final parameter estimates for clearance maturation using pooled data were similar to values identified by Germovsek et al. [21] in their pooled analysis of gentamicin studies. These values are compared, along with the values suggested by Rhodin et al. [159] in their model of glomerular filtration maturation in Table 3, noting that these beta-lactams undergo tubular secretion alongside filtration.

It is worth noting that Germovsek et al. [21], in common with other similar studies that estimate maturation, exclude results from older adults to avoid the confounding effects of age and the natural decline in renal function. In our analysis, we have successfully described this decline using a sigmoidal function that mirrors that used to describe maturation. We have used age as the covariate. It was not possible to use glomerular filtration to see if it explained all of the age effect, as studies were not consistent in the reporting of renal function. Some did not report it at all, some reported plasma creatinine and those that did report glomerular filtration used a variety of methods. It is likely that there will remain some age effect, even after taking filtration into account, as active excretion plays a part in the elimination of these drugs. A further related limitation is that, for similar reasons, no account was taken in our model for studies that did include a creatinine clearance function in their clearance models. The AGE_{50} parameter associated with decline in clearance with age was similar for amoxicillin and piperacillin at 79 and 74.8 years respectively (Table 2). The value of 31.3 years for meropenem suggests the model may have been skewed by one higher clearance value in children from the study by Petit et al. [79]. The use of a decline function such as this therefore has merit as part of efforts toward dose optimisation for all age groups, although investigating the validity of the decline function presented here requires pooled data across age groups with a consistent method of measuring renal function.

When comparing clearance parameters across these populations, it is perhaps interesting to note that mean clearance parameters were similar between critically and non-critically ill individuals (Table 1). Whilst the prevalence of acute kidney injury in critical illness might lead one to expect lower clearance values in this population, other physiological changes including high cardiac output/low vascular resistance states have been recognised to increase clearance for some patients [160-162]. It is therefore not unexpected that mean clearance values in critically ill populations are similar to those in healthy populations. We think it is important to note that the confidence intervals for the estimates of clearance were greater in critical illness studies compared to healthy volunteer studies and suggest this may indicate greater pharmacokinetic variability between critically ill individuals. The obvious counter argument to this is that this observation is simply explained by greater or systematic experimental error in critically ill studies. However, the observation arises from multiple studies (e.g. 25 critically ill and 7 healthy volunteer datasets for piperacillin) and confidence intervals for clearance in critically ill studies were also greater than hospital inpatient studies (Appendix 1 and Figure 2) where the same systematic experimental errors would reasonably be expected. In addition, the number of participants (n) was greater in critically ill studies (piperacillin mean n of 26 in critically ill versus 13 in healthy volunteer) which one would ordinarily anticipate leading to greater certainty in parameter estimates. Increased pharmacokinetic variability might be clinically significant for drugs with concentration-time dependent killing. For example, the 95% confidence interval for piperacillin clearance in the study by Shikuma et al. [89] had an almost 3-fold difference between lower and upper bounds (11.5–33.2 L/hr/70kg). Indeed Roberts et al., in an observational study of beta-lactams, reported that 16% of patients failed to achieve pharmacokinetic-pharmacodynamic targets and that this was associated with treatment failure [163]. It was also interesting to note that the clearance values identified in the literature review for healthy individuals are lower than those published in the summary of product characteristics (Table 1). For example, the mean weight-adjusted clearance for amoxicillin identified in healthy volunteer studies was 13.5 L/h/70kg, compared to 25L/hr published in the summary of product characteristics [164]. It is not immediately clear why this should be. It may be that the summary of product characteristic values arise from unpublished data.

Changes in volume status are common in septic patients. Altered vascular tone and endothelial dysfunction lead to shifts in the distribution of fluid from the vascular to extravascular space [165]. This is reflected in the significantly greater volume of distribution described in the patient groups who are likely to be the most unwell (critically ill patients receiving

piperacillin-tazobactam and meropenem). Variability in volume of distribution was also marked in critical illness studies. For example, Jeon et al. [16] reported a 100-fold variation between lower and upper bounds of the confidence interval of the mean for volume of distribution in a study of burns patients (10.2–1004 L/70kg). This wide variation was all the more remarkable given this was a relatively large study, including 50 participants. The relatively larger volume of distribution of amoxicillin in neonates compared to adults reflects recognised physiological differences in this age group [20] and Eleveld et al. [166, 167] have recently described similar volume of distribution changes for remifentanil and propofol. The absence of such an effect in meropenem and piperacillin is probably explained by the fact that adult distributions of body water are reached relatively early in life and there were no studies in the very young of these drugs. Indeed, the pivot point of 34 years in the amoxicillin volume of distribution model is much later than one might expect. This probably reflects a lack of data in young children and adolescents to inform the pivot point in this empirical model fit.

The greatest limitation of the maturation-decline functions described is the degree of uncertainty associated with the parameter estimates. The PMA_{50}, for example, varied from 49 to 398 weeks between drugs, with the large uncertainty for meropenem and tazobactam (relative standard error 236% and 151% respectively), probably reflecting the lack of data in young children. These estimates are derived from what are, in general, small pharmacokinetic studies, with a median of 14 participants. Furthermore, the uncertainty of pharmacokinetic parameter estimates from these studies was not taken into account in the estimation of the parameters of the maturation-decline function. By using only mean (or median) values, information is clearly lost and each study contributes identically to the model fit, regardless of size of the study or uncertainty reported. Although it is worth noting that the median number of participants was similar across drugs (Table 1) and weighting for sample size might have led to over-influence of larger studies in specific patient groups, e.g. Jeon et al. [16] n=50 burns patients. Similarly, requesting raw data was impractical and unlikely to yield a significant response in the limited time available for this study. Indeed Germovsek et al. [168] in their review of gentamicin obtained data from only 2 of 8 authors. Such a low response rate was felt unlikely to improve the inferences that can be made from this retrospective review. Particularly as some of the research dates back to the mid 20th century, further decreasing the potential for obtaining raw data. A prospective age-inclusive pharmacokinetic study could improve the accuracy of the parameter estimates.

5 Conclusions

Over the last decade a standardised method has been developed to handle maturation of clearance throughout childhood. Much less work has been undertaken to describe the effect of ageing on clearance, limiting the potential to fit models across all age groups. Antimicrobial resistance and high sepsis-related mortality is a problem for patients of any age. The beta-lactam model presented here could be used for dose optimisation throughout life, although a prospective study to evaluate our model is warranted. We also foresee a number of other potential uses for our model by others. For example, for those conducting focussed PK studies with narrow age ranges, the size and maturation parameters in our model could be fixed, thereby allowing for the exploration of other covariates after size and age are delineated. The parameters could potentially assist with the conduct of in vitro hollow fibre experiments seeking to mimic human concentration-time profiles in specific age groups. For secondary analysis of clinical trials where no PK are collected, our parameters could be used to predict typical exposure for given dose schemes.

6 Acknowledgements, conflicts and ethical statement

Acknowledgements

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Compliance with ethical standards

This article does not contain any previously unpublished studies with human participants. Ethical approval was not required. No funding was received for the conduct of this study or preparation of this manuscript. B Philips is in negotiation with the British National Formulary

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Table 1 Summary statistics from literature review of pharmacokinetic studies

Drug	Amoxicillin	Piperacillin	Meropenem	Clavulanic acid	Tazobactam
Number of studies	23	54	53	6	31
By age (neonates/children/adults)	7/4/13	3/8/47	3/8/43	0/3/3	3/5/23
By setting (healthy/hospital/ITU)	9/5/10	9/20/29	7/15/32	1/2/3	4/14/13
Haemodialysis/filtration	1	7	9	0	4
Median number of participants	13	14	15	13	12
Age range (post-menstrual age)	29 weeks – 82 years	25 weeks – 71 years	27 weeks – 76 years	2.6–62 years	30 weeks – 71 years
Weight range, kg	1.1–79.4	0.9–164.0	0.9–200.4	14.4–75.0	1.4–161.0
Mean drug clearance (all ages), L/h/70kg (range)	10.9 (1.3–22.4)	10.6 (1.9–22.4)	10.0 (1.0–24.1)	13.9 (8.9–17.9)	8.9 (2.1–25.2)
Mean clearance values (adults) by setting L/h/70kg (standard deviation)					
Healthy volunteer	13.5 (4.6)	11.3 (3.8)	11.8 (2.4)	16.1 (–)	10.0 (4.9)
Hospital inpatient	11.3 (9.4)	13.5 (4.2)	10.8 (4.2)	–	12.3 (6.8)
Critically ill	10.7 (1.7)	11.3 (5.3)	11.0 (4.5)	11.0 (3.0)	10.5 (4.9)
Mean volume of distribution (all ages), L/70kg (range)	28.9 (10.7–53.5)	25.0 (9.8–203.7)	23.8 (8.8–50.4)	23.9 (21.0–30.4)	23.6 (9.1–63.0)
Mean volume of distribution (adults) by setting L70kg (standard deviation)					
Healthy volunteer	22.3 (9.3)	13.4 (4.8)	16.1 (2.9)	23.1 (–)	23.9 (26.1)
Hospital inpatient	18.3 (3.1)	20.4 (4.7) **p=0.04**	22.0 (10.0)	–	21.0 (5.7)
Critically ill	22.2 (4.7)	25.3 (9.9) **p<0.001**	26.2 (8.2) **p=0.02**	21.1 (0.2)	27.2 (9.6)
Summary of product characteristics [30-32]					
Clearance (L/hr)	25	10–17	17	Not published in SPC	
Volume of distribution (L)	21–28	17	17.5		

Note some studies included multiple age groups or clinical settings. ANOVA undertaken on clearance and volume of distribution values by setting in adults. Healthy volunteer used as reference. $p<0.05$ only shown. Comparison is not possible in other age groups as healthy volunteer studies were not found. Studies in haemodialysis settings were excluded from the analysis of clearance data

Table 2 Parameter estimates for clearance maturation-decline function

Model parameter	Amoxcillin	Piperacillin	Meropenem	Pooled data
CL_{STD} (L/hr/70kg)	17.0 (8)	12.7 (9)	34.6 (193)	12.9 (6)
θ_1	4.29 (34)	1.8 (31)	1.1 (26)	3.45 (77)
PMA_{50} (weeks)	49.0 (16)	71.6 (23)	398 (236)	49.7 (32)
θ_2	1.95 (41)	13.8 (361)	1.11 (65)	4.0 (44)
AGE_{50} (years)	79.0 (14)	74.8 (27)	31.3 (257)	86.8 (9)
σ^2	0.08	0.11	0.11	0.13

$$CL = CL_{STD}.\left(\frac{WT}{70}\right)^{0.75}.\left(\frac{PMA^{\theta_1}}{PMA^{\theta_1}+PMA_{50}^{\theta_1}}\right).\left(1-\frac{AGE^{\theta_2}}{AGE^{\theta_2}+AGE_{50}^{\theta_2}}\right).\exp(\varepsilon)$$

Where: CL is the model predicted clearance; CL_{STD} is a standardised clearance; PMA is post menstrual age in weeks and PMA_{50} is the PMA age at which 50% of adult function is achieved; AGE is age in years and AGE_{50} is the AGE at which 50% of decline has occurred; θs are Hill coefficients. σ^2 is the estimated variance of ε. Data presented above are mean parameter estimates (% Relative standard error (RSE))

Table 3 Maturation-decline function parameters from this review compared with published values from similar studies

Model	$\boldsymbol{\theta_1}$	$\boldsymbol{PMA_{50}}$ **(weeks)**
Germovsek et al. [21]	4.19 (17)	45.1 (7)
Rhodin et al. [36]	3.40	47.7
Pooled from this review	3.45 (77)	49.7 (32)

$$\left(\frac{PMA^{\theta_1}}{PMA^{\theta_1}+PMA_{50}^{\theta_1}}\right)$$

PMA is post menstrual age in weeks and PMA_{50} is the PMA age at which 50% of adult function is achieved. $\theta_1$is the Hill parameter. PMA_{50} and θ_1 are estimated in the model fitting process.

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Haemodialysis/filtration	1	7	9	0	4
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Weight range, kg	1.1–79.4	0.9–164.0	0.9–200.4	14.4–75.0	1.4–161.0
Mean drug clearance (all ages), L/h/70kg (range)	10.9 (1.3–22.4)	10.6 (1.9–22.4)	10.0 (1.0–24.1)	13.9 (8.9–17.9)	8.9 (2.1–25.2)
Mean clearance values (adults) by setting L/h/70kg (standard deviation)					
Healthy volunteer	13.5 (4.6)	11.3 (3.8)	11.8 (2.4)	16.1 (–)	10.0 (4.9)
Hospital inpatient	11.3 (9.4)	13.5 (4.2)	10.8 (4.2)	–	12.3 (6.8)
Critically ill	10.7 (1.7)	11.3 (5.3)	11.0 (4.5)	11.0 (3.0)	10.5 (4.9)
Mean volume of distribution (all ages), L/70kg (range)	28.9 (10.7–53.5)	25.0 (9.8–203.7)	23.8 (8.8–50.4)	23.9 (21.0–30.4)	23.6 (9.1–63.0)
Mean volume of distribution (adults) by setting L70kg (standard deviation)					
Healthy volunteer	22.3 (9.3)	13.4 (4.8)	16.1 (2.9)	23.1 (–)	23.9 (26.1)
Hospital inpatient	18.3 (3.1)	20.4 (4.7) **p=0.04**	22.0 (10.0)	–	21.0 (5.7)
Critically ill	22.2 (4.7)	25.3 (9.9) **p<0.001**	26.2 (8.2) **p=0.02**	21.1 (0.2)	27.2 (9.6)
Summary of product characteristics [169, 164, 170]					
Clearance (L/hr)	25	10–17	17	Not published in SPC	
Volume of distribution (L)	21–28	17	17.5		

Note some studies included multiple age groups or clinical settings. ANOVA undertaken on clearance and volume of distribution values by setting in adults. Healthy volunteer used as reference. $p<0.05$ only shown. Comparison is not possible in other age groups as healthy volunteer studies were not found. Studies in haemodialysis settings were excluded from the analysis of clearance data

Table 2 Parameter estimates for clearance maturation-decline function

Model parameter	Amoxcillin	Piperacillin	Meropenem	Pooled data
CL_{STD} (L/hr/70kg)	17.0 (8)	12.7 (9)	34.6 (193)	12.9 (6)
θ_1	4.29 (34)	1.8 (31)	1.1 (26)	3.45 (77)
PMA_{50} (weeks)	49.0 (16)	71.6 (23)	398 (236)	49.7 (32)
θ_2	1.95 (41)	13.8 (361)	1.11 (65)	4.0 (44)
AGE_{50} (years)	79.0 (14)	74.8 (27)	31.3 (257)	86.8 (9)
σ^2	0.08	0.11	0.11	0.13

$$CL = CL_{STD}.\left(\frac{WT}{70}\right)^{0.75}.\left(\frac{PMA^{\theta_1}}{PMA^{\theta_1} + PMA_{50}^{\theta_1}}\right).\left(1 - \frac{AGE^{\theta_2}}{AGE^{\theta_2} + AGE_{50}^{\theta_2}}\right).\exp(\varepsilon)$$

Where: CL is the model predicted clearance; CL_{STD} is a standardised clearance; PMA is post menstrual age in weeks and PMA_{50} is the PMA age at which 50% of adult function is achieved; AGE is age in years and AGE_{50} is the AGE at which 50% of decline has occurred; θs are Hill coefficients. σ^2 is the estimated variance of ε. Data presented above are mean parameter estimates (% Relative standard error (RSE))

Table 3 Maturation-decline function parameters from this review compared with published values from similar studies

Model	$\boldsymbol{\theta_1}$	$\boldsymbol{PMA_{50}}$ **(weeks)**
Germovsek et al. [21]	4.19 (17)	45.1 (7)
Rhodin et al. [159]	3.33	55.4
Pooled from this review	3.45 (77)	49.7 (32)

$$\left(\frac{PMA^{\theta_1}}{PMA^{\theta_1} + PMA_{50}^{\theta_1}}\right)$$

PMA is post menstrual age in weeks and PMA_{50} is the PMA age at which 50% of adult function is achieved. $\theta_1$is the Hill parameter. PMA_{50} and θ_1 are estimated in the model fitting process.

Figure 1 Flow diagram of studies identified in the review of antimicrobial pharmacokinetics

Figure 2 Weight-standardised clearance values identified from literature search plotted against age

Mean clearance values (standardised to a 70-kg individual) from each study are plotted with an associated confidence interval (where available). The size of the points is proportional to the number of participants. Colours are used to denote the setting of the study. There appears to be greater uncertainty in parameter estimates of studies in critically ill compared with healthy populations. As expected, there is a lower clearance in neonates and elderly populations, despite standardising values allometrically

Figure 3 Weight-standardised volume of distribution values identified from literature search plotted against age

Mean volume values (standardised to a 70-kg individual) from each study are plotted with an associated confidence interval (where available). The size of the points is proportional to the number of participants. Colours are used to denote the setting of the study. There appears to be greater uncertainty in parameter estimates of studies in critically ill compared with healthy populations. Weight-based allometric scaling appears to control for effects of age, except for amoxicillin where there appears to be a greater volume of distribution for neonates compared to adults.

Figure 4 Visual predictive check of maturation-decline model for clearance using pooled data from amoxicillin, piperacillin, meropenem and tazobactam

The shaded area is the interval between the 2.5th and 97.5th centiles of clearance values simulated using the maturation-decline function (solid black line). Simulations from the model encapsulate literature clearance values (coloured dots) relatively well, although some sit below the lower confidence level

Figure 5 Visual predictive check of amoxicillin volume of distribution values using 'hockey-stick' function

Shaded area is the interval between 2.5^{th} and 97.5^{th} centiles of amoxicillin volume of distribution values simulated using hockey-stick function (dashed line)

Appendix 1: Summary of pharmacokinetic parameters identified in literature search

Ref	Population (n)	Age (years unless other specified)	Weight (kg)	Structural model	Clearance (L/h/70kg)	Volume at steady state (L/70kg)	Comments/modelling approach
Amoxicillin							
[136]	Adults, critically ill (13)	62 IQR (58–72)	75 IQR (70–79)	Two compartment	9.5 (95% CI: 8.2–12.0)	25.6 (95% CI: 20.4–42.4)	Population approach
[137]	Adults, critically ill (haemorrhagic shock) (12)	Med 33 range (18–51)	Med 75 range (61–90)	Two compartment	12.0 (6.3–22.2) range only	18.9 (7.7–28.7) range only	Population approach + non-compartmental analysis
[138]	Adults, hospitalised (57)	67 sd (±16)	78 sd (± 20)	One compartment	12.3 (95% CI: 10.9–13.6)	21.7 (95% CI: 20.4–23.0)	Parameters derived from pre-specified model using observed concentrations
[139]	Adults, long term dialysis (8)	39 range (17–74)	54.2 range (43–66)	Two-compartment linear model	4.6 (95% CI: 3.8–5.4)	20.5 (95% CI: 13.3–27.8)	Predefined model
[140]	Adults, pregnant requiring amoxicillin (44)	30 sd (±6.9)	79.4 sd (±14.0)	Three compartment	17.9 (95% CI: 16.1–19.7)	16.0 (95% CI: 13.7–18.4)	Population approach
[137]	Adults, healthy volunteers (12)	Med 32 Range (20–54)	Med 74 range (53–89)	Two compartment	14.4 (12.7–18.4) *range only*	30.1 (11.2–26.6) *range only*	
[141]	Adults, healthy volunteers (9)	28.3 range (21–45)	66.4 range (46–88)	Two compartment	13.8 (95% CI: 11.0–16.7)	17.6 (95% CI: 14.4–20.8)	Pre-specified model
[142]	Adults, healthy volunteers (24)	range (18–32)	range (57–98)	Two compartment	22.4 (95% CI: 19.5–25.3)	42.7 (95% CI: 36.3–49.1)	Regression analysis with pre-specified model. Mean weight not available. Assumed 70 kg
[143]	Adult, elderly (12)	73.9 range (69–83)	64.9 range (52–83)	Two compartment	11.5 (95% CI: 10.4–12.6)	19.6 (95% CI: 18.7–20.5)	Nonlinear least squares regression analysis, pre-specified structural model
[144]	Adult, elderly (8)	82 range (69–87)	67 range (51–82)	Non-compartmental analysis	6.7 (95% CI: 3.0–10.4)	21.9 (95% CI: 14.1– 29.8)	Parameters calculated using trapezoid rule and log-linear regression
[145]	Adults, healthy volunteers (9)	29 range (21–38)	75.0 range (63–94)	Two compartment	11.1 (95% CI: 9.7–12.5)	14.7 (95% CI: 13.2–16.2)	Nonlinear least squares regression analysis, pre-specified structural model
[146]	Adults, healthy volunteers (8)	range (20–30)	74.5 range (59–91)	Two compartment	18.8 (95% CI: 17.6–20.0)	21.8 (95% CI: 20.0–23.6)	Iterative least-squares process, pre-specified structural model
[147]	Adults, healthy volunteers (12)	27 sd (± 3.8)	64.8 sd (± 5.1)	Two compartment	10.8* Calculated from other parameters	10.7 (95% CI: 10.4–11.0)	Pre-specified model
[148]	Children, critically ill (50)	2.6 range (1/12–15)	14.4 range (4–65)	Three compartment	18.0 (95% CI: 15.3–21.3)	25.7 (95% CI: 17.0–38.9)	Population approach
[149]	Children, 'seriously ill' (15)	6.9 range (2–14)	Not recorded	Non-compartmental	16.7 (95% CI: 15.3–18.1)	32.8 (95% CI: 29.8–35.8)	Trapezoidal rule
[150]	Children, treated for viral infection or neurological disease (12)	10 range (2–14.5)	Not reported	Two-compartment	21.6 (95% CI: 19.6–23.6)	53.5 (95% CI: 44.5–62.5)	Regression/trapezoidal rule
[151]	Infants and Children treated for infection (14)	14.6 months (mean only)	Not reported		14.5 (mean only reported)	24.3 (mean only reported)	Regression analysis using least mean squares
[152]	Neonates, hypothermia (125)	GA 40 weeks range (36–42)	Median 3.3 (2.1–5.1)	Two compartment	2.9 (95% CI: 2.7–3.2)	50.3 (95% CI: 40.6–60.5)	Population approach; allometric scaling

		PNA 5 days (2–5)					
[153]	Neonates, premature (40)	GA 28.9 weeks range (24–32) PNA 1.1 days (1–3)	1.1 (0.6–1.5)	One compartment	2.0 (CV 6.6%)	43.1 (CV 7.6%)	Population approach
[154]	Neonates, premature (17)	GA 29 weeks sd (± 6/7) PNA 3 days	1.2 (±0.3)	One compartment	1.3 (95% CI: 1.0–1.5)	33.8 (95% CI: 27.8–39.8)	Visual inspection used to determine structural model
[155]	Neonates, premature (150)	GA 34.6 weeks range (24.9–42.4) PNA 0.8 days range (0–9)	2.3(±1.1)	One compartment	2.9 (95% CI: 2.7–3.0)	45.5 (95% CI: 44.0–47.0)	Iterative two stage Bayesian fitting procedure, pre-specified model
[156]	Neonates, premature (11)	PNA 26 days range (1–63)	3.4 range (2.9–3.8)	One compartment	2.8 (95% CI: 2.7–2.9)	28.7 (95% CI: 26.8–30.6)	Pre-specified model
[157]	Neonates, PNA > 9 days (32)	PNA 24.7 days range (10–52)	2.3 range (0.8–4.3)	One compartment	5.4 (95% CI: 4.3–6.4)	46.2 (95% CI: 39.4–53.0)	Iterative two stage Bayesian fitting procedure, pre-specified model
[158]	Neonates (11)	GA 38 weeks sd (±3)	3 (±0.8)	Non-compartmental	8.6 (95% CI: 5.9–11.3)	–	Continuous infusion study, steady state assumed
Clavulanic acid							
[136]	Adults, critically ill (13)	62 IQR (58–72)	75 IQR (70–79)	Two compartment	8.9 (95% CI: 6.0–12.2)	21.8 (95% CI: 14.2–68.1)	Population approach
[137]	Adults, critically ill (haemorrhagic shock) (12)	33 range (18–51)	Med 75 range (61–90)	Two compartment	13.1 range (6.6–22.8)	21 range (13.5–32.3)	Population approach + non-compartmental analysis
[137]	Adults, well volunteers (12)	32 range (20–54)	74 range (53–89)	Two compartment	16.1 range (9.0–33.6)	23.1 range (17.8–99.2)	Population approach + non-compartmental analysis
[148]	Children, critically ill (50)	2.6 range (1/12–15)	14.4 range (4–65)	Two compartment	12.2 (95% CI: 10.5–14.6)	21.6 (95% CI: 14.2–68.1)	Population approach
[149]	Children, ‘seriously ill’ (15)	6.9 range (2–14)	Not recorded	Non-compartmental	17.9 (95% CI: 13.3–22.5)	30.4 (95% CI: 23.5–37.3)	Trapezoidal rule
[150]	Children, with viral infection & neurological disease (12)	10 range (2–14.5)	Not reported	Two-compartment	15.2 (95% CI: 13.4–17.0)	25.8 (95% CI: 23.6–28.0)	Regression/trapezoidal rule

Mean or median values presented. With associated range, interquartile range (IQR) or standard deviation (sd). 95% confidence intervals have been calculated, where standard deviation or standard error data was available, assuming a student’s t-distribution. GA is gestational age, PMA is post-menstrual age

Ref	Population (n)	Age (years unless other specified)	Weight (kg)	Structural model	Clearance (L/h/70kg)	Volume at steady state (L/70kg)*	Comments/modelling approach
Piperacillin							
[85]	Adults, critically ill (15)	62 IQR (58–72)	78 IQR (70–79)	Two compartment	12.2 IQR (9.4–20.9)	23.1 IQR (15.7–22.6)	Population approach
[86]	Adults, critically ill, septic shock (high creatinine) (15)	66 IQR (59, 79)	80 IQR (70.2,95)	Two compartment	3.3 (95% CI: 2.1–4.4)	9.8 (95% CI: 7.4 –12.2)	Non-linear mixed-effects methods
[87]	Adults, critically ill (18)	56 range (31.4–80.8)	80.0 range (47–140)	Two compartment (+ lung compartment)	10.9 (95% CI: 7.9 –14.0)	*10.2 (95% CI: 8.1 –12.4)	Non-parametric population approach. *central compartment only available
[88]	Adults, critically ill (22)	65 range (22–89)	70 range (38–120)	One compartment	10.0 (95% CI: 7.0 –13.0)	32.1 (95% CI: 25.7–38.5)	Non-linear mixed-effects methods
[89]	Adults, critically ill surgical (11)	43.6 sd (±15.9)	76 sd (±11.0)	Two compartment	22.4 (95% CI: 11.5–33.2)	23.0 (95% CI: 12.4–33.7)	Non-linear least-squares regression analysis
[90]	Adults, critically ill with sepsis (16)	30.5 range (22–65)	76.5 range (64–86)	Two compartment	16.0 (95% CI: 13.5–19.3)	22.9 (95% CI: 17.6–31.5)	Non-linear mixed-effects methods
[91]	Adults, critically ill, indigenous Australian (9)	43 sd (±11)	76 sd (±11)	Two compartment	5.3 (95% CI: 3.0–7.6)	*13.4 (95% CI: 8.7–18.0)	P-metrics compartmental analysis—parametric/non-parametric not specified. *central compartment only published
[28]	Adults, critically ill with augmented renal clearance (48)	47.3 sd (±17.9)	88.4 sd (±24.2)	Two compartment	13.7 (95% CI: 11.8–15.9)	30.6 (95% CI: 9.3–47.6)	Non-linear mixed-effects methods
[15]	Adults, critically ill with burns and infection (10)	37.7 range (22–50)	77.8 range (45–105)	Non-compartmental	6.8 (95% CI: 4.3–9.3)	14.2 (95% CI: 10.8–17.7)	Unspecified
[16]	Adults, critically ill with burns and infection (50)	50.1 range (20–83)	66.9 range (50–90)	Two compartment	17.2 (95% CI: 13.9–19.0)	43.3 (95% CI: 10.2–1004.5)	Non-linear mixed-effects methods
[92]	Adults, critically ill with burns and infection (9)	38 range (20–58)	80 range (55–96)	Two compartment	13.5 (95% CI: 9.1–17.9)	48.1 (95% CI: 18.4–77.9)	Nonlinear least-squares regression
[93]	Adults, critically ill, obese and non-obese (50)	50 sd (±15)	104 sd (±35)	Two compartment	10.4 (95% CI: 8.9–11.9)	33.0* (95% CI: 29.3–36.6)	Not specified. Presume population approach based on analysis of residuals. *central compartment only published
[94]	Adults, critically ill, obese (9)	57 sd (+11)	164 sd (±50)	One compartment	3.2 (95% CI: 2.5–3.8)	13.2 (95% CI: 10.7–15.7)	trapezoidal rule and log-linear least squares
[95]	Adults, critically ill, hospital acquired pneumonia (50)	68.4 sd (± 7.1)	66.7 sd (± 8.6)	Non-compartmental	11.7 (95% CI: 11.0–12.4)	Volume not published	Log trapezoidal method
[96]	Adults, critically ill requiring haemofiltration (16)	57 sd (± 16)	74 sd (±8)	Two compartment	7.6 (95% CI: 4.7–11.0)	40.0 (95% CI: 26.7–57.3)	Population approach
[97]	Adults, critically ill requiring haemofiltration (20)	63 IQR (54–74.8)	81.7 IQR (64.6, 93.2)	Non-compartmental	3.9 IQR (2.9–5.5)	Volume not published	Unspecified
[98]	Adults, critically ill, requiring haemofiltration (42)	56.8 sd (± 15.5)	95.1 sd (±26.8)	One compartment	3.1 IQR (0.2–6.0)	25.4 IQR (2.9–47.8)	‘standard first-order equations’
[99]	Adults, critically ill, requiring haemofiltration (10)	62 IQR (54.5–68.8)	87.5 IQR (68.5–98.8)	Two compartment	5.8 (95% CI: 5.2–6.7)	16.2 (95% CI: 13.0–20.2)	Non-linear mixed-effects methods
[100]	Adults, critically ill, requiring haemofiltration (19)	70 range (39–82)	80 range (45–129)	Two compartment	5.5 (95% CI: 4.5–6.7)	28.3 (95% CI: –6.8*–72.3)	Non-linear mixed-effects methods. *-ve bootstrap estimate
[101]	Adults, critically ill, requiring haemofiltration (9)	56.4 sd (±15.2)	86.6 sd (±22.6)	Two compartment	2.1 (95% CI: 1.2–3.0)	20.9 (95% CI: 12.9–29.0)	Weighted non-linear least-square regression

[102]	Adults, critically ill, requiring haemofiltration (10)	51.6 sd (±15.6)	83.4 sd (±21.8)	Non-compartmental	4.3 IQR (3.7–5.4)	29.4 IQR (20.3–34.3)	Log-transformed concentration-time plots
[103]	Adults, critically ill and hospitalised (13)	53.2 sd (±13.2)	79.6 sd (±13.8)	Non-compartmental	7.8 (95% CI: 6.2–9.5)	19.4 (95% CI: 27.3–21.6)	Linear regression of log-concentration plots and trapezoidal rule
[104]	Adults, hospitalised, nosocomial infections (50)	57 sd (± 16)	61.1 sd (± 10.1)	One compartment	15.2 (95% CI: 14.1–16.3)	24.9 (95% CI: 21.9–27.8)	Non-linear mixed-effects methods
[105]	Adults, obese, hospitalised, treated for infection (14)	49 sd (±10)	161 sd (± 29)	Unspecified	7.3 (95% CI: 5.7–8.9)	14.5 (95% CI: 11.0–18.0)	Non-linear least squares regression
[106]	Adults, hospitalised and critically ill, treated for infection (11)	44.7 sd (± 12.5)	78 sd (± 22.1)	Two compartment	16.1 (95% CI: 12.3–19.9)	17.0* (95% CI: 11.4–22.5)	Non-parametric population approach. *central volume of distribution only published
[107]	Adults, hospitalised, treated for infection (33)	68.8 sd (±11)	58.2 sd (±10)	Two compartment	7.9 (95% CI: 2.1–15.1)	28.0 (95% CI: 22.7–40.1)	Non-linear mixed-effects methods
[108]	Adults, treated for intra-abdominal infection (56)	48 range (18–85)	81.8 range (55–136)	One compartment	13.0 (95% CI: 9.3–16.7)	19.1 (95% CI: 16.4–21.8)	Non-linear mixed-effects methods
[109]	Adults, treated for intra-abdominal infection (18)	31.1 sd (±8.5)	75.6 sd (±16.9)	Non-compartmental	13.9 (95% CI: 12.1–15.8)	19.4 (95% CI: 17.5–21.4)	Unspecified, LAGRAN computer program
[110]	Adults, haematological malignancy, receiving chemotherapy (16)	31.9 sd (± 15.4)	56.4 sd (± 11.2)	Non-compartmental	11.7 (95% CI: 7.6–15.7)	23.8 (95% CI: 17.1–30.5)	Calculated from time concentration plots
[111]	Adults, haematological malignancy, febrile neutropenic (12)	64.5 IQR (60.5–71.0)	75.0 IQR (63.7–93.2)	Non-compartmental	19.2 (95% CI: 14.7– 23.7)	27.7 (95% CI: 23.0–32.5)	PKSolver
[112]	Adults, cystic fibrosis with infection (9)	33 sd (± 12.6)	53.6 sd (± 6.5)	Two compartment	20.2 (95% CI: 17.1–23.3)	17.3* (95% CI: 9.4–25.2)	Population approach, two compartment pre specified. *Central volume of distribution only published.
[113]	Adults, volunteers with cystic fibrosis (8)	21 sd (± 4)	43.1 sd (± 7.8)	Two compartment	16.3 (95% CI: 15.1–17.7)	15.6 (95% CI: 14.0–17.2)	Population approach
[114]	Adults, cystic fibrosis with infection (13) *450mg/kg/day	21.3 sd (±6.3)	41.8 sd (±13)	Non-compartmental	18.3 (95% CI: 12.6–24.0)	21.7 (95% CI: 15.4–28.0)	Least squares regression analysis of log-linear plots and trapezoidal rule
[115]	Adults, undergoing elective surgery (18)	66.8 sd (±12)	72.3 sd (±11.4)	Non-compartmental	11.3 (95% CI: 10.1–12.6)	17.5 (95% CI: 16.1–18.9)	Linear regression of log-concentration plots and trapezoidal rule
[116]	Adults, undergoing prostate surgery (24)	70.8 sd (±6.6)	61.9 sd (±9.7)	Three compartment	10.0 (95% CI: 2.5–17.5)	17.3 (95% CI: 4.3–30.3)	Non-linear mixed-effects methods
[117]	Adults, hydrocephalus, treated for infection (9)	58.6 sd (±9.6)	81.2 sd (±10.3)	Non-compartmental	10.9 (95% CI: 9.1–12.7)	15.8 (95% CI: 14.1–17.4)	Linear regression of log-concentration and trapezoidal rule
[118]	Adults, healthy volunteers (11)	29 sd (±8.9)	69.8 sd (±15.7)	Non-compartmental	10.9 (95% CI: 9.2–12.6)	12.7 (95% CI: 11.3–14.2)	Least squares regression analysis of log-linear plots and trapezoidal rule
[119]	Adults, healthy volunteers (12)	25 range (23–30)	78.4 range (60.4–96.3)	Non-compartmental	10.9 (95% CI: 10.2–11.6)	10.6 (95% CI: 9.8–11.5)	Non-linear iterative least-squares method
[120]	Adults, healthy volunteers (10)	range (25–64)	70.9 sd (±13.9)	Non-compartmental	20.5 No uncertainty reported	30.7 No uncertainty reported	Data fitted to regression lines
[113]	Adults, healthy volunteers (26)	25 sd (± 4)	71.1 sd (± 11.8)	Two compartment	11.2 (95% CI: 10.7–11.6)	10.4 (95% CI: 9.7–10.8)	Population approach
[121]	Adults, healthy volunteers (12)	25.7 sd (± 2.4)	68.4 sd (± 11.7)	Two compartment	10.0 (95% CI: 8.7–11.2)	21.8 (95% CI: 14.1–29.5)	Non-linear least squares method
[122]	Adults, healthy volunteers (12)	28 sd (±8)	70 sd (±17)	Non-compartmental	10.2 (95% CI: 8.9–11.5)	10.5 (95% CI: 9.6–11.4)	Least squares regression analysis of log-linear plots and trapezoidal rule

[123]	Adults, healthy volunteer (10)	25.7 sd (±3.1)	69.6 sd (±9.7)	Three compartment	11.0 Intervals not disclosed	10.9 Intervals not disclosed	Non-linear mixed-effects methods
[124]	Adults, healthy volunteers (10)	30.4 range (23–44)	68.1 sd (±12.1)	Two compartment	11.2 (95% CI: 9.0–13.4)	12.7 (95% CI: 11.0–14.3)	Nonlinear regression analysis
[125]	Adults, healthy volunteers, high dose piperacillin (10)	30.7 sd (±7.6)	73.7 sd (±15.5)	Non-compartmental	6.1 (95% CI: 4.7–7.6)	9.9 (95% CI: 7.7 –12.1)	Least squares regression analysis of log-linear plots and trapezoidal rule
[126]	Children, critically ill (13)	2 range (0.75–6)	14.5 sd (± 6)	Two compartment	14.1 (95% CI: 10.4–17.8)	17.4* (95% CI: 8.5–26.4)	Non-parametric. *central compartment only published
[127]	Children, critically ill (47)	2.8 range (0.17–15)	14 range (3.4–45)	Two compartment	13.4 (95% CI: 11.7–18.4)	17.0 (95% CI: 14.9–19.6)	Non-linear least squares method
[128]	Children, critically ill (12)	5 IQR (1.75–6.5)	17.8 IQR (11.4,20)	One compartment	9.8 (95% CI: 8.5–11.1)	25.9 (95% CI: 19.8–31.9)	Non-linear least squares method
[129]	Children, oncology patients febrile neutropenia (21)	7.4 sd (± 2.1)	28.5 sd (± 9.7)	Two compartment	11.4 (95% CI: 9.5–13.3)	13.9* (95% CI: 10.5–17.3)	Non-parametric. *Central volume only published
[130]	Children with suspected infection (11)	Range (6–12)	Not reported	Non-compartmental	8.6 (95% CI: 7.9–9.2)	19.6 (95% CI: 14.9–24.3)	Least squares regression analysis of log-linear plots and trapezoidal rule
[130]	Children with suspected infection (12)	Range (2–5)	Not reported	Non-compartmental	8.0 (95% CI: 6.6–9.4)	19.6 (95% CI: 15.2–24.0)	Least squares regression analysis of log-linear plots and trapezoidal rule
[130]	Children with suspected infection (12)	Range (0.5–2)	Not reported	Non-compartmental	6.8 (95% CI: 5.1–8.5)	21 (95% CI: 16.6–25.4)	Least squares regression analysis of log-linear plots and trapezoidal rule
[130]	Children with suspected infection (12)	Range (0.2–0.4)	Not reported	Non-compartmental	4.8 (95% CI: 4.1–5.5)	23.1 (95% CI: 18.7–27.5)	Least squares regression analysis of log-linear plots and trapezoidal rule
[114]	Children, cystic fibrosis with infection (15)	9.4 sd (±1.8)	23.4 sd (±7.2)	Non-compartmental	16.0 (95% CI: 13.3–18.7)	22.4 (95% CI: 18.5–26.3)	Least squares regression analysis of log-linear plots and trapezoidal rule. 900mg/kg/day dose
[114]	Children, cystic fibrosis with infection (15)	8.3 sd (±3.3)	20.8 sd (±6.3)	Non-compartmental	16.6 (95% CI: 13.5–19.7)	23.1 (95% CI: 19.2–27.0)	Least squares regression analysis of log-linear plots and trapezoidal rule. 600mg/kg/day dose
[131]	Infants and neonates treated for infection (71)	PMA 37.5 weeks sd (±5)	2.76 sd (±1)	Two compartment	4.2 (95% CI: 3.9–4.5)	18.8* (95% CI: 14.8–21.8)	Non-linear mixed-effects. *Central compartment only published
[132]	Infants and neonates, treated for infection (77)	PMA 29 weeks range (23–40)	0.9 range (0.4–2.5)	One compartment	11.6 (95% CI: 8.5–14.7)	203.7 (95% CI: 114.8–393.1)	Non-linear mixed-effects. Scavenged samples
[133]	Infantes and neonates treated for infection (32)	PMA 32 weeks range (25–48)	1.4 range (0.4–4.0)	One compartment	1.9 (95% CI: 1.6–2.3)	29.4 (95% CI: 25.2–35.7)	Non-linear mixed-effects. Dried blood spot samples
Tazobactam							
[87]	Adults, critically ill (18)	56 range (31.4–80.8)	80.0 range (47–140)	Two compartment (+lung compartment)	8.8 (95% CI: 6.3 –11.3)	*13.0 (95% CI: 9.8–16.1)	Non-parametric population approach. *central compartment only available
[96]	Adults, critically ill requiring haemofiltration	57 sd (± 16)	74 sd (±8)	Two compartment	6.7 (95% CI: 4.6–8.6)	39.4 (95% CI: 17.7–53.6)	Population approach
[98]	Adults, critically ill, requiring haemofiltration (42)	56.8 sd (± 15.5)	95.1 sd (±26.8)	One compartment	2.3 IQR (0.08–4.5)	28.0 IQR (7.7–48.4)	'standard first-order equations'
[99]	Adults, critically ill, requiring haemofiltration (10)	62 IQR (54.5, 68.8)	87.5 IQR (68.5, 98.8)	Two compartment	4.3 (95% CI: 3.5–5.3)	14.0 (95% CI: 10.8–18.2)	Non-linear mixed-effects methods
[101]	Adults, critically ill, requiring haemofiltration (9)	56.4 sd (±15.2)	86.6 sd (±22.6)	Two compartment	3.8 (95% CI: 2.3–5.3)	37.7 (95% CI: 27.1–48.2)	Weighted non-linear least-square regression
[102]	Adults, critically ill, requiring haemofiltration (10)	51.6 sd (±15.6)	83.4 sd (±21.8)	Non-compartmental	3.3 IQR (2.9–3.7)	22.4 IQR (16.8–25.2)	Log-transformed concentration-time plots

[15]	Adults, critically ill with burns and infection (10)	37.7 range (22-50)	77.8 range (45-105)	Non-compartmental	17.2 (95% CI: 11.7–22.6)	31.1 (95% CI: 23.6–38.7)	Unspecified
[103]	Adults, critically ill and hospitalised (13)	53.2 sd (±13.2)	79.6 sd (±13.8)	Non-compartmental	5.9 (95% CI: 4.6–7.2)	17.9 (95% CI: 13.0–22.7)	Linear regression of log-concentration plots and trapezoidal rule
[104]	Adults, hospitalised, nosocomial infections (50)	57 sd (± 16)	61.1 sd (± 10.1)	One compartment	6.4 (95% CI: 4.3–7.6)	18.3 (95% CI: 15.2–19.8)	Non-linear mixed-effects methods
[105]	Adults, obese, hospitalised, treated for infection (10)	49 sd (±10)	161 sd (± 29)	Unspecified	5.9 (95% CI: 4.3–7.6)	16.3 (95% CI: 11.5–21.1)	Non-linear least squares regression. Note low parameter estimates after scaling in this obese cohort.
[106]	Adults, hospitalised and critically ill, treated for infection (11)	44.7 sd (± 12.5)	78 sd (± 22.1)	Two compartment	14.0 (95% CI: 11.1–16.8)	19.0* (95% CI: 12.5–25.4)	Non-parametric population approach. *central volume of distribution only published
[107]	Adults, hospitalised, treated for infection (33)	68.8 sd (±11)	58.2 sd (±10)	Two compartment	7.5 (95% CI: 3.3–13.1)	32.4 (95% CI: 29.3–42.2)	Non-linear mixed-effects methods
[108]	Adults, treated for intra-abdominal infection (56)	48 range (18-85)	81.8 range (55-136)	One compartment	9.2 (95% CI: 5.9–12.5)	19.7 (95% CI: 16.4–23.0)	Non-linear mixed-effects methods
[109]	Adults, treated for intra-abdominal infection (18)	31.1 sd (±8.5)	75.6 sd (±16.9)	Non-compartmental	14.0 (95% CI: 11.9–16.0)	20.8 (95% CI: 17.0–24.6)	Unspecified, LAGRAN computer program
[115]	Adults, undergoing elective surgery (18)	66.8 sd (±12)	72.3 sd (±11.4)	Non-compartmental	11.0 (95% CI: 9.5–12.5)	20.8 (95% CI: 18.2–21.0)	Linear regression of log-concentration plots and trapezoidal rule
[116]	Adults, undergoing prostate surgery (24)	70.8 sd (±6.6)	61.9 sd (±9.7)	Three compartment	9.7 (95% CI: 2.4–16.9)	14.8 (95% CI: 3.7–25.9)	Non-linear mixed-effects methods
[117]	Adults, hydrocephalus, treated for infection (9)	58.6 sd (±9.6)	81.2 sd (±10.3)	Non-compartmental	10.7 (95% CI: 8.0–13.5)	29.1 (95% CI: 16.4–21.7)	Linear regression of log-concentration and trapezoidal rule
[134]	Adults, cystic fibrosis (20)	25.4 sd (±9.7)	53.2 sd (±8.2)	Two compartment	25.2 (95% CI: 22.7–27.7)	10.3* (95% CI: 8.7–12.0)	Non-parametric approach. Ceftolazone-tazobactam study. *central compartment only published
[135]	Healthy adults, japanese/chinese/white (29)	34 sd (± 8.3)	63.0 sd (± 7.8)	Non-compartmental	23.6 (95% CI: 21.9–25.3)	28.4 (95% CI: 26.7–30.2)	Log-linear transformation, trapezoidal methods. Ceftolazone-tazobactam study.
[118]	Adults, healthy volunteers (11)	29 sd (±8.9)	69.8 sd (±15.7)	Non-compartmental	11.6 (95% CI: 10.5–12.8)	11.6 (95% CI: 10.5–12.8)	Least squares regression analysis of log-linear plots and trapezoidal rule
[119]	Adults, healthy volunteers (12)	25 range (23-30)	78.4 range (60.4-96.3	Non-compartmental	11.1 (95% CI: 10.4–11.8)	11.9 (95% CI: 10.7–13.1)	Non-linear iterative least-squares method
[122]	Adults, healthy volunteers (12)	28 sd (±8)	70 sd (±17)	Non-compartmental	9.2 (95% CI: 8.3–10.1)	9.1 (95% CI: 8.9–9.3)	Least squares regression analysis of log-linear plots and trapezoidal rule
[125]	Adults, healthy volunteers, high dose tazobactam (10)	30.7 sd (±7.6)	73.7 sd (±15.5)	Non-compartmental	8.0 (95% CI: 6.7–9.3)	63 (95% CI: 39.3–86.7)	Least squares regression analysis of log-linear plots and trapezoidal rule
[127]	Children, critically ill (47)	2.8 range (0.17-15)	14 range (3.4-45)	Two compartment	10.0 (95% CI: 9.0–11.1)	17.2 (95% CI: 11.9–23.3)	Non-linear least squares method
[128]	Children, critically ill (12)	5 IQR (1.75, 6.5)	17.8 IQR (11.4,20)	One compartment	9.6 (95% CI: 8.3–10.8)	21.8 (95% CI: 17.5–26.0)	Non-linear least squares method
[130]	Children with suspected infection (11)	6-12	Not reported	Non-compartmental	4.9 (95% CI: 0.5–9.3)	19.6 (95% CI: 14.9–24.3)	Least squares regression analysis of log-linear plots and trapezoidal rule
[130]	Children with suspected infection (12)	2-5	Not reported	Non-compartmental	6.7 (95% CI: 5.1–8.2)	19.6 (95% CI: 15.2–24.0)	Least squares regression analysis of log-linear plots and trapezoidal rule
[130]	Children with suspected infection (12)	0.5-2	Not reported	Non-compartmental	4.9 (95% CI: 3.7–6.1)	21 (95% CI: 16.6–25.4)	Least squares regression analysis of log-linear plots and trapezoidal rule

[130]	Children with suspected infection (12)	0.2-0.4		Non-compartmental	3.9 (95% CI: 3.3–4.6)	23.1 (95% CI: 18.7–27.5)	Least squares regression analysis of log-linear plots and trapezoidal rule
[131]	Infants and neonates treated for infection (71)	PMA 37.5 weeks sd (±5)	2.76 sd (±1)	Two compartment	4.7 (95% CI: 4.3–5.0)	30.3 (95% CI: 22.3–38.2)	Non-linear mixed-effects
[133]	Infantes and neonates treated for infection (32)	PMA 32 weeks range (25–48)	1.4 range (0.4–4.0)	One compartment	2.1 (95% CI: 1.7–2.5)	39.9 (95% CI: 36.4–44.8)	Non-linear mixed-effects. Dried blood spot samples

Mean or median values presented. With associated range, interquartile range (IQR) or standard deviation (sd). 95% confidence intervals have been calculated, where standard deviation or standard error data was available, assuming a student's t-distribution. GA is gestational age, PMA is post-menstrual age

Ref	Population (n)	Age (years unless other specified)	Weight (kg)	Structural model	Clearance (L/h/70kg)	Volume at steady state (L/70kg)*	Comments/modelling approach
Meropenem							
[32]	Adults, critically ill, (19)	49 sd (±15.9)	95 sd (±22)	Two compartment	12.3 (95% CI: 10.0–14.6)	8.6* (95% CI: 6.6–10.6)	Non-parametric adaptive grid algorithm. *central volume only published
[33]	Adults, critically ill, requiring haemofiltration (15)	59 range (33-85)	82.3 range (45-128.5)	Two compartment	7.9 range (1.8–23.9)	29.3 range (17.5–69.4)	Non-linear mixed-effects methods
[34]	Adults, critically ill (55)	63.4 sd (± 15.1)	78.4 sd (±18.4)	Three compartment (one for lung)	9.4 (95% CI: 7.6–10.0)	25.5 (95% CI: 17.0–57.8)	Non-linear mixed-effects methods
[35]	Adults, critically ill (15)	73 IQR (52, 94)	78 IQR (65.5, 90.5)	Two compartment	4.1 (95% CI: 2.7–7.2)	14.1 (95% CI: 12.7–19.4)	Non-linear regression (WinNonlin)
[36]	Adults, critically ill (27)	62 sd (±12)	76.2 sd (±30.3)	One compartment	8.8 (95% CI: 7.1–10.5)	24.1 (95% CI: 18.8–29.4)	Non-linear mixed-effects methods
[37]	Adults, critically ill (10)	67 sd (±19)	72 sd (±15)	Two compartment	11.3 (95% CI: 9.1–13.4)	26.3 (95% CI: 21.0–31.7)	Extended least squares regression method, trapezoidal rule
[38]	Adults, critically ill (15)	55.3 sd (±14.3)	83.6 sd (±15.4)	Not specified	7.5 (95% CI: 6.7–8.3)	21.9 (95% CI: 19.8–24.1)	Kinetica program
[39]	Adults, critically ill with severe infection/septic shock (50)	67.5 (±13.9)	62.2 sd (±11.2)	One compartment	15.1 (95% CI: 13.2–16.9)	30.7 (95% CI: 29.2–32.3)	WinNonlin
[40]	Adults, critically ill, elderly (178)	75 range (65-94)	77 range (37-147)	Two compartment	4.9 (95% CI: 4.7–5.1)	25.2 (95% CI: 19.5–31.2)	Non-linear mixed-effects methods
[41]	Adults, critically ill, elderly (75)	75.6 sd (±8.9)	64.4 sd (±12.3)	Two compartment	9.6 (95% CI: 7.9–11.2)	34.8 (95% CI: 24.2–45.8)	Non-linear mixed-effects methods
[42]	Adults, critically ill, requiring haemofiltration (10)	67 range (20–75)	76 range (50–113)	Non-compartmental	4.5 IQR (3.4, 14.3)	17.4 IQR (14.1, 23.4)	Log-linear least squares regression and linear trapezoidal rule
[43]	Adults, critically ill with sepsis/septic shock (9)	57.2 sd (±16.1)	62.9 sd (±11.6)	One compartment	8.5 (95% CI: 4.2–12.8)	26.4 (95% CI: 18.7–34.0)	Non-linear mixed-effects methods
[44]	Adults, critically ill, obese (9)	55.4 sd (± 10.1)	152.3 sd (± 31)	Two compartment	5.7 (95% CI: 3.5–7.8)	17.2 (95% CI: 12.0–22.4)	Non-linear least squares regression
[45]	Adults, critically ill with central nervous system infection (21)	52 range (46-80)	76 range (55-105)	Three compartment	14.2 range (7.6–29.9)	12.7* range (5.1–15.0)	Non parametric adaptive grid algorithm. *central volume only published
[46]	Adults, critically ill with central nervous system infection (9)	45.1 sd (±17.6)	70.3 sd (±12.6)	Three compartment (two csf)	7.2 (95% CI: 4.0–15.8)	99.6* (95% CI: 43.1–162.8)	Non-linear mixed-effects methods. *central volume only published. Unusually high volume.
[47]	Adults, critically ill with central nervous system infection (10)	61.5 IQR (54.3, 68.3)	80 IQR (70, 79.7)	Two compartment (one csf)	14.6 (95% CI: 9.9–19.3)	10.7* (95% CI: 8.2–13.1)	Non-parametric adaptive-grid Unusually high volume. *central volume only published
[48]	Adults, critically ill with central nervous system infection (82)	43.4 sd (±13.1)	65.2 sd (±11.6)	Three compartment (one csf)	23.4 (95% CI: 21.6–25.3)	19.4 (95% CI: 17.4–21.0)	Non-linear mixed-effects methods
[49]	Adults, critically ill requiring haemofiltration (10)	57 IQR (49, 61)	70 IQR (66, 103)	Non-compartmental	6.0 IQR (5.2, 6.2)	25.9 IQR (22.4, 32.2)	Linear trapezoidal rule and log-linear least squares regression
[50]	Adults, critically ill requiring haemofiltration (10)	64.9 sd (± 8.0)	79.8 sd (±18.5)	Two compartment	3.9 (95% CI: 3.0–4.8)	23.9 (95% CI: 17.8–30.0)	Non-linear regression

[51]	Adults, requiring haemofiltration (10)	54.3 sd (±9.4)	76.7 sd (±15.0)	Non-compartmental	4.7 range (2.4–11.2)	50.4 range (26.8–213.2)	WinNonLin
[52]	Adults, anuric and requiring haemofiltration (9)	54.2 sd (±19.7)	69.4 sd (±9.7)	Two compartment	3.1 (95% CI: 2.3–3.9)	18.2 (95% CI: 13.3–23.0)	Weighted least squares regression.
[53]	Adults, critically ill requiring haemofiltration (15)	60 sd (±8.3)	71 sd (±16.3)	Four compartment	5.4 (95% CI: 1.0–9.9)	24.0 (95% CI: 9.2–38.8)	Compartmental approach. Kinetica program.
[54]	Adults, critically ill requiring haemofiltration (24)	68.5 range (50-81)	75 range (68-126)	One compartment	3.5 (95% CI: 2.8–4.2)	30.8 (95% CI: 24.9–36.7)	Non-linear mixed-effects methods
[55]	Adults, critically ill burn patients (59)	47.3 range (19–86)	65.9 range (42–95)	Two compartment	15.6 (95% CI: 14.2–19.0)	28.8 (95% CI: 22.8–37.9)	Non-linear mixed-effects methods
[56]	Adults, critically ill burns patients (12)	46 sd (±16)	82.9 sd (±17.5)	Two compartment	14.3 (95% CI: 12.3–16.3)	40.7 (95% CI: 31.1–50.3)	Non-linear mixed-effects methods
[57]	Adults, critically ill with ventilator associated pneumonia (9)	39.6 sd (±15.8)	54.2 sd (± 11.6)	One compartment	10.3 (95% CI: 7.3–13.3)	20.7 (95% CI: 17.0–24.3)	Trapezoidal rule
[58]	Adults, critically ill with ventilator associated pneumonia (39)	49.3 sd (±19.4)	83.1 sd (±22.6)	Three compartment (one lung)	13.4 (95% CI: 10.6–16.1)	10.6* (95% CI: 7.0–14.2)	Non-parametric adaptive-grid. *central compartment only
[59]	Adults, critically ill surgical patients (32)	68.5 IQR (62, 76)	73.5 IQR (69, 89)	Not reported	10.4 (95% CI: 8.8–12.6)	Not reported	Non-linear mixed-effects methods
[60]	Adults, surgical patients with moderate or severe infection (11)	63.1 sd (±18.3)	72 range (47.6–95)	Two compartment	11.2 (95% CI: 8.8–13.5)	20.1 (95% CI: 16.6–23.7)	Extended or least squares method
[61]	Adults, intra-abdominal infection (12)	29.5 sd (±13.1)	70.95 sd (±7.7)	Non-compartmental	18.7 (95% CI: 16.0–21.4)	26.3 (95% CI: 22.0–30.6)	LAGRAN program
[33]	Adults, haematological malignancy and infection (10)	52 range (35-75)	72 range (48-85)	Two compartment	12.8 range (10.5–20.7)	22.7 range (15.0–37.0)	Non-linear mixed-effects methods
[62]	Adults, haematological malignancy and febrile neutropenia (57)	36 range (17-68)	61.4 range (45-95.8)	One compartment	10.7 (95% CI: 8.3–13.0)	16.6 (95% CI: 12.6–20.6)	Non-linear mixed-effects methods
[63]	Adults, haematological malignancy and febrile neutropenia (12)	61 range (36–82)	Not published	Non-compartmental	8.94 (95% CI: 6.2–11.6)	16.2 (95% CI: 13.7–18.7)	Least square regression analysis, trapezoidal rule
[64]	Adults, hospitalised with infection (68)	71.5 sd (±13.5)	52.1 sd (±13.9)	One compartment	13.9 (95% CI: 11.4–16.5)	45.1 (95% CI: 32.5–56.6)	Non-linear mixed-effects methods
[65]	Adults, hospitalised with infection (42)	62.2 sd (±19.6)	56 sd (± 10.4)	Two compartment	10.7 (95% CI: 5.0–16.4)	21.1 (95% CI: 17.9–24.6)	Non-linear mixed-effects methods
[66]	Adults, obese, hospitalised with infection (10)	49.1 sd (±12.0)	200.4 sd (±67.9)	Two compartmetns	3.7 (95% CI: 2.8–4.5)	8.8 (95% CI: 6.5–11.0)	Nonlinear least-squares regression
[67]	Adults, obese, hospitalised with infection (375)	64.7 sd (±13.4)	95.3 sd (±18)	One compartment	7.0 (95% CI: 6.5–7.5)	20.6 (95% CI: 20.5–20.7)	ADAPT 5 program
[68]	Adults, healthy volunteers (12)	29.4 sd (±6)	80.3 sd (±7.2)	Non-compartmental/two compartment	14.4 (95% CI: 13.3–15.5)	18.6 (95% CI: 15.9–21.3)	Log trapezoid rule, iterative least squares method
[69]	Adults, healthy volunteers (12)	32.6 sd (± 8.9)	59.7 sd (±7.8)	One compartment	11.5 (95% CI: 7.9–15.1)	19.7 (95% CI: 15.9–23.5)	WinNonlin
[70]	Adults, healthy volunteers (9)	36.6 range (23–59)	79.0 range (67.9–89.7)	Two compartment	13.7 (95% CI: 12.0–15.4)	14.8 (95% CI: 12.8–16.8)	Least squares regression

[71]	Adults, healthy volunteers (18)	38 sd (±10)	74.4 sd (±9.1)	Two compartment	13.1 (95% CI: 11.6–14.7)	9.7* (95% CI: 8.3–11.1)	Nonparametric adaptive grid program. *Central volume only reported
[72]	Adults, healthy volunteers (25)	39.0 sd (±10.6)	80.3 sd (9.4)	Non-compartmental	10.0 (95% CI: 9.2–10.8)	14.2 (95% CI: 13.3–15.1)	Linear trapezoidal method
[73]	Adults, healthy elderly (8) Included as no other elderly studies	73 sd (±4.6)	68.9 sd (±8.3)	Non-compartmental	8.3 (95% CI: 6.9–9.7)	13.2 (95% CI: 12.0–14.4)	Least-squares regression, log-trapezoidal rule
[74]	Children with malignancy and severe infection (14)	7.1 sd (±2.4)	22.7 sd (±9.7)	Two compartment	15.2 (95% CI: 12.8–18.4)	12.5 (95% CI: 9.6–17.1)	Non-linear mixed-effects methods
[75]	Children with infection following stem cell transplant (21)	9.6 sd (±5.4)	36.1 sd (±20.5)	Non-compartmental	8.2 IQR (5.0, 15.6)	Not calculated	Clearance at steady state calculated from infusion rate/concentration at steady state
[76]	Children with infection (99)	4.3 sd (±3.8)	16.8 sd (± 11.6)	Two compartment	12.3 (95% CI: 11.5–13.7)	12.2 (95% CI: 9.7–14.4)	Non-linear mixed-effects methods
[77]	Children (40) *pooled data from Japanese articles	6.6 sd (±4.4)	23.2 sd (±13.5)	Two compartment	13.5 (95% CI: 8.9–18.0)	35 (95% CI: 19.3–44.5)	Non-linear mixed-effects methods. Pooled participant group.
[78]	Children, hospitalised with infection (50)	3.1 sd (±3.2)	14.8 sd (±8.1)	Two compartment	10.4 (95% CI: 9.7–11.2)	23.8 (95% CI: 30.1–39.2)	Non-linear mixed-effects methods
[79]	Children with cystic fibrosis and lung infection (30)	12.7 sd (±2.9)	40.9 sd (±12.2)	Two compartment	24.1 (95% CI: 18.9–29.3)	21.0* (95% CI: 16.7–25.3)	Non-parametric adaptive grid. *central volume only published
[80]	Children, requiring haemofiltration (7) *included as only study in children	14.3 sd (±5.8)	48.6 sd (±17.4)	Not specified	3.7 (95% CI: 2.1–7.7)	24.5 (95% CI: 19.0–30.0)	Bayesian estimation using MWPharm
[81]	Infants and children, hospitalised with infection (63)	4 sd (±3.5)	16.5 sd (±11)	Non-compartmental	16.2 (95% CI: 14.9–17.4)	30.1 (95% CI: 28.2–32.1)	Linear trapezoidal rule and log-linear least squares regression
[82]	Neonates (188)	PMA 33 weeks range (24-51)	1.1 range (0.3-4.8)	One compartment	2.9 (95% CI: 2.8–3.1)	32.2 (95% CI: 30.3–34.1)	Non-linear mixed-effects methods
[83]	Neonates (22)	PNA 10 days (±15) GA 34 (±5)	2.4 sd (±1)	One compartment	1.0 range not published	28 range not published	Non-linear mixed-effects methods
[84]	Neonates (9)	GA 26.9 sd (±1.4) wk PNA 15.6 sd (±8.6) days	0.9 sd (±0.2)	Non-compartmental	1.4 (95% CI: 0.9–1.9)	21.0 (95% CI: 13.3–28.7)	WinNonlin

Mean or median values presented. With associated range, interquartile range (IQR) or standard deviation (sd). 95% confidence intervals have been calculated, where standard deviation or standard error data was available, assuming a student's t-distribution. GA is gestational age, PMA is post-menstrual age

7 References

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