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Title

Beta-lactam antimicrobial pharmacokinetics and target attainment in critically ill patients aged 1 day to 90 years – the ABDose study.

Short running title

ß-lactam PK in critically ill patients of all ages

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Structured synopsis (250 words)

Background

The pharmacokinetics of beta-lactam antibiotics in critical illness remain poorly characterised, particularly in neonates, children and the elderly. We undertook a pharmacokinetic study of commonly used beta-lactam antibiotics in critically ill patients of all ages. The aims were to produce a whole-life beta-lactam pharmacokinetic model and describe the extent to which standard doses achieve pharmacokinetic-pharmacodynamic targets associated with clinical cure.

Patients and methods

212 critically ill participants with an age range from 2 days (gestational age 24 weeks) to 90 years old were recruited from a UK hospital, providing 1339 pharmacokinetic samples. Population pharmacokinetic analysis was undertaken using non-linear mixed effects modelling (NONMEM) for each drug. Pooled data were used to estimate maturation and decline of beta-lactam pharmacokinetics throughout life.

Results

Pharmacokinetic models for 8 drugs were described, including what is thought to be the first benzylpenicillin model in critically ill adults. We estimate that 50% of adult beta-lactam clearance is achieved at 43 weeks post-menstrual age (chronological plus gestational age). 50% of decline from peak adult clearance occurs by 71 years. Paediatric participants were significantly less likely than adults to achieve pharmacokinetic-pharmacodynamic targets with standard antibiotic doses ($p<0.01$).

Discussion and conclusion

We believe this to be the first prospective whole-life antibiotic pharmacokinetic study in the critically-ill. The study provides further evidence that standard antibiotic doses fail to achieve pharmacokinetic-pharmacodynamic targets associated with clinical success in adults, children and neonates. Maturation and decline parameters estimated from this study could be adopted as a standard for future prospective studies.

Introduction

Beta-lactam antibiotics are extensively used in critically unwell patients who have infections. The pharmacokinetic-pharmacodynamic (PKPD) target associated with treatment success with these drugs is the fraction of time that the unbound drug concentration is above the minimum inhibitory concentration (ft>MIC) of the pathogen being treated.[1,2] Pharmacokinetic changes in critical illness, antimicrobial resistance and increasing MICs have led to concerns that failure to achieve ft>MIC targets may cause treatment failure. In critically ill adults, a large multicentre observational investigation (the DALI study) of PK target attainment found lower ft>MIC was associated with poor clinical outcomes.[2] This led to prospective randomised trials of continuous infusion versus standard dosing, such as the BLING studies[3] and recommendations for beta-lactam therapeutic drug monitoring (TDM).[4, 5] The DALI and BLING studies focussed solely on adult patients, excluding those aged less than 18 years. Yet infection causes significant mortality and morbidity in both the paediatric intensive care unit (PICU) and the neonatal intensive care unit (NICU).[6,7] Data from a recent single centre suggests subtherapeutic beta-lactam PKPD exposure in these age groups.[8]

Fundamentally, antimicrobial PKPD target attainment for beta-lactams concerns plasma drug concentrations relative to microorganism susceptibility. Consequently, although there may be differences in clinical presentation and infection type between adults and children, the age of the patient should not be important when considering antimicrobial PKPD target attainment. A possible reason that children are excluded from large scale interventional pharmacokinetic antimicrobial trials is that PK variability during the first 18 years of life is much larger than in adult studies.[9] For example, body weight can range 250-fold (400g to 100kg) in a study including pre-term neonates and adolescents. In a recent systematic review, we have shown that the pharmacokinetics of three commonly used beta-lactams can be described from birth to old age. This was done by using models that include allometric weight scaling and sigmoidal maturation and decline functions that increase with early (postmenstrual) age and decrease with old age respectively.[10] Others have published whole-life models for remifentanil, propofol and vancomycin.[11-13] The optimal dosing strategy to combat resistant pathogens should be similar across all ages. It should be feasible for trials in this area to recruit across all ages.

We therefore report a prospective PKPD beta-lactam study – the ABDose study - conducted simultaneously on the neonatal, paediatric and adult intensive care units. The primary objective was to model the PK of commonly used beta-lactam antibiotics and investigate whether common maturation and decline age parameters could be estimated.

Methods

Study participants

Critically ill neonatal, paediatric and adult patients receiving beta-lactam antibiotics for the treatment or prevention of infection were enrolled following informed consent or assent from relatives or parents. The study was conducted at a large teaching hospital (St George's University Hospitals NHS Foundation Trust, UK), with enrolment

occurring over an 18-month period. Study drugs (antibiotic choice) were prescribed in line with local guidelines and dosed according to recommendations from the British National Formulary (BNF).[14,15] Inclusion criteria were: neonate, child or adult patient admitted to an intensive care receiving one of the study antibiotics via the intravenous route. Exclusion criteria were treating clinician opinion that death was likely within 48-hours of enrolment or treatment withdrawal for reasons of palliation.

Study drugs and sampling schedule

The beta-lactams studied were as follows: amoxicillin (or amoxicillin/clavulanate), benzylpenicillin, cefotaxime, ceftriaxone, ertapenem, flucloxacillin, meropenem and piperacillin/tazobactam. These drugs are the most commonly prescribed beta-lactams at the study centre. Participants provided a minimum of two and a maximum of eight samples at steady state (after 4 half-lives, as determined from summary of product characteristics). Sampling times were set for common dosing schedules rather than for each drug, for reasons of practicality (supplementary material table S1). The optimal sampling schedule suggested by Felton *et al.*[16]was used as the basis for this with timings spread to cover two dosing intervals during the antibiotic course. In adults, samples were drawn from indwelling vascular catheters (generally radial arterial lines). In paediatric and neonatal participants without indwelling lines, sampling was at the same time as routine clinical blood samples.

Laboratory methods

Samples were placed immediately on ice and plasma separated via centrifugation at 4°C. Plasma was then frozen at -80°C for analysis at a later date (4–6 weeks). Antibiotic concentrations were measured by Analytical Services International, using ultra-high-performance liquid chromatography tandem mass spectrometry. This methodology has been described previously.[17]

For pharmacokinetic-pharmacodynamic target attainment analysis, the unbound fraction of the drug concentration was calculated with reference to the % protein-binding described in the summary of product characteristics for each antibiotic (supplementary material table S1).[18,19]

Clinical data collected

Data were managed using the REDCap electronic data capture tool.[20] Baseline data were collected as follows: demographics including age, sex, weight, height/length (where recorded). For neonates and children birth weight and gestational age were also recorded, and post-menstrual age calculated (gestational age plus chronological age). Measures of organ function included sequential organ failure assessment (SOFA) and paediatric sequential organ failure assessment (pSOFA) scores. Results of haematological and biochemical investigations included white cell count, lactate, creatinine, albumin and bilirubin. Additional data included ventilation requirements, necessity for renal replacement therapy and Glasgow Coma Scale (GCS) and sickness severity score. Details of antimicrobial prescriptions including drug, dose, frequency and number of doses received prior to enrolment were recorded. Finally, the infection type for which the antibiotic was prescribed for was classified in line with guidance

from the European Medicines Agency.[21] During the sampling period, repeat measures of serum creatinine were recorded for time-varying covariate analysis.

Statistical analysis

Pharmacokinetic model

Population pharmacokinetic and pharmacodynamic modelling was undertaken using non-linear mixed-effects modelling techniques with the software NONMEM (version 7.3) and GFortran (version 6.3) compiler [22,23] using the first-order conditional estimation method with interaction (FOCE-i). Modelling was undertaken using the Piraña user-interface for NONMEM.[24]

Structural model

One- and two-compartment structural models were tested for each drug with random effects tested on each parameter. Linear elimination was assumed. Inter-occasion variability was tested on clearance. Proportional, additive and combined residual error models were tested.

Allometric scaling and modelling changes in pharmacokinetic parameters through life

Pharmacokinetic parameters were scaled to a 70 kg individual. Volume of distribution was scaled linearly with weight and clearance was scaled with an allometric exponent of 0.75, as described previously[10,25] (Equations 1). A sigmoidal maturation-decline function was fitted to clearance values (Equation 2) to model changes with age as described previously.[9,10,26,27] For these maturation functions, data were pooled and the model fitted simultaneously to all beta-lactams to provide better accuracy of parameter estimation. This was felt appropriate as the drugs studied have similar elimination pathways and it was assumed that they would likely mature and decline at the same rate (supplementary table S2). Changes in volume of distribution in early life were modelled for individual drugs using the hockey stick function that we used in our previous systematic review of beta-lactam antibiotics[10], this methodology was compared to the exponential model used by Eleveld *et al.*[12,13] (supplementary material equations S1).

Structural models were established on individual drug data sets before all data were pooled and parameters estimated for the pooled model (including estimation of parameters for individual drugs and the shared maturation-decline function).

Covariate analysis

Renal function was modelled as a covariate effect on clearance using serum creatinine. For this, a power model was used, referenced to the expected serum creatinine for age and sex (supplementary material equation S2&3). This methodology was developed by Ceriotti *et al.*[28] and Johansson *et al.*[29] The number of participants receiving renal replacement therapy was too small to model its effect.

Model evaluation

Model evaluation was undertaken using established statistical and graphical methods, including likelihood-based diagnostics (objective function value), goodness-of-fit

plots, and assessment of model simulation properties.[30,31] The drop in objective function value required for the addition of one parameter to be significant at the p=0.05 level was 3.84,[32] where models were nested. Where models were not nested, Akaike information criterion was used.[33] Model plots and graphical analysis was undertaken using R language and environment for statistical computing.[34] Simulations for visual predictive checks were undertaken using Perl-speaks-NONMEM (PsN).[35]

Pharmacokinetic-pharmacodynamic indices

Time of free drug concentration above the target minimum inhibitory concentration (*f*T>MIC) in the first 24 hours of treatment was the pharmacokinetic-pharmacodynamic index used. This was estimated for each participant using their full dosing history during the NONMEM run. The appropriate target *f*T>MIC in critically ill patients is not definitively established. Attainment of *f*T>MIC for 50% and 100% of the dosing interval as well as at the more challenging *f*T>4∗MIC level were tested. These targets have been used previously.[2]

Target minimum inhibitory concentrations (MIC) were taken from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint tables.[36] As treatments are often initiated without knowledge of the causative organism, the greatest susceptible MIC for each antibiotic was chosen. For example, amoxicillin-clavulanic acid 8mg/L (E.coli), flucloxacillin 2m/L (S.aureus). Full list in supplementary material table S3. This method of MIC selection is commonly used in pharmacokinetic-pharmacodynamic studies.[2,16,37]

Finally, simulated pharmacokinetic profiles (n=10000) of the first 24 hours of treatment for amoxicillin, meropenem and piperacillin (the most commonly prescribed drugs) were undertaken to predict proportion of time with drug concentration above a range of MIC values using standard BNF doses.[14,15]

Ethical approval was provided by the national research ethics (REC) committee London (Harrow), REC reference 14/LO/1999.

Results

Baseline characteristics

Baseline characteristics of the 212 participants enrolled are presented in Table 1. The youngest participant recruited had a gestational age of 24 weeks (post-natal age 2 days). The oldest was 90 years old. Median sequential organ failure assessment (SOFA/pSOFA) score was 6 for adults, and 4 for children and neonates. Most (194, (92%)) received antibiotics to treat suspected infection and 18 (8%) were prescribed antibiotics as surgical prophylaxis. The most common indication for antibiotics across all age groups was lower respiratory tract infection (supplementary Table S4). Combination or changes in therapy meant the number of antibiotic courses sampled was 245. Amoxicillin, piperacillin and meropenem were the most common drugs used, in keeping with local practice (Table 1). In total 1339 plasma samples were collected for PK analysis (supplementary Table S5).

Pharmacokinetic model

Two compartment structural models provided a better fit to the data for all drugs compared to one compartment models, with a combined additive and proportional error model. Model fit was further improved with the addition of creatinine as a covariate effect on clearance with an age matched reference creatinine (Δ objective function value (OFV) -128, supplemental table S6). There was no improvement in model fit with inter-occasion variability. Shrinkage for the individual drug models ranged from 1–24%. However, the combined model shrinkage values ranged from 60–82%. The likely reason for this discrepancy is that in the combined model, data was not available for all drugs for all participants and shrinkage estimates for these individuals would be 100%. Since shrinkage was much lower in individually modelled drugs, individual predictions ought to be reliable.

Parameter estimates for the beta-lactam models are provided in Table 2. Models for amoxicillin and piperacillin initially over-predicted peak concentrations for paediatric participants. Addition of a hockey-stick volume maturation function improved the model fit significantly (ΔOFV -85). This method of volume maturation modelling was preferred to the Eleveld et al.[12,13] exponential maturation function (ΔOFV -57).

Addition of a clearance maturation and decline function further improved the model fit (ΔOFV -117) and estimated half adult beta-lactam clearance was achieved by 43 weeks post-menstrual age and 50% of decline in old age was reached at 71 years (Table 2). Visual predictive check of the final model (Figure 1) showed good model fit for adults and children. Goodness of fit plots are provided in supplemental Figure S1 with a sample of individual plots in supplemental Figure S2.

Pharmacokinetic-pharmacodynamic attainment

Overall, 71% of antibiotic courses achieved the most conservative pharmacokinetic-pharmacodynamic target of 50% fT>MIC. Target attainment dropped markedly with the more challenging targets of 50% fT>4* MIC and 100%fT>4*MIC, which just 32% and 7% of antibiotic courses achieved respectively. Target attainment also varied by age. Children were significantly less likely to achieve even the lowest pharmacokinetic-pharmacodynamic target compared to adults, with 49% versus 74% achieving 50%*f*T>MIC respectively ($p<0.01$, Chi-squared). Neonates had similar target attainment to adults with 86% achieving 50%*f*T>MIC.

Table 3 shows a breakdown of all pre-specified pharmacokinetic-pharmacodynamic targets. There was considerable variation between drugs. Amoxicillin had the lowest target attainment with just 36% of courses achieving 50% fT>MIC. Benzylpenicillin and flucloxacillin had similarly low rates with 58% and 50% of courses achieving 50% fT>MIC respectively. The difference between adults and children was particularly stark for amoxicillin where only 4% of paediatric amoxicillin courses achieved 50% fT>MIC compared to 47% of adult amoxicillin courses. Conversely, 100% of ceftriaxone, cefotaxime and ertapenem courses achieved 50% fT>MIC.

Figure 2 shows the results of the simulated pharmacokinetic profiles (n=10000), displaying the proportion of the dosing interval with free drug (amoxicillin,

meropenem, piperacillin) above MIC for a range of MICs. Standard dosing regimens are predicted to fail to achieve 100%fT above the EUCAST breakpoint MIC for a proportion of patients for all three drugs. For children, this is particularly marked with amoxicillin.

Discussion

Pharmacokinetic model

To our knowledge, this is the first prospective clinical study of antimicrobial pharmacokinetics in critical illness to include participants of all ages. Pooling data and undertaking simultaneous modelling has allowed us to describe changes in beta-lactam pharmacokinetics throughout life. Estimates for clearance suggest 50% maturation is achieved shortly after term (43 weeks). This estimate is in keeping with other studies of antibiotics[9-11] and the Rhodin *et al.*[38] study of renal function maturation (Table 4). Wang et al. have recently shown that sigmoid maturation functions such as these have good predictive performance for clearance maturation when coupled with allometric scaling.[39]

The estimate of age at which 50% decline in clearance occurs differs from the finding of our systematic review of beta-lactam pharmacokinetics,[10] 71 years in this study versus 87 years in the review. The parameter is estimated with greater precision in this study and has the advantage of being derived from a prospective data set. In addition, this study includes a covariate effect for renal function, which could not be included in the model developed from the systematic review. Of note, the combined model has been run with patients receiving renal replacement therapy excluded. In this run, there was no change in population clearance estimates, indicating these patients were not influencing overall final model fit.

The similarity in estimates between the present study and the other studies cited[9-11, 38] is such that there is little difference between the scaled parameter estimates for clearance using each model. Taking the published maturation parameters from these studies and using an example of a 7.5kg baby at 1.5 years post-menstrual age (approximately the point of maximum deviation of the models), the range of scaled clearance estimates of piperacillin is 1.8–2.0 L/hr (scaled from the adult piperacillin clearance estimated from the present study). There is therefore an argument that, along with Holford *et al.*'s[40] suggestion of defining allometric scaling parameters a priori when modelling with neonatal data, maturation function parameters could also be pre-specified for antibiotics with significant renal elimination. Indeed, running the final model with fixed values for maturation from each of the studies cited in Table 4 produced very similar results for pharmacokinetic parameter estimates. For example, piperacillin volume of distribution estimates ranged from 20.6–20.7 L/70kg, with similar clearance estimates and negligible change in OFV (supplementary table S7, Figure S3).

Weight standardised estimates for clearance of the drugs studied were broadly in keeping with previously published pharmacokinetic studies in clinical settings.[10,41-44] The exception being benzylpenicillin which, as far as we are aware, has no previously

published population-pharmacokinetics in critically ill adults. Clearance estimates from this study, along with the cited previous studies are all consistently lower than those published in summary of product characteristics (SPC, supplementary table S2). Examples of SPC versus this study clearance (L/h) include amoxicillin 19 versus 15.9, meropenem 12–17 versus 8.7 and cefotaxime 16–23 versus 10.1. Perhaps the most straightforward explanation for this discrepancy is a failure in clearance mechanisms in these critically ill patients that is not adequately captured by the creatinine function used in our model to capture the effect of changes in renal function.

Allometric scaling of volume of distribution led to overestimates of peak antibiotic concentration in neonates receiving piperacillin and amoxicillin. Addition of a volume maturation function to the piperacillin and amoxicillin models significantly improved the model fit and accuracy of estimates of peak antibiotic concentrations for neonates. Changes in body composition, with a greater proportion of mass being water in neonates is a possible explanation for this finding. This finding is in keeping with the work by Eleveld *et al.*[12,13] The volume maturation function did not improve model fit when applied to other individual drug models, with parameters consistent with and without this function (supplementary material table S8) so is not included for other drugs in the final model presented here. This is likely due to the lower numbers of neonates in the other drug datasets. Weight standardised volume of distribution parameters were also similar to previous clinical studies, but conversely to clearance, volume estimates in these critically ill patients were generally higher than those published in the SPC. This likely reflects the shifts in fluid distribution associated with sepsis and the fluid therapies used in its management.

Pharmacokinetic-pharmacodynamic attainment

There was marked heterogeneity between study drugs and age groups with respect to the attainment of pharmacokinetic-pharmacodynamic targets. This likely reflects differences in dose administered, the mode of administration (bolus versus prolonged infusion) alongside variability in pharmacokinetic parameters driven by critical illness. For example, the mean dose of amoxicillin given to neonatal participants was 60 mg/kg 8-hourly. For paediatric participants, who were more frequently prescribed co-amoxiclav, compared to the stand-alone amoxicillin given to neonates, the mean dose of amoxicillin was 25 mg/kg 8-hourly. The difference in doses is driven by the lower quantity of amoxicillin in recommended doses of co-amoxiclav. The consequence of this difference is a far lower %*f*T>MIC (target 8mg/L) for paediatric participants compared with neonates (Table 3).

Variability in %fT>MIC in adults was also notably greater than in children (supplemental Figure S4). In part, this is likely to result from variable organ function prior to and because of critical illness. There may also be a contribution from the fixed dosing recommendation in adults. For example, the range of benzylpenicillin doses prescribed to adults was 10–34mg/kg, a three-fold dose/kg range, resulting from the fixed 1.2g dose recommended in the adults.[15] This degree of variation was not seen in children and neonates where weight-based dosing is standard (the range of benzylpenicillin doses in neonates was 47–55mg/kg). It is reasonable to assume that

this makes a significant contribution to the range of observed %*f*T>MIC for the beta-lactams in adults.

Simulations show that standard antibiotic doses fail to achieve 50% fT>MIC for a proportion of simulated patients even at MICs lower than the EUCAST breakpoint MIC (Figure 2). Using amoxicillin/clavulanate as an example, over half of simulated patients are predicted to fail to achieve 50% fT>MIC for the amoxicillin EUCAST breakpoint MIC for E.coli (8mg/L). In children, 17% failed to achieve 50% fT>MIC even at the much lower MIC of 2 mg/L. This is at the lower amoxicillin/clavulanate intravenous dose recommended in the BNFc[14]–30mg/kg/dose (25mg/kg amoxicillin). Simulations of an increase in the dose in children to 60 mg/kg reduces this to 7% of simulated children failing to achieve 50% fT>MIC of 2mg/L (supplementary figure S5). It would therefore seem that higher doses of intravenous amoxicillin/clavulanate (doubling the current recommended dose) may be required when treating ill children with presumed Gram negative infections, for example complicated urinary tract infections or intra-abdominal infections, likely caused by *E. coli.* This is in keeping with previous work by De Cock *et al.*[37] The models of other drugs presented here could be used in simulations to predict doses that would achieve their breakpoint MIC for all patients.

Limitations

Our pharmacokinetic model and parameter estimate for maturation-decline were limited by heterogenous recruitment to each study drug and age group, although we aimed to mitigate this by pooling of the data. An extensive covariate analysis was also not undertaken because of the complexity of our combined model and the lack of a common measure of illness severity or organ dysfunction across the age groups (APACHE is not validated in neonates for example). Our PK/PD target analysis shares the limitation common to these studies of having to assume a likely pathogen. Choosing a 'worse-case' (highest susceptible MIC) target will result in more failures to obtain pharmacokinetic-pharmacodynamic targets. However, this methodology is in keeping with clinical practice where the pathogen is unknown at the start of treatment and drug choices are made to cover possible options which will include this highest susceptible MIC.[45] Similarly, measuring total, rather than unbound antibiotic concentrations and modelling serum, rather than tissue (site of infection) concentrations are a further limitation.

Conclusion

This work is believed to be the first study of antimicrobial pharmacokinetics to prospectively include all age groups. We successfully used this dataset to estimate a pooled clearance maturation and decline function applicable to all beta-lactams. The parameter estimates from this study could be adopted as a standard for future prospective studies. In addition, this study provides further evidence that standard doses of certain antibiotics fail to achieve recognised pharmacokinetic-pharmacodynamic targets in critical illness. This contribution is particularly important in paediatrics and neonates, where data are limited. For amoxicillin/clavulanate, this work adds to previous research to support use of higher doses than are currently licensed for the treatment of infections likely caused by *E.coli* with higher MICs, and suggests that the BNFc dose recommendations for amoxicillin/clavulanate may need

revision, specifically for clinical infections typically caused by Gram negative pathogens.

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Author contributions

All authors contributed to the design and performance of the research study and drafting of the manuscript. DL, EB and JS analysed the data. KK and AJ undertook analysis of pharmacokinetic samples.

Transparency declarations

The authors declare no conflict of interest in relation to this study.

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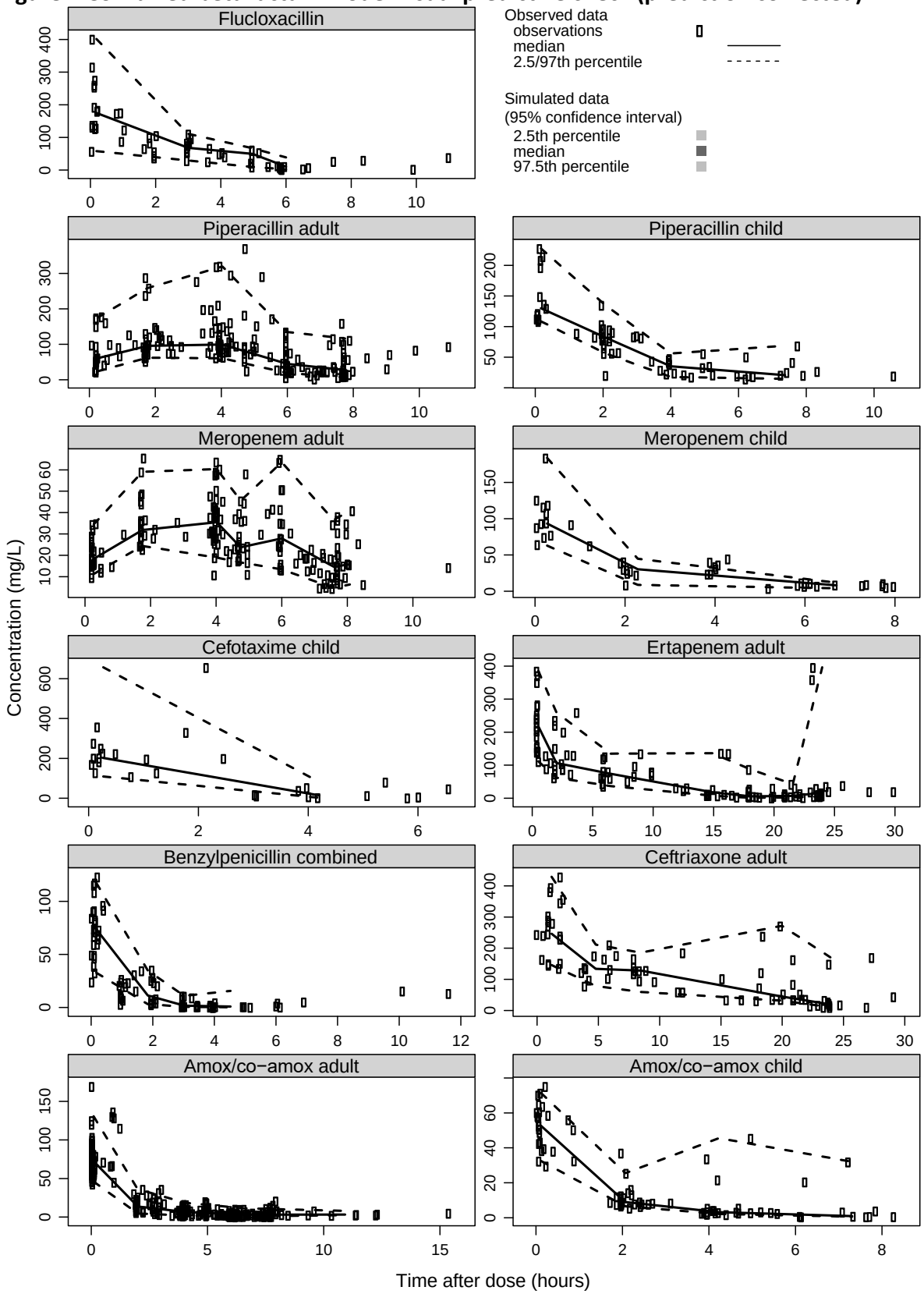
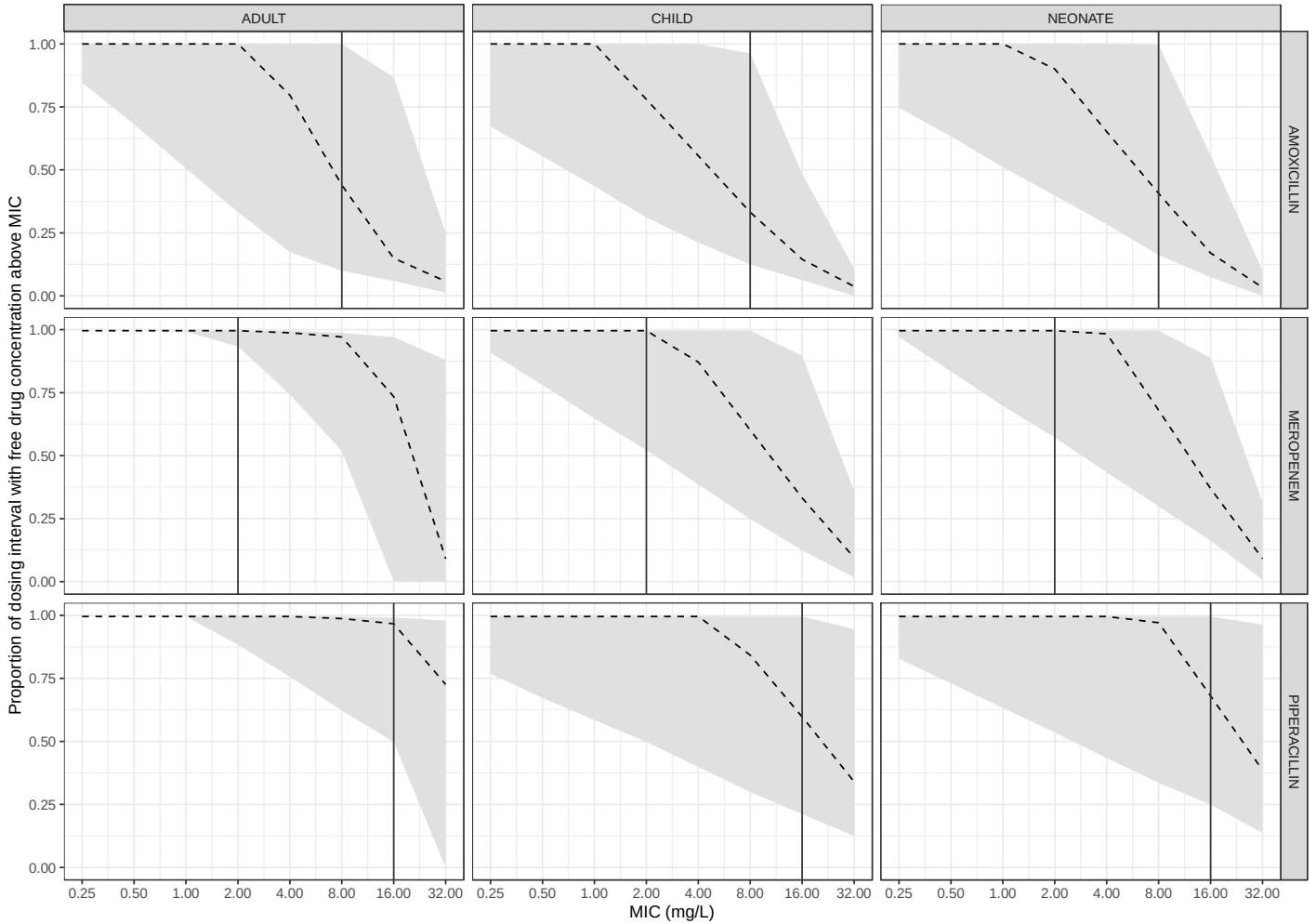
Figure 1 Combined beta lactam model visual predictive check (prediction corrected)



Visual predictive check of the combined beta lactam model. Points are observed data, lines represent median (solid line) and 2.5th/97.5th (dashed lines) centiles of observed data. Shaded areas represent the 95% confidence interval for the 2.5th, median and 97.5th centiles, derived from simulated data

Figure 2 Proportion of time above a range of minimum inhibitory concentration for simulated patients using the final model



The proportion of time with free drug concentration above the minimum inhibitory concentration is shown for simulated patients for the three most commonly prescribed drugs by age group. The dashed line indicates simulated median and shaded area 95% of simulated patients' time with free drug concentration above MIC. Horizontal line indicates the EUCAST break-point MIC for each drug.

Table 1 Demographics and baseline characteristics of participants providing samples for ABDose

Characteristic	Adults	Paediatrics	Neonates
Number of participants (n)	141	51	20
Chronological age	62 [46–71] years	2 [1–6] years	7 [2–28] days
Gestational age (weeks)	–	–	33 [27–37]
Post menstrual age (weeks)	–	148 [86–376]	38 [29–41]
Sex (female/male)	57/84 (40%/60%)	25/26 (49%/51%)	10/10 (48%/52%)
Weight (kg)	70.0 [64.0–92.0]	12.7 [9.0–20.4]	2.4 [1.3–3.0]
Serum creatinine (µmol/L)	93.0 [63.0–134.0]	28.0 [23.0–55.0]	49.5 [27.8–68.5]
CRP (mg/L)	90.7 [25.2–234.2]	19.7 [3.7–100.0]	1.7 [1.0–21.8]
Serum albumin (g/L)	26.0 [22.0–31.0]	26.0 [20.5–31.5]	23.5 [19.3–26.0]
Ventilated on admission (n)	77 (55%)	41 (80%)	19 (95%)
During study period (n)	125 (89%)	46 (90%)	19 (95%)
Vasopressors/inotropes on admission (n)	72 (51%)	20 (39%)	5 (25%)
During study period (n)	79 (56%)	22 (43%)	6 (30%)
Dialysis or haemofiltration on admission (n)	6 (4%)	2 (4%)	0 (0%)
During study period (n)	14 (10%)	4 (8%)	0 (0%)
Sickness severity			
APACHE II	17 [13.0–21.5]	–	–
PIM 2 score	–	3.7 [1.3–5.9]	–
SOFA/pSOFA	6 [4–8]	4 [3–7]	4 [1–5]
Recruitment to drug (n)			
Amoxicillin	49	24	7
Benzylpenicillin	12	0	7
Cefotaxime	0	7	4
Ceftriaxone	12	0	0
Ertapenem	17	0	0
Flucloxacillin	9	0	1
Meropenem	31	13	1
Piperacillin/tazobactam	32	16	3

Data are presented as median [interquartile range] or total (% total), as applicable. Only participants contributing pharmacokinetic samples are included

Table 2 Final model parameter estimates for individual drugs

Parameter	Piperacillin	Amoxicillin	Meropenem	Benzylpenicillin	Ceftriaxone	Cefotaxime	Ertapenem	Flucloxacillin
Fixed effects								
θ_{CL}(L/hr/70kg)	12.0 (8.0%)	15.9 (6.7%)	8.7 (7.6%)	29.8 (16.2%)	2.0 (13.5%)	10.1 (16.1%)	1.5 (13.0%)	7.7 (13.4%)
θ_{V_1}(L/70kg)	13.6 (12.6%)	11.5 (6.9%)	8.8 (10.1%)	12.9 (20.5%)	6.8 (43.8%)	6.7 (22.2%)	3.4 (19.8%)	9.9 (18.8%)
θ_{Q_2}(L/hr/70kg)	8.4 (37.8%)	15.4 (33.4%)	13.8 (20.5%)	41.4 (17.7%)	15.5 (67.1%)	18.0 (25.2%)	5.9 (13.1%)	2.2 (27.7%)
θ_{V_2}(L/70kg)	7.0 (24.4%)	17.2 (15.1%)	10.6 (7.8%)	17.9 (15.4%)	7.8 (24.8%)	22.9 (68.6%)	3.4 (9.7%)	5.3 (18.0%)
θ_{renal}	0.47 (16.2%)							
Random effects								
$\omega_1^2(CL)$	0.16 (24%)	0.15 (19%)	0.10 (25%)	0.26 (31%)	0.12 (42%)	0.21 (32%)	0.17 (32%)	0.10 (44%)
$\omega_2^2(V_1)$	0.21 (40%)	0.06 (33%)	0.10 (46%)	0.37 (47%)	0.39 (74%)	–	0.52 (54%)	0.29 (45%)

Residual error		**Volume maturation**		**Clearance maturation decline**			
σ_1^2 (proportional)	0.03 (10%)	θ_{Vage}	-0.09 (19.8%)	$\theta_{Hill\,1}$	3.27 (16.4%)	$\theta_{Hill\,2}$	2.74 (16.6%)
σ_2^2 (additive)	0.06 (64%)	AGE_{cutoff} (years)	20.7 (14.1%)	PMA_{50} (weeks)	43.4 (6.0%)	AGE_{50} (years)	71.1 (6.0%)

Values provided are parameter estimates produced during the NONMEM run for the final model with associated relative standard error (%RSE). CL clearance, V_1 central volume of distribution, $V_{2,3}$ peripheral volumes, Q inter-compartmental clearance, θ_{renal} creatinine effect (equation S3).

Volume maturation decline defined as follows:

$$V = \begin{cases} V_{STD}.\left(\frac{WT}{70}\right).\left(1+\theta_{Vage}.\left(AGE - AGE_{cutoff}\right)\right), & AGE < AGE_{cutoff} \\ V_{STD}.\left(\frac{WT}{70}\right).exp(\varepsilon), & AGE \geq AGE_{cutoff} \end{cases}$$

V is the model predicted volume of distribution; V_{STD} is non-age corrected volume of distribution; AGE is age in years; AGE_{cutoff} is the age at which the plateau in volume of distribution is reached; θ dictates the slope. AGE_{cutoff} and θ are estimated in the model fitting process.

Clearance maturation decline defined as follows:

$$\left(\frac{PMA^{\theta_{Hill\,1}}}{(PMA^{\theta_{Hill\,1}} + PMA_{50}^{\theta_{Hill\,1}}}\right).\left(1 - \frac{AGE^{\theta_{Hill\,2}}}{(AGE^{\theta_{Hill\,2}} + AGE_{50}^{\theta_{Hill\,2}}}\right)$$

Where: 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; θHills are Hill coefficients. Data presented are mean parameter estimates (% relative standard error)

Table 3 Pharmacokinetic-pharmacodynamic target attainment

	Parameter	Piperacillin	Amoxicillin	Meropenem	Benzylpenicillin	Ceftriaxone	Cefotaxime	Ertapenem	Flucloxacillin
Total (all ages)	50% *f*T>MIC	47/51 (92%)	29/80 (36%)	42/45 (93%)	11/19 (58%)	12/12 (100%)	11/11 (100%)	17/17 (100%)	5/10 (50%)
	100% *f*T>MIC	13/51 (25%)	8/80 (10%)	32/45 (71%)	3/19 (16%)	8/12 (67%)	10/11 (91%)	9/17 (53%)	1/10 (10%)
	50% *f*T>4*MIC	11/51 (22%)	2/80 (3%)	36/45 (80%)	3/19 (16%)	6/12 (50%)	11/11 (100%)	9/17 (53%)	0/10 (0%)
	100% *f*T>4*MIC	0/51 (0%)	1/80 (1%)	7/45 (16%)	0/19 (0%)	0/12 (0%)	5/11 (45%)	3/17 (18%)	0/10 (0%)

	Parameter	Piperacillin	Amoxicillin	Meropenem	Benzylpenicillin	Ceftriaxone	Cefotaxime	Ertapenem	Flucloxacillin
By age group	50% *f*T>MIC								
	Adults	30/32 (94%)	23/49 (47%)	31/31 (100%)	4/12 (33%)	12/12 (100%)	–	17/17 (100%)	5/9 (56%)
	Paediatrics	14/16 (88%)	1/23 (4%)	10/13 (77%)	–	–	7/7 (100%)	–	–
	Neonates	3/3 (100%)	5/7 (71%)	1/1 (100%)	7/7 (100%)	–	4/4 (100%)	–	0/1 (0%)
	100% *f*T>MIC								
	Adults	6/32 (19%)	7/49 (14%)	25/31 (81%)	3/12 (25%)	8/12 (67%)	–	9/17 (53%)	1/9 (11%)
	Paediatrics	5/16 (31%)	0/24 (0%)	7/13 (54%)	–	–	6/7 (86%)	–	–
	Neonates	2/3 (67%)	1/7 (14%)	0/1 (0%)	0/7 (0%)	–	4/4 (100%)		0 (0%)
	50% *f*T>4*MIC								
	Adults	10/32 (31%)	2/49 (4%)	29/31 (94%)	3/12 (25%)	6/12 (50%)	–	9/17 (53%)	0/9 (0%)
	Paediatrics	1/16 (6%)	0/24 (0%)	7/13 (54%)	–	–	7/7 (100%)	–	–
	Neonates	0/3 (0%)	0/7 (0%)	0/0 (0%)	0/7 (0%)	–	4/4 (100%)	–	0/0 (0%)
	100% *f*T>4*MIC								
	Adults	0/32 (0%)	1/49 (2%)	4/31 (13%)	0/12 (0%)	0/12 (0%)	–	3/17 (18%)	0/9 (0%)
	Paediatrics	0/16 (0%)	0/24 (0%)	3/13 (23%)	–	–	3/7 (43%)	–	–
	Neonates	0/3 (0%)	0/7 (0%)	0/1 (0%)	0/7 (0%)	–	2/4 (50%)	–	0/0 (0%)

Values are summaries of pharmacokinetic-pharmacodynamic target attainment. Targets are % of time with free drug concentration above the minimum inhibitory concentration of the target organism (%*f*T>MIC) in the first 24-hours of treatment (e.g. 50% *f*T>MIC means at least half of the time free drug concentration is above MIC). Values were calculated using empirical Bayes estimates from the final pharmacokinetic model

Table 4 Parameter estimates for maturation decline function compared to other similar studies

Parameter	This study	Germovsek et al. (14)	Rhodin et al. (19)	Lonsdale et al. (15)	Colin et al. (18)
θ_1	3.27	4.2	3.4	3.45	2.89
PMA_{50} (weeks)	43.4	45.1	47.7	49.7	46.4
θ_2	2.74	–	–	4.0	2.24
AGE_{50} (years)	71.1	–	–	86.8	61.6

Comparator estimates for similar functions in Germovsek et al. (14) study of gentamicin, Rhodin et al. (19) study of renal function maturation, Lonsdale et al. (15) review of beta-lactam pharmacokinetics and Colin et al. (18) whole-life model of vancomycin.

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).

Equation 2 Clearance maturation decline function

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

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[10].