Review of population pharmacokinetic models of first choice beta-lactam antibiotics in severely afflicted pediatric patients: Discrepancy in dosage regimens

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ABSTRACT – Background: To perform a review describing the pharmacokinetic (PK) parameters and covariates of interest of the eight first choice β-lactams (BL) antibiotics for treatment of severe infections in pediatric population. Pediatric sepsis and septic shock reportedly affect 30% of children admitted to pediatric intensive care units, with a 25% mortality rate. Eight BL are included as first choice antibiotic for severe infections in pediatric population in the World Health Organization model list of essential medicines for children. **Methods:** The PubMed/Medline databases was searched and included studies if they described a population PK model of piperacillin, amoxicillin, ampicillin, cefotaxime, ceftriaxone, cloxacillin, imipenem or meropenem in neonates or children. We compared the PK parameters for each drug. We analysed the used covariates to estimate PK parameters. We compared the pharmacokinetics/pharmacodynamics (PK/PD) targets and the drug dosing recommendations. **Results:** Thirty-four studies met inclusion criteria with seven studies for piperacillin, five for amoxicillin, three for ampicillin, three for cefotaxime, two for ceftriaxone, two for imipenem and twelve for meropenem. None met inclusion criteria for cloxacillin. Ages ranged from 0-19.1 years with 12 studies including preterm. Body weight, age and renal function were the three major covariates in neonates and children. Different PK/PD targets were observed (between 40% to 100% of the dosing regimen interval of time over which the unbound (or free) drug concentration remains above the minimal inhibitory concentration (MIC) (fT>MIC) or four times the MIC (fT>4xMIC)). Several drug-dosing regimens were fond recommended according to the age and pathogens MIC using intermittent, timed or continuous infusions. **Conclusions:** Consensus is lacking on the optimal dosing regimens for these eight first choice antibiotics. A more personalized approach to antibiotic drugs dosing with individual characteristics of patient and pathogen susceptibility is required. According PK/PD targets and used dosing regimens, prospective clinical studies are required to investigate clinical cure, patient survival and emergence of antimicrobial resistance.

INTRODUCTION

Pediatric sepsis and septic shock reportedly affect 30% of children admitted to pediatric intensive care units (ICUs), with a 25% mortality rate (1). Gram-negative organisms represent one-third of cases of late onset sepsis but are associated to the highest mortality. Indeed, these agents are responsible for 40–69% of sepsis-related deaths and critically ill children or those suffering from an underlying condition such as malignancy, or immunodeficiency, are at particular risk (2). Sepsis and septic shock are medical emergencies that warrant prompt resuscitation and antimicrobial therapy in order to improve prognosis (3-5). Choosing the antimicrobial agent adapted to the potential bacterial susceptibility is crucial. But as importantly successful microbiological eradication and clinical cure also depends on an adequate dosing regimen. According to the World Health Organization, antibiotic resistance is one of the greatest threats to global health today and leads to longer hospital stays, higher medical costs and increased mortality (6).

Beta-Lactams (BL), the most commonly prescribed class of antibiotics, are recommended as

the first-line therapy in many infectious disease guidelines (7,8). Due to their broad antimicrobial spectrum and relatively low toxicity, BL are commonly used in pediatric critical care for treating community-acquired infections (9). Eight BL are included as first choice antibiotic for severe infections in the pediatric population in the WHO model list of essential medicines in children (10). As recently described by van den Anker and Allegaert (11) BL are commonly prescribed in the neonate intensive care unit since ampicillin (rank 1), cefotaxime (rank 15), piperacillin (rank 41), amoxicillin (rank 43), meropenem (rank 52) and ceftriaxone (rank 91) are in the list of the 100 most commonly prescribed (12-14). Since the treatment is time-dependent, drugs concentration should be above the MIC throughout the dosing interval (15). The pharmacokinetics (PK) target for BL is currently debated, with studies reporting values varying between 50% and 100% of the dosing interval being over which the unbound (or free) drug concentration remains above the minimal inhibitory concentration (MIC) (fT>MIC) or four times the MIC (fT>4xMIC))(4).

Critically ill children frequently experience organ dysfunction and/or physiological changes, leading to alterations in PK parameters (16), i.e., altered BL concentrations (17). Neonates and young infants present a special subgroup of the population in whom optimization of antimicrobial dosing can be particularly challenging (18). A recent study has shown that 95% of critically ill children did not achieve the *a priori* primary PD endpoint (fT>4-6 x MIC for 40% of the dosing interval) with the current published pediatric BL dosing recommendations (18). Dosing recommendations are often extrapolated from evidence generated in older patient populations (19).

This paper provides an overview of the current literature on first choice BL population PK studies in pediatrics.

METHOD

Inclusion criteria

We included all described PK population models of piperacillin/tazobactam, ampicillin, amoxicillin, cefotaxime, ceftriaxone, cloxacillin, imipenem and meropenem. The articles were included if they met the following inclusion criteria: studied populations: neonates and infants hospitalized in pediatric intensive care units, treatment: intravenous of piperacillin, ampicillin, amoxicillin, cefotaxime or ceftriaxone, and PK analysis: modelling by a population approach.

Exclusion criteria

The articles were excluded if they are reviews, methodology articles or if the analysis did not used a population PK modelling and population studies not involving a mixed-effects models analysis.

Search strategy

A literature search was conducted from the Medline/PubMed database, from their inception through March 2019 using the following terms: (*piperacillin* OR/AND *ampicillin* OR/AND *amoxicillin* OR/AND *cefotaxime* OR/AND *ceftriaxone OR/AND imipenem OR/AND meropenem)* AND [(*pharmacokinetics*/ or *renal elimination*/) OR (*pharmacokinetic** OR ((*pharmaco* OR *drug*) ADJ *kinetic**) OR *area under curve*? OR *AUC* OR (*renal* ADJ (*elimination*? or *excretion*? or *clearance*?))) OR (((*nonlinear* OR *non-linear*) ADJ *mixed effect model**) OR *NONMEM* OR *WinNonMix* OR *P-PHARM* OR *NLMIXED* OR *ADAPT*)] AND (EXP *population*/ OR *population groups*/ OR (*population*? OR *ethnic group*?)) AND (*neonatal*/ OR *neonate*/ OR *infant* OR *children*/ OR *newborn*/ OR *pediatric*). Moreover, additional studies were identified from the reference list of selected papers. The search was additionally limited to "English language" and "clinical data." The different phases of review are displayed in a flowchart (Figure 1), as described by the PRISMA 2009 statement (21).

Data extraction

The results of these investigations were closely evaluated, and articles were retained if they met the inclusion criteria. Pertinent articles were assessed and the following data were extracted: year of publication, pathology, number of patients, number of samples, structural model, value and expression of PK parameters, included covariates, inter- and intra-individual variability and dosing regimens recommendations according the used MIC and PK/PD targets. Quality control of the extracted data was performed internally by an independent party to confirm the validity of the included results.

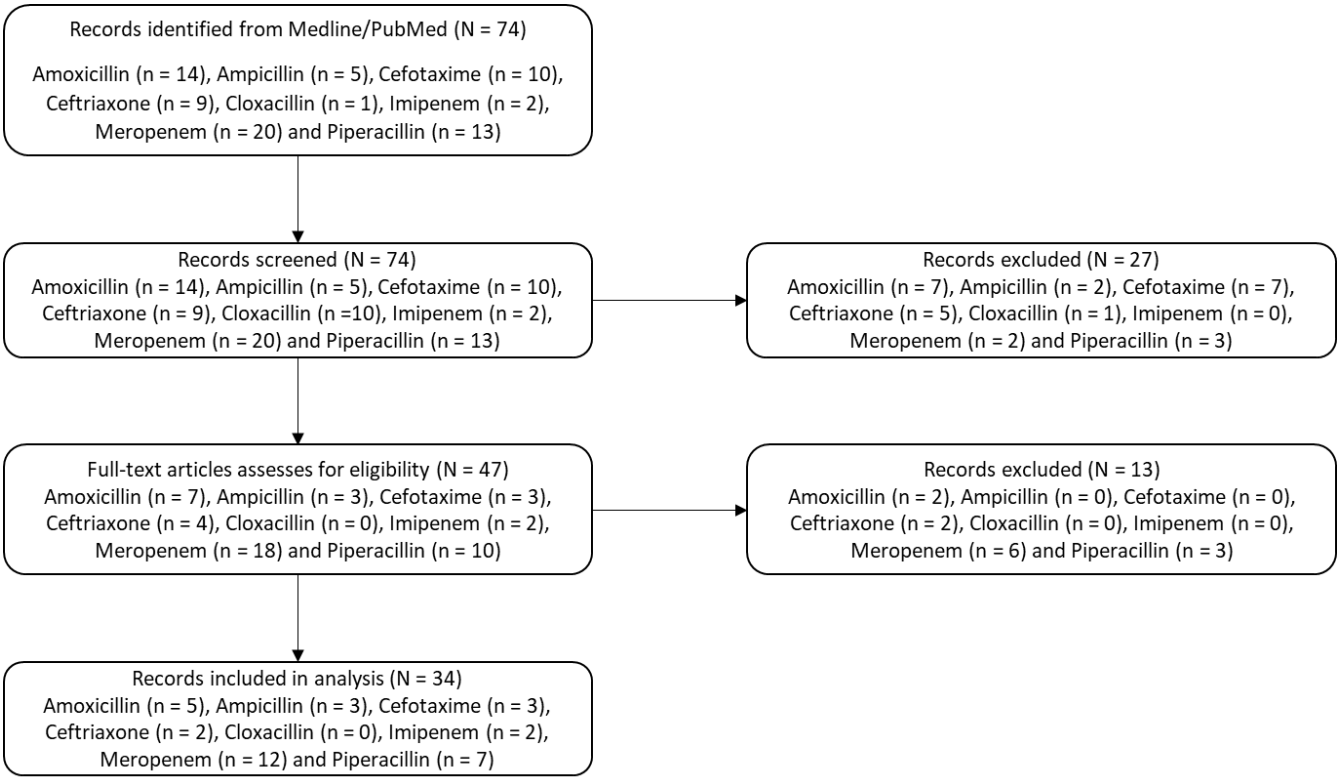

Figure 1. Flow chart for inclusion of studies in this review

RESULTS

Trial flow

A total of 74 articles were first selected. Among these, 40 were excluded based on the inclusion and exclusion criteria. A total of 34 articles were finally retained (20-53). (Figure 1)

Study characteristics

The 34 studies described a PK population model of first choice BL (piperacillin (n=7), ampicillin (n=3), amoxicillin (n=5), cefotaxime (n=3), ceftriaxone (n=2), cloxacillin (n=0), imipenem (n=2) and meropenem (n=12)) and were published between 1995 and 2019 (20-53). Studied populations consisted of critically ill patients including preterms (in 12 studies) with documented or suspected Gram-negative infection, mainly sepsis and pneumonia (Table 1) (22, 24, 25, 28, 29, 38-40, 47, 50-52). BL were administered as intermittent or extended infusions according to different dosing regimens: once-, twice-, three- or four-daily dose.

Data analysis

Among the 34 published studies, 12 focused on meropenem (23, 26, 33, 34, 36, 37, 42, 44-46, 48, 52) and 7 on piperacillin (20, 27, 29, 30, 40, 43), and 12 included preterms population (22, 24, 25, 28, 29, 38-40, 47, 50-52) The following covariates were selected as interindividual variability factors for clearance (CL) and volume of distribution (V): age (post menstrual age (PMA) or post conceptional age (PCA), post-natal age (PNA) or gestational age (GA)), body weight, serum creatinine (SCR), creatinine clearance (CLcr), glomerular filtration rate (GFR), cystatin C, urine output, severity (PEdiatric Logistic Organ Dysfunction-2 (PELOD-2) score, oedema, temperature) and vasopressor and gentamicin coadministration (Figure 2). However, only three covariates were frequently used to estimate the clearance while one was used for volume of

distribution. Indeed, the body weight was the most used covariate to estimate the clearance or volume of distribution to estimate the clearance among the 30 studies using the body weight and to estimate the volume of distribution among the 28 studies using the body weight. The second used covariate was age; indeed, 16 studies included this covariate in the equation of the clearance. The age was differently expressed as post conceptionnal age or post menstrual age (PCA or PMA), postnatal age (PNA) and gestational age (GA). For the estimation of clearance, eight studies using the PMA or PCA, seven studies used the PNA and three studies used the GA. The last covariate frequently used was renal function. To estimate clearance, this covariate was expressed by several parameters: the creatinine clearance (CLcr), the serum creatinine (Scr), cystatine C, urine output or the glomerular filtration rate (GFR). Thirteen studies used this covariate, six studies the SCr, four studies the CLcr, one study the cystatine C, one study the urine output and one study GFR. Table 1 summarizes mean values of clearance and volume of distribution described in these studies. For piperacillin, the median estimate value (range) of clearance and volume of distribution (range) were 0.25 L/h/kg (0.08-0.48 L/h/kg) and 0.37 L/kg (0.24-2.91 L/kg), respectively (n=7). For amoxicillin, the median estimate value (range) of clearance and volume of distribution (range) were 0.10 L/h/kg (0.08-0.26 L/h/kg) and 0.65 L/kg (0.37-1.21 L/kg), respectively (n=5). For ampicillin, the median estimate value (range) of clearance and volume of distribution (range) were 0.07 L/h/kg (0.03-0.11 L/h/kg) and 0.40 L/kg (0.40-0.52 L/kg), respectively (n=3). For cefotaxime, the median estimate value (range) of clearance and volume of distribution (range) were 0.12 L/h/kg (0.10-0.13 L/h/kg) and 0.44 L/kg (0.31-0.64 L/kg), respectively (n=3). For ceftriaxone, the median estimate value (range) of clearance and volume of distribution (range) were 0.60 L/h/kg (0.42-0.79 L/h/kg) and 2.57 L/kg (1.63-3.51 L/kg), respectively (n=2). For imipenem, the median estimate value of clearance (range) and volume of distribution (range) were 0.36 L/h/kg (0.24-0.48 L/h/kg) and 0.57 L/kg (0.37-0.76 L/kg). For meropenem, the median estimate value (range) of clearance and volume of distribution (range) were 0.31 L/h/kg (0.10-0.43 L/h/kg) and 0.42 L/kg (0.20-1.35 L/kg). Figure 3 depicts the used MIC and % fT>MIC used targets according the studied drugs. Table 2 summarizes the recommended drug dosing regimens by the authors.

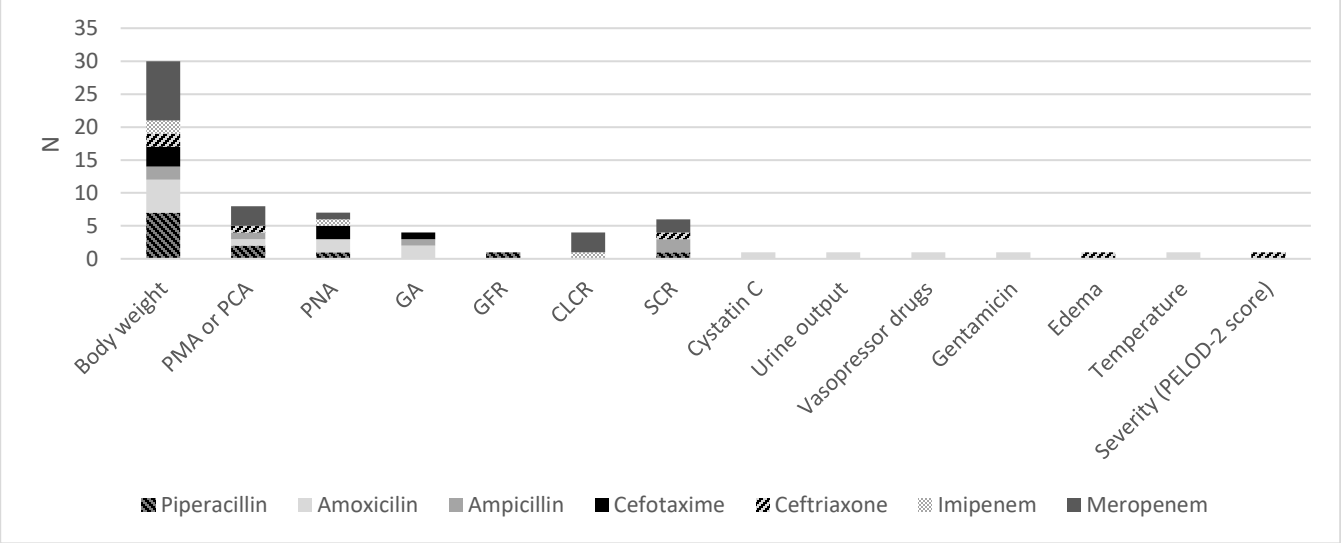

Figure 2. Number of studies that include covariates of interest on clearance and/or volume of distribution estimates

Table 1. Clearance and volume of distribution according population characteristics as reported in the listed sources

Drug	Reference	Year	Age (yr)	PNA (day)	GA (wk)	PMA (wk)	WT (kg)	CL (L/h/kg)	Vd (L/kg)
Piperacillin	Beranger A (20)	2019	2.3 (0.1-18)	N/A	N/A	N/A	11.9 (2.7-50)	0.28	0.35
	Cohen-Wolkowiez M (29)	2014	N/A	8 (1-60)	30 (23-40)	32 (25-48)	1.439 (0.473-3.990)	0.08	0.57
	Cohen-Wolkowiez M (28)	2012	N/A	17 (1-77)	25 (22-32)	29 (23-40)	0.867 (0.400-2.580)	0.48	2.91
	De Cock PA (30)	2017	2.83 (0.17-15)	N/A	N/A	N/A	14 (3.40-45)	0.25	0.24
	Nichols K (43)	2016	5 (1.75-6.5)	N/A	N/A	N/A	17.8 (11.4-20)	0.20	0.37
	Cies JJ (27)	2014	2 (0.5-6)	N/A	N/A	N/A	14.5 +/-6	0.30	0.25
	Li Z (40)	2013	N/A	14.4 (1-56)	35.5 (26.0-41.1)	37.5 (26.1-45.0)	2.76 (0.93-4.72)	0.18	0.37
Amoxicillin	Tang BH (50)	2019	N/A	7.00 (1.00-37.0)	38.1 (28.3-41.4)	39.0 (28.4-46.3)	3.21 (1.06-4.58)	0.25	1.21
	Bijleveld YA (22)	2018	N/A	5 (2-5)	40 (36-42)	NA	3.340 (2.090-5.070)	0.10	0.69
	De Cock PA (31)	2015	2.58 (0.08-15)	N/A	N/A	-N/A-	14.4 (4.07-65)	0.26	0.37
	Charles BG (24)	1997	N/A	1.1 (1-3)	28.9 (24-32)	NA	1.123 (0.630-1.470)	0.08	0.60
	Pullen J (47)	2006	N/A	0.76 (0-9)	34.6 (24.9-42.4)	NA	2.29 (0.57-4.7)	0.10	0.65
Ampicillin	Le J (38)	2018	N/A	8 (1-26)	37.3 (27.0-41.0)	NA	3.120 (0.930-4.110)	0.11	0.40
	Cies JJ (25)	2017	N/A	NA	38.77 (36-41)	NA	3.34 (2.4-4.9)	0.03	0.52
	Tremoulet A (51)	2014	N/A	5.0 (0-25.0)	36.1 (24.0-41.0)	NA	NA	0.07	0.40
Cefotaxime	Beranger A (21)	2018	1.98 (0.02-19.08)	N/A	N/A	N/A	10.9 (2.5-68)	0.10	0.31
	Leroux S (39)	2016	N/A	9.0 (0-69.0)	31.5 (23.0-42.0)	33.0 (25.0-44.0)	1.647 (0.530-4.200)	0.13	0.64
	Maksoud E (41)	2018	9.6 (1.1-18.7)	N/A	N/A	N/A	25 (9.5-80.2)	0.12	0.44
Ceftriaxone	Standing JF (49)	2018	1.25 (0.17-3.75)	N/A	N/A	N/A	5.88 (2.53-10.9)	0.79	1.63
	Iida S (35)	2010	8.00 (0.05-17.00)	N/A	N/A	N/A	21.5 (3.0-51.0)	0.42	3.51
Imipenem	Dong L (32)	2019	4.69 (2.03-11.82)	N/A	N/A	N/A	18.00 (10.00-44.00)	0.48	0.76
	Yoshizawa K (53)	2013	10.5 days (0-34) (neonates)	NA	38.3 (30.4-41.1)	NA	2.93 (1.76-4.90)	0.22	0.47
			9.61 (3.00-16.2)	N/A	N/A	N/A	29.5 (13.8-65.0)	0.26	0.26
eropenem	Ciess JJ (26)	2017	3.1 (1-9)	N/A	N/A	N/A	17.1 ± 11.9	0.42	1.35
	Kongthavonsakul K (37)	2016	6.0 (4.5-11.8)	N/A	N/A	N/A	20.0 (14.0-46.5)	0.33	0.20

Table 1 continues ……

Nehus EJ (42)	2014	0 to >18	N/A	N/A	N/A	2.9-78.5	NC	NC
Smith PB (48)	2011	N/A	21 (1-92)	28 (23-40)	33 (24-51)	Birth weight 1.080 (0.330-4.768)	0.12	0.46
Ohata Y (44)	2011	3.1 (0-13)	N/A	N/A	N/A	14.8 (6.5-50.0)	0.43	0.34
Ikawa K (36)	2010	6.6 (0.2-14.8)	N/A	N/A	N/A	23.2 (3.8-64.0)	0.40	0.50
Van der Anker (52)	2009	N/A	NA	Pre-term: 32 ± 2 (29-36) Full-term: 39 ± 1 (37-42)	NA	Pre-term: 1.87 (0.952-2.83) Full-term: 3.17 (2.34-4.05)	0.19 (pre-term) 0.16 (full-term)	0.52 (pre-term) 0.31 (Full-term)
Bradley JS (23)	2008	N/A	10.0 (1-60)	34.0 (23-41)	NA	2.4 1.0 (0.8-4.0)	0.10	0.40
Du X (33)	2006	3.17 (0.08-17.3)	N/A	N/A	N/A	13.50 (3.70-65.00)	0.31	0.38
Germovsek E (34)	2018	N/A	13 (1-90)	33.3 (22.6-41.9)	NA	2.12 (0.48-6.32)	0.24	0.55
Padari H (45)	2012	N/A	GR1: 15.6 ± 8.6 GR2: 20.5 ± 6.6	GR1: 26.9 ± 1.4 GR2: 25.8 ± 25.8	NA	GR1: 0.9846 ± 0.2916 GR2: 0.9695 ± 0.1029	NC	NC
Parker EM (46)	1995	(2 months-12 years)	N/A	N/A	N/A	(3.7-46)	NC	NC

NC: not calculated; NA: not available; N/A :not applicable ; GR1: group 1; GR2: group 2; PMA: post mentrual age; GA: gestational age; PNA: post-natal age; CL: clearance; Vd: volume of distribution

Table 2. Drug-dosing regimens recommendations according to the different studies

Reference	PK/PD target	Total daily dosing recommendations (mg/kg)	Conditions	Interval (h)	Type of infusion recommendation
Piperacillin					
Beranger A (20)	50% or 100% fT>16mg/L	300	N/A	24	PI or CI
		400	Augmented renal function	24	
Cohen-Wolkowiez M (29)	75%fT>32 mg/L	300	PMA≤30 weeks	8	II
		320	30<PMA≤35 weeks	6	II
		480	35<PMA≤49 weeks	4	II

Table 2 continues ..

Cohen-Wolkowiez M (28)	50% and 75% fT>16mg/L	*NA*	*N/A*	*NA*	*NA*
De Cock PA (30)	50% fT>16 or 32 mg/L	300	MIC=16mg/L	24	CI
		350	MIC=32mg/L	24	CI
Nichols K (43)	50% fT>MIC 16 mg/L	320	*N/A*	8	PI (4h-infusion)
Cies JJ (27)	50% fT>16mg/L	400	*N/A*	6	PI (3h-infusion)
		400	*N/A*	24	CI
Li Z (40)	50 % fT>4 mg/L	*NA*	*N/A*	*NA*	II
Amoxicillin					
Tang BH (50)	70% fT>1 or 2 mg/L	50	GA<37 weeks and MIC=1mg/L	12	II
		75	GA≥37 weeks and MIC=1mg/L	8	II
		100	MIC=2mg/L	6	II
Bijleveld YA (22)	40–50% fT>1 mg/L	150	36≤GA≤37 weeks	8	II
		225	38≤GA≤42 weeks	8	II
De Cock PA (31)	40% fT >8 mg/L	100	*N/A*	6	II
Charles BG (24)	NA	*NA*	*N/A*	*NA*	NA
Pullen J (47)	40% or 50% fT>8 mg/L	45	GA≤30 weeks	8	II
		60	30<GA≤34 weeks	8	II
Ampicillin					
Le J (38)	NA	*NA*	*N/A*	*NA*	NA
Cies JJ (25)	50% fT >8 mg/L	25	*N/A*	24	II
	100% fT >8 mg/L	50	*N/A*	24	II
Tremoulet A (51)	50-100% fT>8 mg/L	100	GA≤34 weeks and PNA≤7 days	12	II
		150	GA≤34 weeks and 8≤PNA≤28 days	12	II
		150	GA>34 weeks and PNA≤28 days	8	II

Table 2 continues ..

Cefotaxime					
Beranger A (21)	100% fT>0.5 or 2 mg/L	100	N/A	24	CI
Leroux S (39)	75% fT>4 mg/L	200	*N/A*	6	II
Maksoud E (41)	80 % fT>1 mg/L	400	N/A	6	II
Ceftriaxone					
Standing JF (49)	100 % fT>2 mg/L	80	N/A	24	II
Iida S (35)	70-100% fT>1 mg/L	20	*N/A*	24	II
		60	Low body weight and severe infections	24	II
Imipenem					
Dong L (32)	70% fT > 0.5 mg/L	*NA*	*NA*	*NA*	*NA*
Yoshizawa K (53)	40% fT >16 mg/L	75	neonates	8	II
		100	children	12	II
Meropenem					
Ciess JJ (26)	80% fT >4 mg/L	120 or 160	N/A	24	CI
Kongthavonsakul K (37)	40% fT > 4 mg/L	20	N/A	*NA*	PI (3h-infusion)
Nehus EJ (42)	40% or 75% fT > 4 mg/L	40	Age >5 years	12	II
		60	Age <5 years	8	II
Smith PB (48)	50% or 75% fT >2 mg/L	40	GA<32weeks and PNA<14days	12	II
		60	GA<32weeks and PNA≥14days or GA≥32weeks and PNA<14days	8	II
		90	GA≥32weeks and PNA≥14days	8	II
Ohata Y (44)	50% fT >2 mg/L	80	N/A	12	PI (4h-infusion)
Ikawa K (36)	40% fT >0.5 mg/L	30-120	N/A	8	II
Van den Anker (52)	40% fT >4 mg/L	160	N/A	8	PI (4h-infusion)
Bradley JS (23)	60% fT >4 mg/L	60	N/A	8	II
Du X (33)	40% fT >0.5 mg/L	120 or 80 or 40	N/A	8 or 12 or 24	II
Germovsek E (34)	61% fT >2 mg/L	60	Late-onset sepsis	8	II

Table 2 continues ..

		120	If increase of MIC	8	II
Padari H (45)	*NA*	40	N/A	12	II
Parker EM (46)	*NA*	*NA*	*NA*	*NA*	*NA*

NA: not available ; N/A :not applicable ; CI: continuous infusion; II: intermittent infusion; PI: prolonged infusion; PMA: post menstrual age; GA: gestational age; PNA: post-natal age; MIC: minimal inhibitory concentration

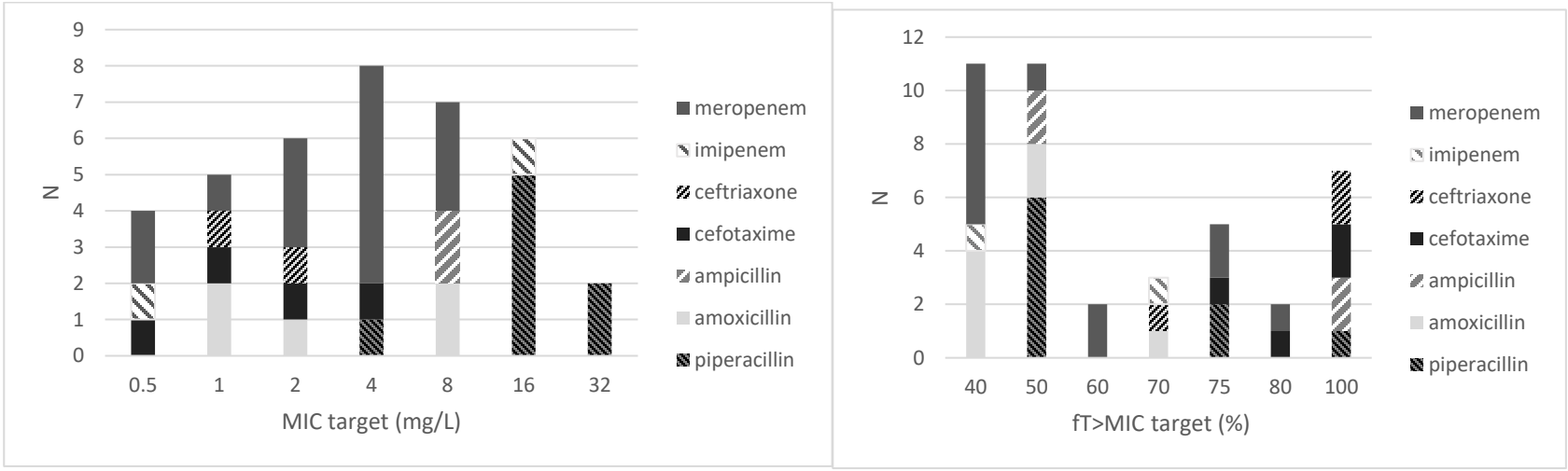

Figure 3. Number of studies versus the used MIC (left) and the chosen PK/PD targets (right) in the simulations according to the drug studied.

DISCUSSION

This is the first review of first choice BL PK studies in children. Despite a comprehensive review strategy, we identified only 34 studies (for eight drugs). Considering the high rate of mortality of pediatric patients with sepsis and the emergence of antimicrobial resistance, concerns have raised regarding the relative paucity of drug PK data, hence less than optimal dosage regimens by the Council of Canadian Academies (54). Recently, Cies et al. (18) observed that 95% of critically ill children did not achieve the *a priori* primary pharmacodynamic endpoint, *i.e.* the target exposure, with current published pediatric BL dosing recommendations. This signifies the need to study, develop and individualize anti-infective dosing in pediatrics. The 34 studies included in this analysis can help to better understand the PK of BL in children and to identify the need for future studies. Most antimicrobial drugs used in preterms, neonates and infants lack some aspects of PK information specific to this population. Without appropriate studies specifically designed for this vulnerable population physicians are often forced to prescribe drugs "off-label," exposing patients to suboptimal drug exposure or potential adverse drug effects.

First element to identify, populations studied in this review were large including preterms, neonates and paediatrics (Table 1). This element needs to be accounted for when we compare these studies. Twelve studies included preterms in their population (22, 24, 25, 28, 29, 38-40, 47, 50-52), with one study including only preterms (28). Age progression in the preterm population is associated with developmental changes over time, which is expected to affect the pharmacokinetic processes (55). The lower protein-binding level in the preterm population compared with older neonates can affect the disposition of drugs (55, 56). The higher extracellular fluid in preterms compared with older infants is expected to increase the distribution volume of hydrophilic drugs such as beta-lactams (55, 57, 58). Moreover, the lower or absence expression of drug-metabolising enzymes and lower glomerular function can contribute to lower clearance (55). Because of the diversity of pathophysiological conditions and developmental changes, comparing pharmacokinetic in a preterm population and explaining variability remains a real challenge.

PK modeling identifies a number of covariates thus explaining some of the PK variability. This review identified the significant covariates, *i.e.* the use of these covariates improves prediction of the time-concentration profile in the individual infant. As described in a previous review (59) body weight, age and renal function are the three major covariates in neonates and young infants. Body weight is the most common covariate used to determine dose in the pediatric population (n=30). The change in body weight with age is significant up to 1 year, body weight increases approximately three- to fourfold from birth to 1 year (60). Allometric size modelling is used with increasing frequency in pediatric PK population analyses (59). It is widely recognised that there is a nonlinear relationship between weight and drug elimination capacity. Allometric "1/4 power" models can be applied to PK parameter estimates in infants, e.g. clearance [0.75] and volume of distribution [1] (60). Age is the second covariate most used (n=16). Indeed, the first few years of life are time of growth and maturation of enzymatic processes. This maturation factor cannot be explained by allometry. The addition of a model describing maturation is required. The sigmoid hyperbolic or Hill model has been found useful for describing this maturation process but this model is little used (61). Maturation of clearance begins before birth, suggesting that covariates like postmenstrual age (PMA) or post conceptional age (PCA) (n=8) or gestational age (GA) (n=3) would be a better predictor of drug elimination than postnatal age (PNA) (n=6). Indeed, the impact of ontogeny on the expression and functional activity of the major drug-metabolizing enzymes may be important. Whatever the definition of age (PMA, PCA, GA or PNA), this factor largely contributes to variability of drugs given to neonates and young infants, but this impact will depend on the speed of maturation and the subpopulation studied. The third covariate is renal function (n=13) often estimated by serum creatinine (SCR) (n=6), creatinine clearance (n=4), glomerular filtration rate (GFR) (n=1), cystatin C (n=1) or urine output (n=1). With this third covariate, we might expect to reflect the influences of size, maturation and organ function.

Other covariates such as comedications with vasopressor drugs or gentamicin, and pathology with severity score or edema are used in some specific studies (20, 24, 31, 49).

The values of PK parameters showed a great variability according to the studied population (preterm, neonates, infants or children). For piperacillin, our review showed that the median clearance and volume of the distribution in pediatric population are in accordance with previously reported values in critically ill adults (0.22 L/h/kg vs 0.33 L/kg) (62). These values were different and largely variable if each parameter is considered according to the studied population. Studies including preterm and neonates showed a large variability on clearance value explained by the maturation of GFR, indeed GFR matures during infancy and approaches an adult rate by 6 months PNA (61). But age is also used to describe maturation of clearance with maturation of clearance begins before birth explaining difference between preterm and neonates clearances (61). For amoxicillin, our review showed that the median clearance in the pediatric population are in accordance with previously reported values in critically ill adults (0.10 L/h/kg vs 0.13 L/kg) (63). Whereas for amoxicillin and cefotaxime, we observed a value of clearance divided by 2.0 for cefotaxime and 3.0 for ampicillin in the pediatric population (21, 22, 24, 31, 39, 41, 47,50). But if we looked at each amoxicillin studies in detail, we observed a large variability on amoxicillin clearance values as for piperacillin, explained by the same maturation process described previously (61) since numerous studies have been conducted in preterms and neonates (22, 24, 47, 50). For imipenem, our review showed increased median clearance (0.36 L/h/kg vs 0.16 L/h/kg in adults) and volume of distribution (0.57 L/kg vs 0.16 L/kg in adults) in the pediatric population (32, 53). However, the values only represent neonates and young children, a different maturation system could explain this increase compared to adults. For meropenem, we observed an increase of clearance in the pediatric population (0.31 L/h/kg vs 0.12 L/h/kg in adults) whereas the volume of distribution seems to be similar to the adult population (23, 26, 33, 34, 36, 37, 42, 44-46, 48, 52).

For all studies drugs except piperacillin and meropenem described previously, our review showed greater volumes of distribution in pediatric population in comparison with adults. For piperacillin, one study presents a large volume of distribution (28). Indeed, this study included only preterms, this specific population has different characteristics compared to newborns and children that have an impact on pharmacokinetics (55, 64). A large volume of distribution of piperacillin in this population can be explained by the high total water content relative to body mass and the hydrophilic nature of the piperacillin (55, 58). For amoxicillin, ampicillin and cefotaxime we observed an increase of 1.5 (range 1.22-1.76) of the observed value in adult population. This greater volume of distribution is most important for ceftriaxone and imipenem, we observed a value of 2.57 L/kg in pediatric population was substantially higher than the one reported in critically ill adults (0.28 L/kg) for ceftriaxone, and we observed an increase of 3.5 for imipenem (65). As previously described, total body water constitutes 85% of the body weight in the preterm neonate and 75% in full-term neonates (61). This decreases to approximately 60% at 5 months and remains relatively constant from this age forward. In neonates and infants, the total body water increased which contributes to an increase in the volume of distribution for hydrophilic drugs. Moreover, albumin, globulin, lipoprotein, and glycoprotein concentrations change over the first year affecting drug binding that could be explained with the large increase of ceftriaxone volume of distribution, since ceftriaxone protein binding is nonlinear (66).

For the BL antibiotics, the PK/PD index associated with the most successful outcome (optimal bacterial killing and/or clinical outcome) is the %f T>MIC, or the percentage of time (T) of the dosing interval during which the unbound (free, f) serum antibiotic concentration remains at least above the MIC for the targeted organism. For BL antibiotics, the traditional minimal target range of 40–60% of the dosing interval was informed by animal studies and confirmed in some human studies (67) but more clinical evidence is needed. For example, from preclinical studies it is learned that for the cephalosporins, the minimum value of fT>MIC for bacteriostasis is 40% for Enterobacteriaceae, while 60–65% is needed for near-maximal bacterial kill (68). More recently, population PK modelling with clinical data from patients with nosocomial pneumonia has

demonstrated that further increasing the percentage of the dosing interval during which concentrations are above the MIC provides an even higher probability of microbiologic eradication and clinical success (69). There is increasing evidence that targeting 100% of the dosing interval for these time dependent antibiotics further increases the probability for improved bacteriologic and clinical outcomes, especially in populations such as the critically ill, whose unpredictable PK increase their risk for inadequate dosing. In these 34 studies we observed six different percentage of time interval objectives (40, 50, 70, 75, 80 and 100% of time interval) for fT>MIC or fT>4xMIC and various MIC breakpoints according the pathogens. There is still debate regarding what the clinical pharmacodynamic target(s) should be and it is unlikely that a single pharmacodynamic target would be appropriate for all drugs, all pathogens, and all indications. The organism may have had a MIC in the intermediate or resistant range of susceptibilities to the BL the patient was being treated with a single pharmacodynamic target was used for the primary outcome analysis. According to these different PK/PD objectives it is impossible to suggest only one optimal drug dosing regimens. The majority of these studies concluded that the proportion of patients achieving surrogate pharmacodynamics target for efficacy was suboptimal. Eight studies (four for piperacillin, three for meropenem and one for cefotaxime) suggested new dosing drug regimens using prolonged (3- or 4-hour infusion) or continuous infusion to attain PK/PD target. These recommendations are in line with the recent BL in adult critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation—SFAR) (70). Nevertheless, more clinical evidence is needed in pediatric population.

CONCLUSION

In conclusion, despite increased use of first choice BL antibiotics for severe infections treatment, there remains no consensus on PK values and optimal dosing. Antibiotic dosing in critically ill neonates and children is highly challenging. Current PK/PD data are insufficient to confidently provide a unique optimal solution for each drug. It seems that many variables contribute to the reported discrepancies in PK values, hence applied dosages regimen including the rapid maturation of the infants. According prospective clinical studies are needed to set PK/PD targets and dosing regimens.

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