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Dose optimization of β-lactam antibiotics in children

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Capita Selecta

19/11/2024

Overview

1. Introduction
2. Population pharmacokinetics of β-lactams in children
3. β-lactams dose optimization strategies
4. Challenges & opportunities
5. Conclusions & take-away messages

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Disclaimers

I am not a

- Clinical pharmacist
- Clinical microbiologist

1. Introduction

1. Optimizing outcomes of antimicrobial therapy

Early diagnosis & adequate treatment:

- Timing: Early – “Golden hour”
- Drug: Broad, empirical → narrow, targeted
- Duration: “Shorter is better”
- **Dose: Optimized based on PK/PD principles**

✓ Efficacy ↑
✓ Toxicity ↓
✓ Drug resistance ↓

Rawson *et al*., 2021 (https://doi.org/10.1038/s41579-021-00578-9)

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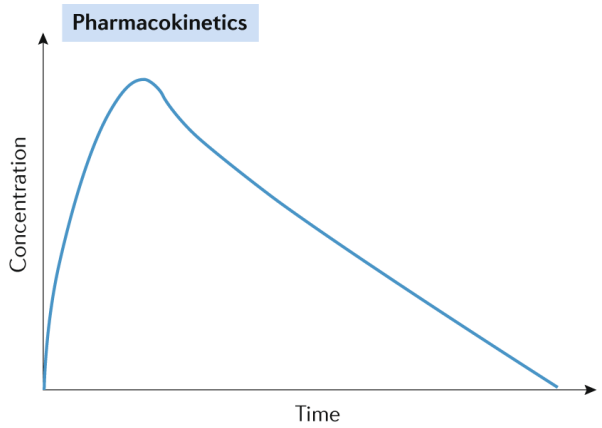
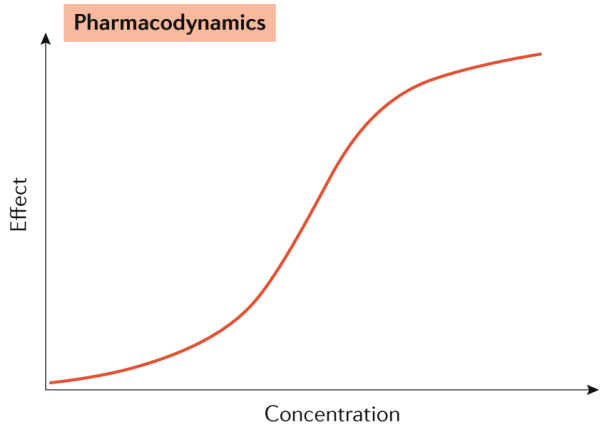
1. Optimizing outcomes of antimicrobial therapy





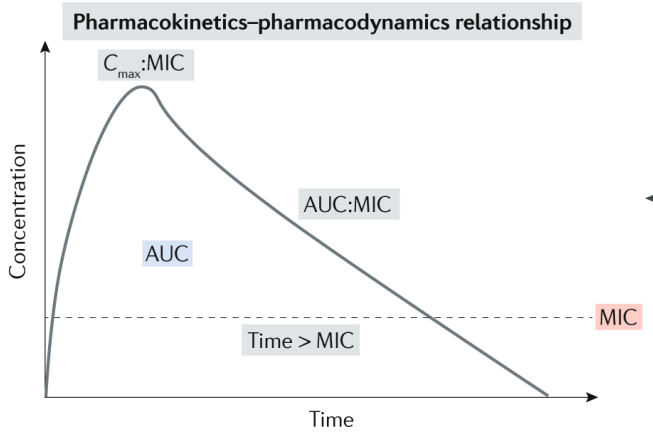
Pharmacokinetic factors

Inter-individual variability:

- Age
- Race
- Ethnicity
- Obesity
- Comorbidities
- Medications

Intra-individual variability:

- Altered fluid balance
- Renal and hepatic dysfunction
- Organ support (renal replacement, ECMO)
- Augmented renal clearance
- Hyperdynamic circulation



Pharmacodynamic factors

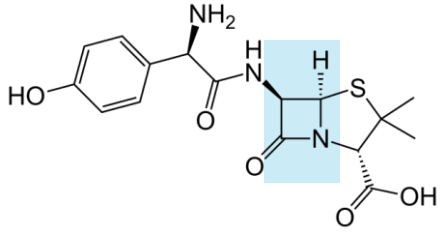
- Host immune response
- Inoculum size
- Site of infection
- Biofilm formation
- MIC of microorganism
- Hetero-resistance
- Laboratory variability
- pH
- Drug penetration
- Post-antibiotic effect

Rawson *et al*., 2021 (https://doi.org/10.1038/s41579-021-00578-9)

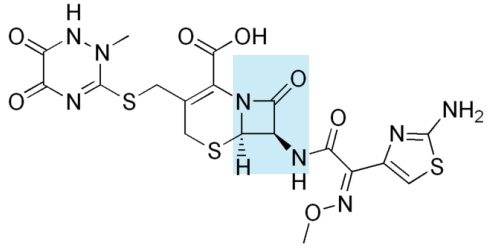
1. β-lactams: overview

- Large class of antibiotics containing **β-lactam ring**
- Most widely used antibiotics
  - Broad spectrum of activity
  - High clinical efficacy in community & hospital
  - Typically well-tolerated, relatively rare:
    - Nephrotoxicity (e.g. piperacillin-tazobactam)
    - Neurotoxicity (e.g. imipenem)
  - Contra-indication: allergy & hypersensitivity

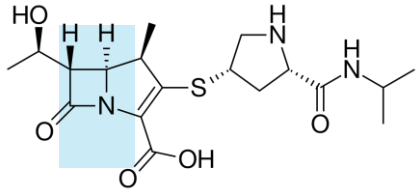
    Children: 5-8% (EU/USA)



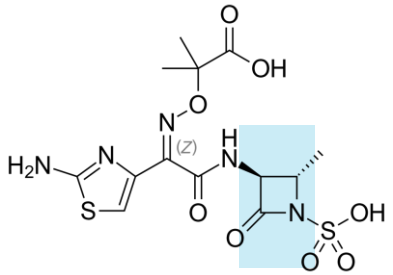
Penicillins
eg: Amoxicillin



Cephalosporins
eg: Ceftriaxone (3GC)



Carbapenems
eg: Meropenem



Monobactams
eg: Aztreonam

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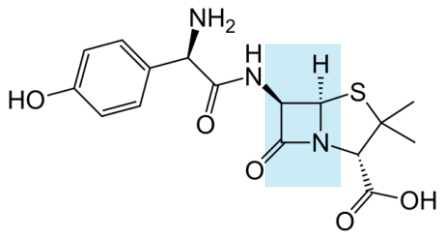
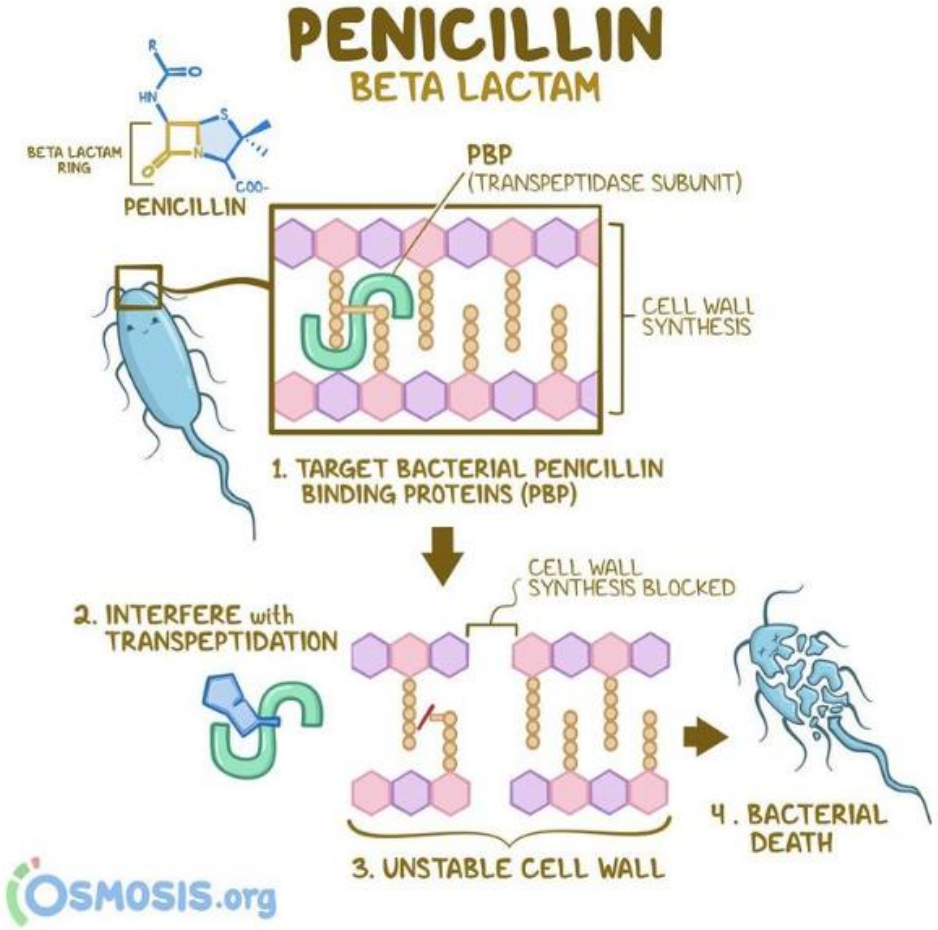
1. β-lactams: mechanism of action

Penicillins
Cephalosporins
Carbapenems
Monobactams

- **MoA: inhibition of cell wall synthesis**
- **Bactericidal activity**
- **Limited to no post-antibiotic effect**



Penicillins
eg: Amoxicillin



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1. β-lactams: mechanisms of resistance

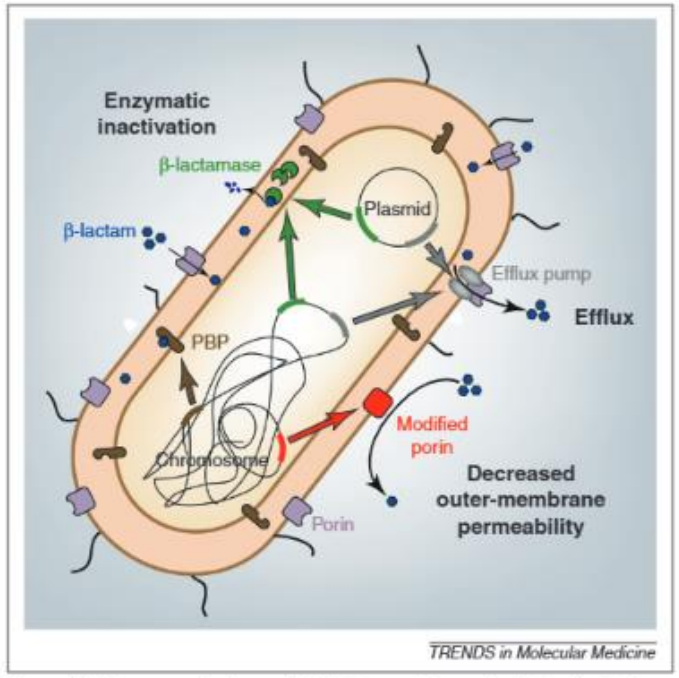

Figure 1. Primary mechanisms of β-lactam resistance in *Enterobacteriaceae*. Hydrophilic channels formed by porins allow the uptake of β-lactams through the outer membrane of the bacterium. In the periplasmic interspace, β-lactam molecules bind irreversibly to the penicillin-binding proteins (PBPs), leading to the inhibition of the peptidoglycan synthesis. Primary mechanisms of β-lactam resistance in *Enterobacteriaceae* include the following: (i) enzymatic inactivation of the antibiotic by chromosome- and/or plasmid-encoded enzymes possessing hydrolytic activity against β-lactam molecules; (ii) decreased outer membrane permeability through production of modified porins, loss of porin expression, or a shift in the types of porins found in the outer membrane; and (iii) efflux of the antibiotic to the outside of the bacterium through production of an efflux pump.

- Target modification:
  - PBP alterations in MRSA
- Uptake ↓ or efflux ↑
  - Porins & efflux pumps in *P. aeruginosa & A. baumannii*
- Enzymatic inactivation via β-lactamases
  - ESBL- & carbapenemase-producing *Enterobacteriaceae*

WHO Bacterial Priority Pathogens List, 2024

Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance

DOI: 10.1016/j.molmed.2012.03.003
https://www.who.int/publications/i/item/9789240093461

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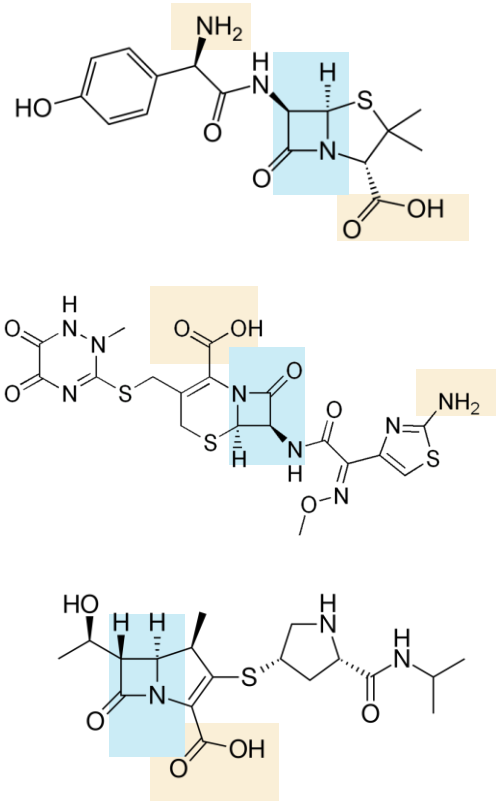
1. β-lactams: pharmacokinetics (PK)



Small & **hydrophilic**

Figure 5: Effects of severe infection and inflammation on pharmacokinetics, according to physicochemical properties of antimicrobials
Adapted from Roberts and Lipman, Crit Care Med. 2009;37(3):840-51.

	HYDROPHILIC ANTIBIOTICS	LIPOPHILIC ANTIBIOTICS
General PK	• Low Vd • Predominant renal CL • Low intracellular penetration	• High Vd • Predominant hepatic CL • Good intracellular penetration
Altered ICU PK	• ↑ Vd • CL ↑ or ↓ dependent on renal function	• Vd largely unchanged • CL ↑ or ↓ dependent on hepatic function
Examples	• Beta-lactams • Aminoglycosides • Glycopeptides • Linezolid • Colistin	• Fluoroquinolones • Macrolides • Lincosamides • Tigecycline
Antimicrobial adaptation	INCREASE INITIAL ANTIMICROBIAL DOSE	INITIAL ANTIMICROBIAL DOSE UNCHANGED

Vd - Volume of distribution; CL - clearance

Typical β-lactam PK

Absorption:	High (po)
Distribution:	Low Vd Low %PPB
Metabolism:	Minimal
Excretion:	**Renal** Short T1/2

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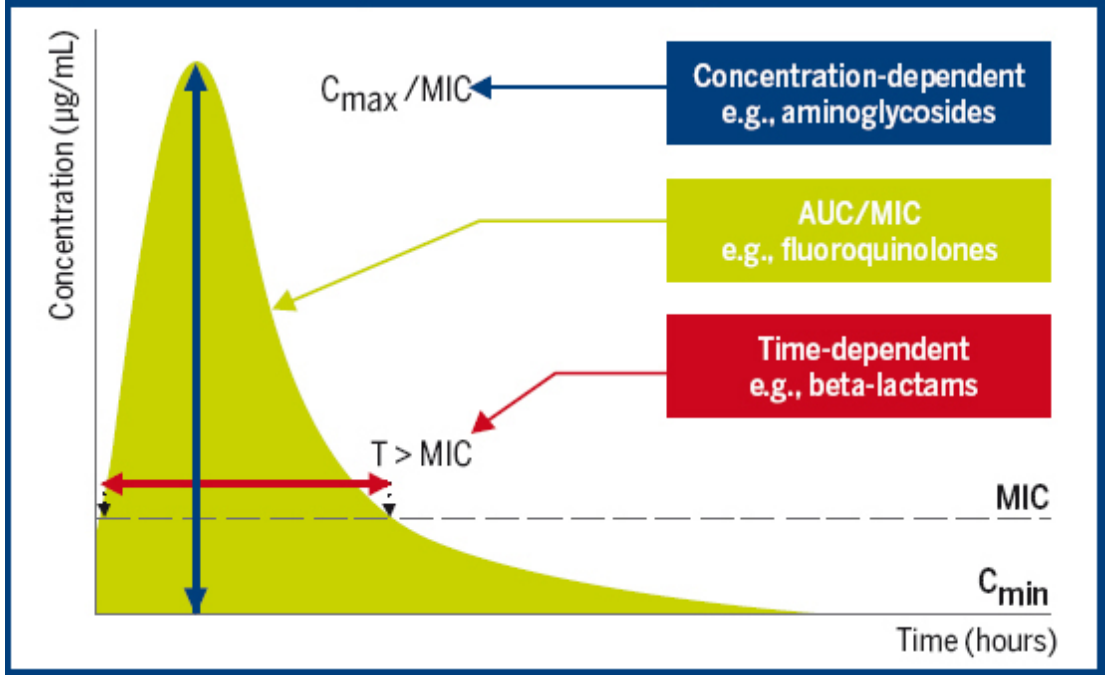
1. β-lactams: PK/PD index = %T>MIC

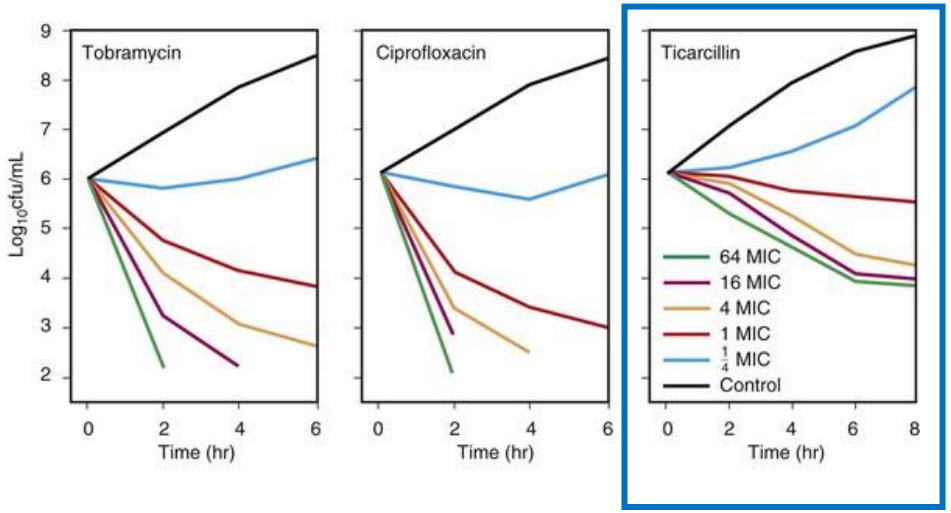
Figure 2: Description of the three different pharmacodynamics classifications of antimicrobials; time-dependent; concentration-dependent and those with a combination of both time- and concentration-dependent effects.
Adapted from Roberts and Lipman, Crit Care Med. 2009;37(3): 840-5



β-lactam antibiotics are time-dependent
- Bacterial killing: time > concentration
- Therapy: optimize exposure time (T>MIC)

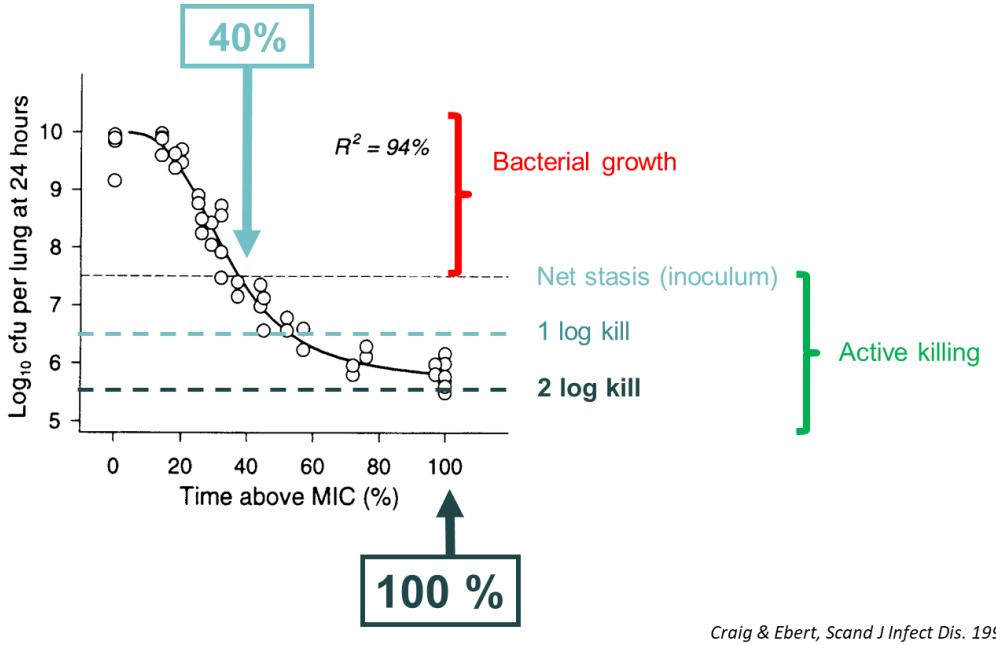
1. β-lactams: PK/PD index = %T>MIC

In vitro:
- MIC ~ bacteriostasis
- 4 x MIC ~ maximal killing



In vivo:
- *f*T>MIC = 40% ~ bacteriostasis
- *f*T>MIC = 100% ~ maximal killing

Cefotaxime in neutropenic mice model of *K. pneumoniae* lung infection



Craig & Ebert, Scand J Infect Dis. 1991; 74:63-70

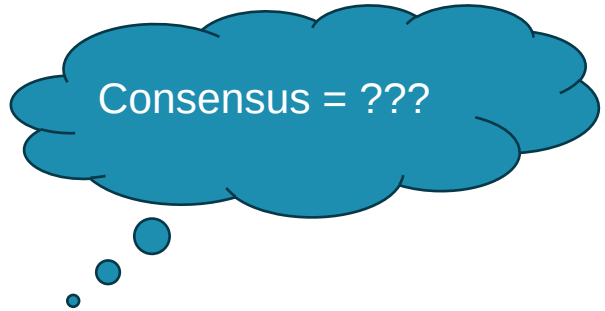
1. β-lactams: what target %T>MIC should we aim for?

Table 1. Percentage of the dosing interval over which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen (*f*T>MIC) for various β-lactams after bolus dosing in animal infection models [13,16].

	*f*T>MIC	
β-lactams	Bacteriostatic effect	Maximal bactericidal effect
Penicillins	30%	50%
Cephalosporins	35–40%[a]	60–70%[a]
Carbapenems	20%	40%

Non-ICU: ≥35%fT>MIC?

ICU: 100%fT>MIC?



β-lactam	Target %fT>MIC
Piperacillin-tazobactam	50% fT> MIC
Meropenem	40% fT > MIC
Cefepime	50-100% fT > MIC
Ceftazidime	100% fT> 4-5 x MIC

Laterre et al., 2017 (DOI: 10.1080/14787210.2017.1338139)

1. β-lactams: are we reaching this target in patients?

ICU:
100%fT>MIC?

JOURNAL ARTICLE

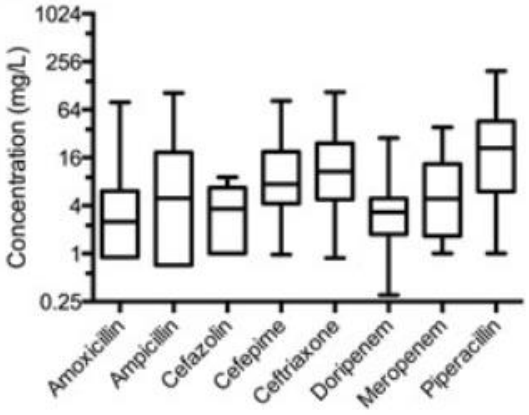
DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Jason A. Roberts ✉, Sanjoy K. Paul, Murat Akova, Matteo Bassetti, Jan J. De Waele, George Dimopoulos, Kirsi-Maija Kaukonen, Despoina Koulenti, Claude Martin, Philippe Montravers ... Show more
Author Notes

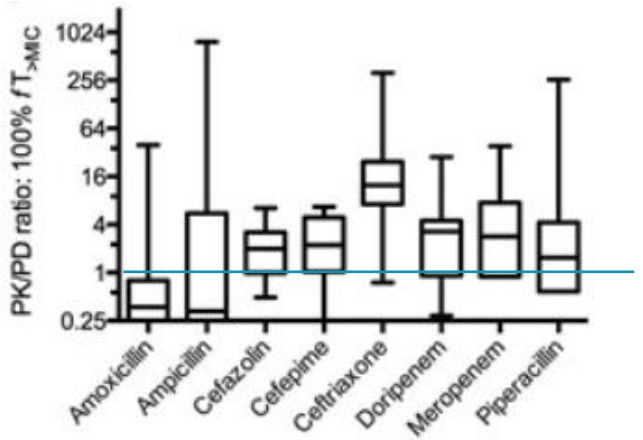
Clinical Infectious Diseases, Volume 58, Issue 8, 15 April 2014, Pages 1072–1083,
https://doi-org.kuleuven.e-bronnen.be/10.1093/cid/ciu027
Published: 14 January 2014 **Article history** ▾

Standard emperical β-lactam doses in ICU patients

Plasma *f*Cmin



PK/PD ratio (1 ~ 100% fT>MIC)

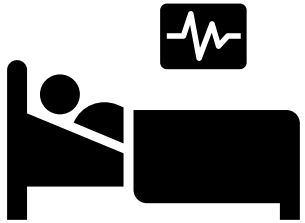


- Significant PK variability (up to 500-fold variations) ☹
- 50% of patients did not reach the target ☹
- Patients that reached the target: clinical outcomes ↑ ☺

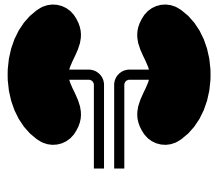
1. β-lactams: who is at risk of incorrect dosing?

Standard dose:

- Subtherapeutic drug exposure → therapy failure, emergence of resistance
- Supratherapeutic drug exposure → toxicity & side effects



Critically ill



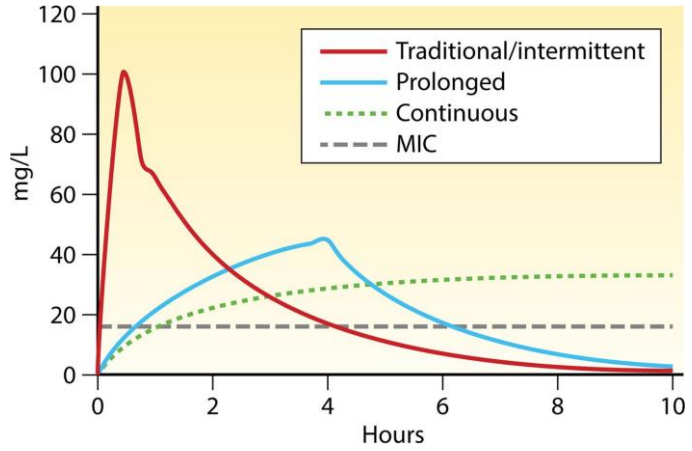
Co-morbidities (e.g. RI, dialysis)

Obsese

Elderly

Children

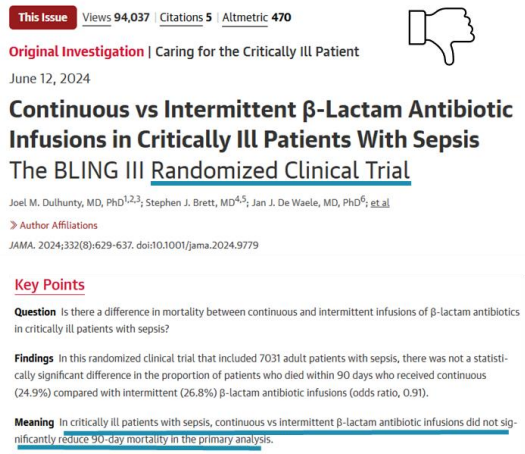
1. β-lactams: how can we maximize %fT>MIC?



MIC

Intermittent < prolonged < continuous infusion (CI)

Pro	Con
Max antibacterial effect	Cost
High-MIC pathogens	Pump set-up
More predictable PK	Drug stability



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Original Investigation | Caring for the Critically Ill Patient

June 12, 2024

Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis

The BLING III Randomized Clinical Trial

Joel M. Dulhunty, MD, PhD[1,2,3]; Stephen J. Brett, MD[4,5]; Jan J. De Waele, MD, PhD[6]; et al

Author Affiliations

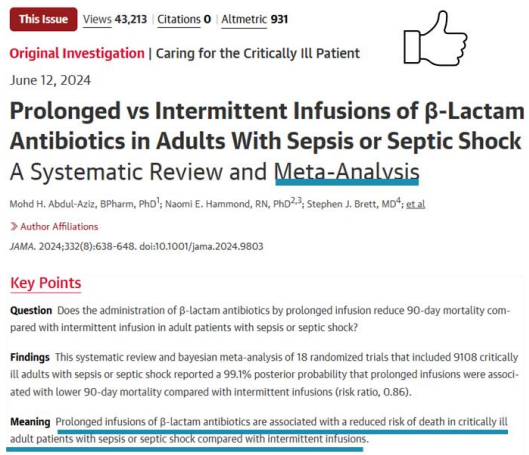
JAMA. 2024;332(8):629-637. doi:10.1001/jama.2024.9779

Key Points

Question Is there a difference in mortality between continuous and intermittent infusions of β-lactam antibiotics in critically ill patients with sepsis?

Findings In this randomized clinical trial that included 7031 adult patients with sepsis, there was not a statistically significant difference in the proportion of patients who died within 90 days who received continuous (24.9%) compared with intermittent (26.8%) β-lactam antibiotic infusions (odds ratio, 0.91).

Meaning In critically ill patients with sepsis, continuous vs intermittent β-lactam antibiotic infusions did not significantly reduce 90-day mortality in the primary analysis.



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Original Investigation | Caring for the Critically Ill Patient

June 12, 2024

Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock

A Systematic Review and Meta-Analysis

Mohd H. Abdul-Aziz, BPharm, PhD[1]; Naomi E. Hammond, RN, PhD[2,3]; Stephen J. Brett, MD[4]; et al

Author Affiliations

JAMA. 2024;332(8):638-648. doi:10.1001/jama.2024.9803

Key Points

Question Does the administration of β-lactam antibiotics by prolonged infusion reduce 90-day mortality compared with intermittent infusion in adult patients with sepsis or septic shock?

Findings This systematic review and bayesian meta-analysis of 18 randomized trials that included 9108 critically ill adults with sepsis or septic shock reported a 99.1% posterior probability that prolonged infusions were associated with lower 90-day mortality compared with intermittent infusions (risk ratio, 0.86).

Meaning Prolonged infusions of β-lactam antibiotics are associated with a reduced risk of death in critically ill adult patients with sepsis or septic shock compared with intermittent infusions.

BLING III: 90-day mortality in septic ICU patients:

- II: 26.8%
- CI: 24,9%

} -2% mortality (but: difference ns)

Editorial: “The results (…) strengthen the recommendation to use continuous β-lactam antibiotics over intermittent dosing in adult patients with sepsis in the ICU”

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2. Population PK of β-lactam antibiotics in children

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
2024, VOL. 20, NO. 8, 787–804
https://doi.org/10.1080/17425255.2024.2385403

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

Dose optimization of β-lactam antibiotics in children: from population pharmacokinetics to individualized therapy

Perrin Ngougni Pokem [a,b*], Dorian Vanneste [c*], Stef Schouwenburg [d,e*], Alan Abdulla [d,e], Matthias Gijsen [c,f], Evelyn Dhont [g,h], Dimitri Van der Linden [i,j], Isabel Spriet [c,f], Pieter De Cock [g,h,k], Birgit Koch [d,e], Françoise Van Bambeke [a], Gert-Jan Wijnant [a,l] and On behalf of International Society of Anti-infective Pharmacology and PK/PD study group of the European Society for Clinical Microbiology and Infectious Diseases.

[a]Pharmacologie Cellulaire et Moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; [b]Department of Microbiology, Cliniques Universitaires Saint-Luc – Université catholique de Louvain, Brussels, Belgium; [c]Clinical Pharmacology and Pharmacotherapy, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; [d]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, Netherlands; [e]Rotterdam Clinical Pharmacometrics Group, Erasmus University Medical Centre, Rotterdam, Netherlands; [f]Pharmacy Department, UZ Leuven, Leuven, Belgium; [g]Department of Basic and Applied Medical Sciences, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium; [h]Department of Pediatric Intensive Care, Ghent University Hospital, Ghent, Belgium; [i]Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium; [j]Pediatric Infectious Diseases, Service of Specialized Pediatrics, Department of Pediatrics, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium; [k]Department of Pharmacy, Ghent University Hospital, Ghent, Belgium; [l]Laboratory of Clinical Microbiology, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium

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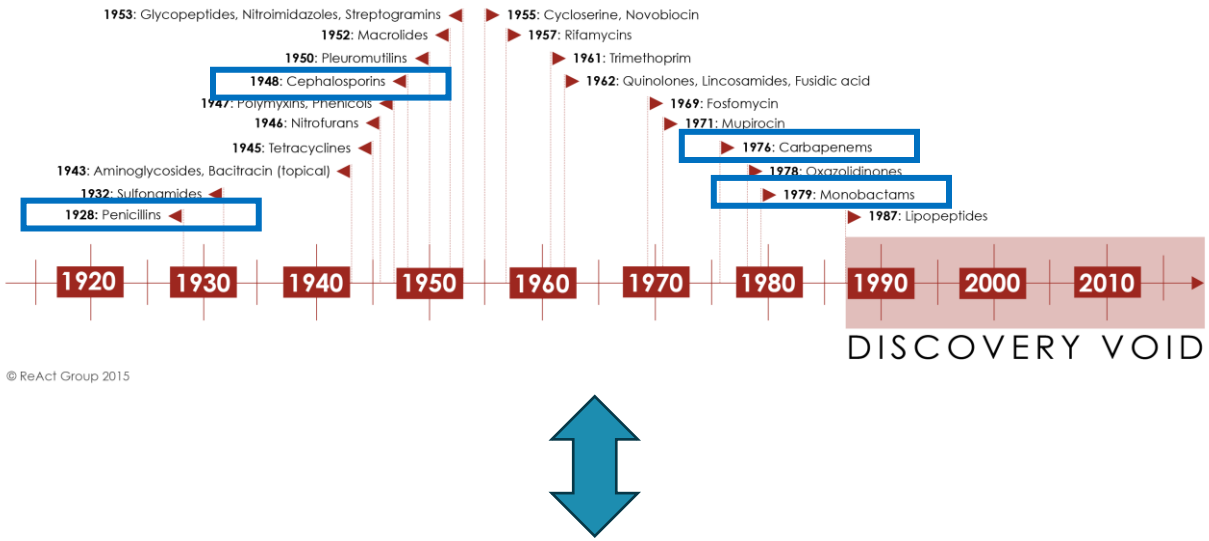
International Society of Anti-Infective Pharmacology
ISAP

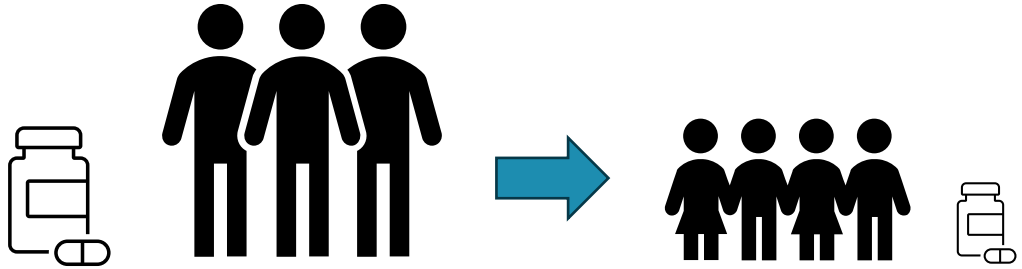
EPASG
ESCMID PK/PD OF ANTI-INFECTIVES STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

2. β-lactam use in children

- Off-label use = common (20-90%)
- Dosing practice heterogeneity = high

- Origin: limited PK/clinical studies in children
- Pediatric dosing regimens: empirically derived from adult dose (mg/kg basis)

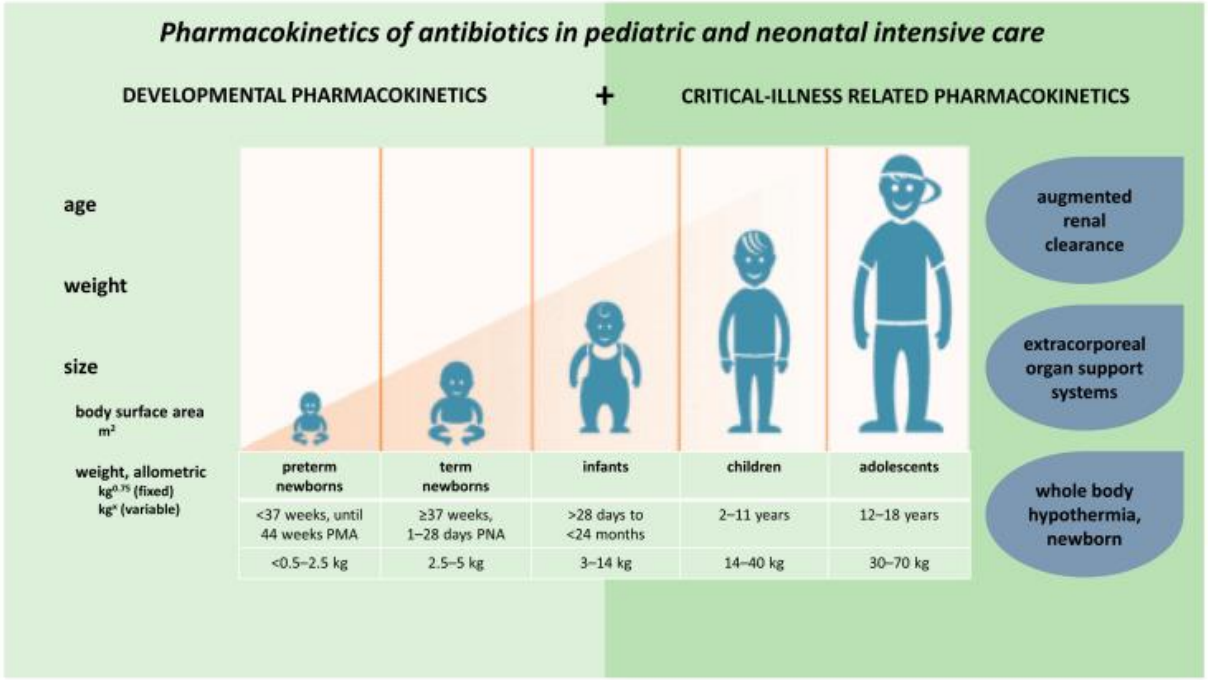




Adult 70 kg = 1000 mg dose

Child 7 kg: 100 mg dose

2. Altered β-lactam PK in children



Developmental PK
~ age-dependent maturational changes

Critical illness-related PK
~ pathophyiological changes

Gijsen et al., 2021 (DOI: 10.3390/antibiotics10101182)
Lu et al., 2014 (doi: 10.5863/1551-6776-19.4.262)

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2. Altered β-lactam PK in children

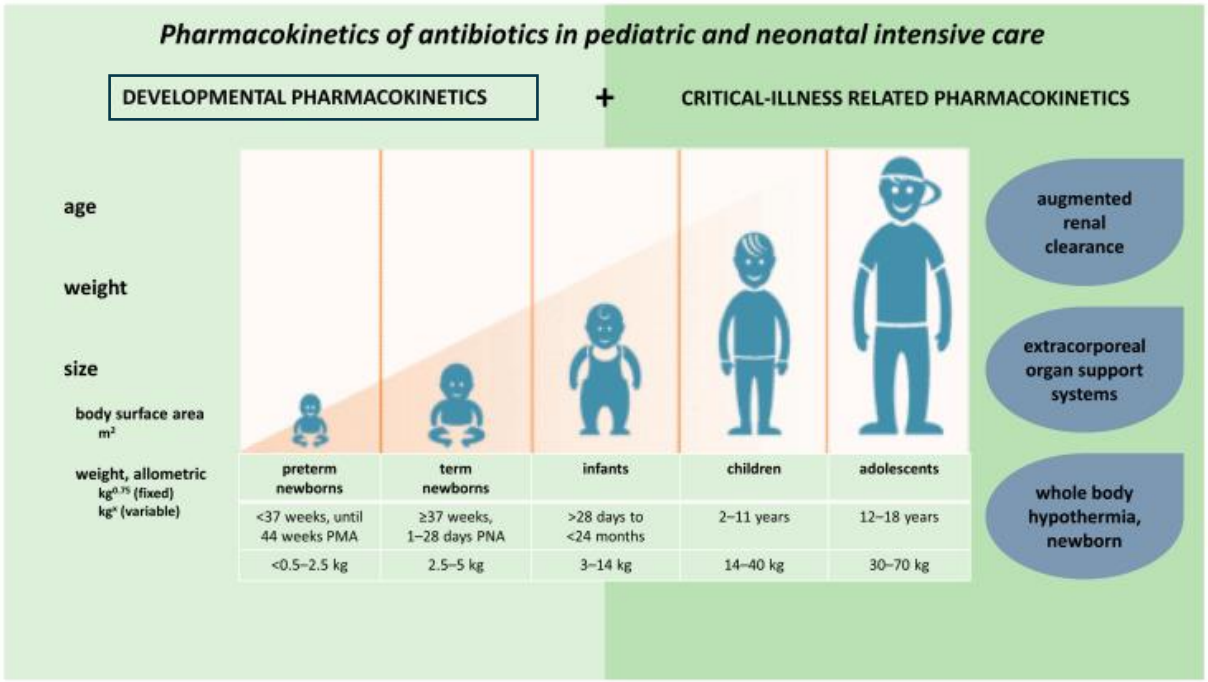

TABLE 291-1. Physiologic Changes in Children That Affect the Pharmacokinetic Characteristics of Drugs[2,3]

Parameter	Neonates	Approximate Age Approaching Adult Level
ABSORPTION		
Gastric pH	↑	3 months
Gastric emptying	↓	6–8 months
Pancreatic function	↓	9 months
DISTRIBUTION		
Body water	↑[a]	Adolescence
Protein binding	↓	12 months
METABOLISM		
Hepatic drug-metabolizing	↓	Adolescence
ELIMINATION		
Renal function	↓	Glomerular filtration: 3–5 months
		Tubular secretion: 8–9 months

[a]The distribution of body water depends on age: the total body water (TBW) of neonates is about 75% of body weight, with about 50% intracellular (IC) and 50% extracellular (EC). A gradual decrease in TBW and a shift to IC distribution occur until adult values of 50% to 60% TBW, 33% EC, and 66% IC are reached at puberty.

Vd ↑

CL ↓

T1/2 ↑
AUC ↑

Newborns & infants: highest risk for overdosing & toxicity

Gijsen et al., 2021 (DOI: 10.3390/antibiotics10101182)
Lu et al., 2014 (doi: 10.5863/1551-6776-19.4.262)

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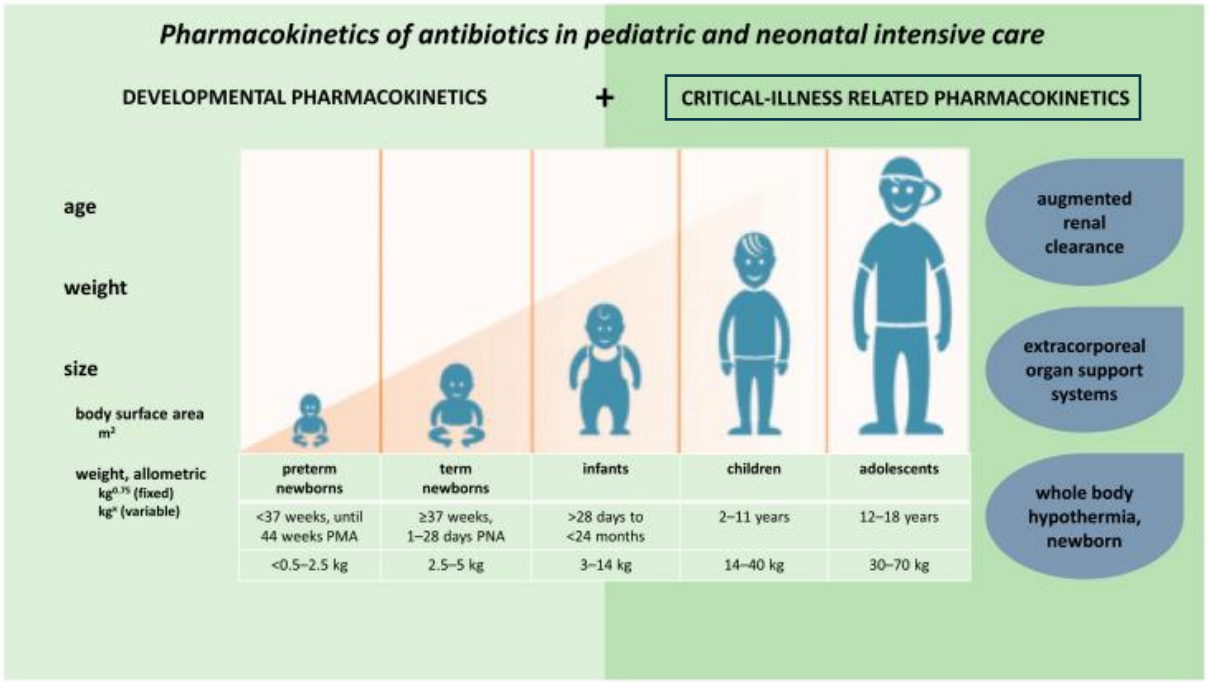
2. Altered β-lactam PK in children



ARC → Cl ↑

Capillary leak, fluid resuscitation → Vd ↑

Newborns → hypothermia to protect brain after asphyxiation → CL ↓

T1/2 ↓
AUC ↓

Critically-ill children: risk of underdosing & treatment failure

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REVIEW

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Dose optimization of β-lactam antibiotics in children: from population pharmacokinetics to individualized therapy

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Most studied drugs:

- Meropenem
- Piperacilline-Tazobactam
- Cefepime
- Ceftazidime
- Ceftriaxone

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Study design:

- Prospective (classic PK study) > retrospective (TDM)
- Monocentric > multicenter
- Patients:
  - All ages
  - Underrepresentation neonates/PICU patients

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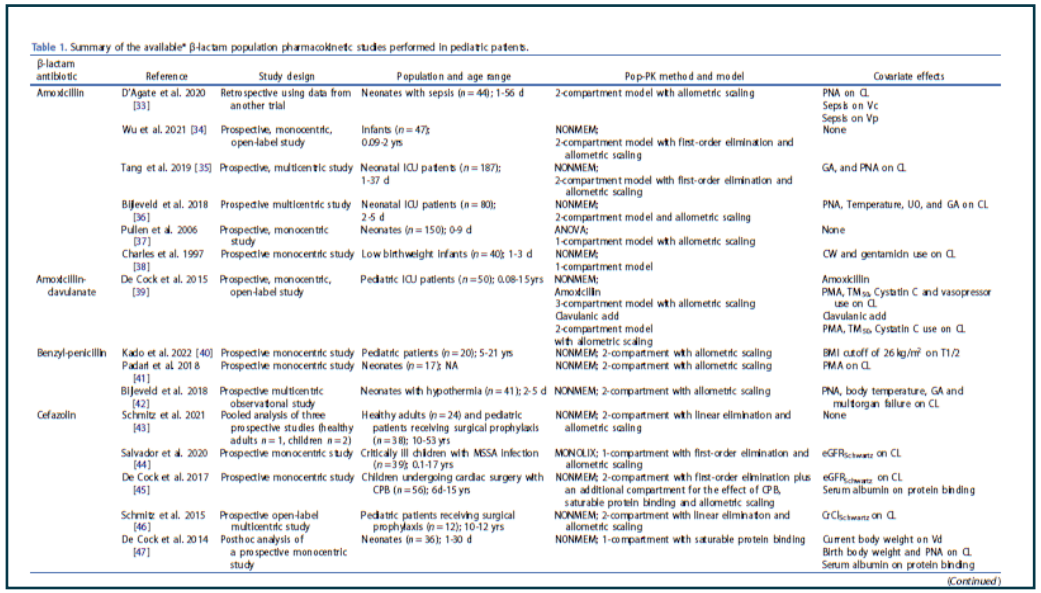
Pop-PK model:

- Fixed effect BW on Vd & CL (= allometric scaling)
- Covariates:
  - eGFR on CL
  - Neonates: maturational factors (PNA) + body temperature
  - PICU: extracorporeal organ support systems

2. β-lactam pop-PK studies in children (n=75)



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PK/PD target attaiment:

- Hetrogeneous targets (from >40% fT>MIC to 100%fT>4xMIC)
- Nearly all studies showed poor target attainment!

3. β-lactam dose optimization strategies in children

3. β-lactam dosing strategies in children

"One dose fits all"
→ Patients with mild infections & predictible PK

- Fixed dosing regimens
- Therapeutic Drug Monitoring (TDM)
- Model-Informed Precision Dosing (MIPD)

Individualized dosing
→ Patients with severe infections & unpredictible PK

Cheap, easy to use

Individualized, resource-intensive

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3. β-lactam dosing strategies in children: fixed

- Dosing based on age/ body weight (renal function)
- Source material
  - SmpC (often incomplete)
  - (Inter)national formularies (references?)
- Dose optimization studies
  - PK study in specific subpopulation
  - Pop-PK model
  - Simulations in 1000 -10000 virtual patients
  - Which dose 90%PTA for chosen target?
- Trends:
  - Most common = fixed intermittent infusion
  - Doses = increasing
    - What concentrations to aim for (PK/PD target)?
    - What concentrations to avoid (toxicity threshold)?

SWISSPEDDOSE

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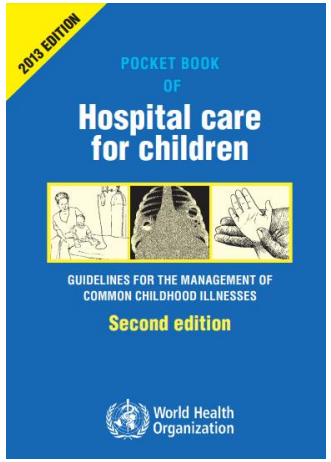
Deutsche Gesellschaft
für Pädiatrische Infektiologie e.V.



Gastine et al., 2021 (doi: 10.1002/cpt.2180)

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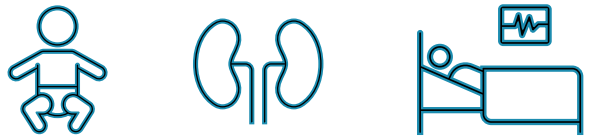
3. β-lactam dosing strategies in children: fixed

Table 2. Summary of pediatric drug dosing information in the summary of product characteristics (SPC) for newer β-lactam antibiotics.

Compound	Labeled pediatric indications	Labeled age categories	Dosing regimen for neonates available	Dosing regimen for renal insufficiency (CrCl ≤50 mL/min/1.73 m^2)	Dosing regimen for augmented renal clearance
Ceftazidime/avibactam [127]	• Complicated intra-abdominal infection • Complicated urinary tract infection • Hospital-acquired pneumonia, including ventilator-associated pneumonia	3 months-18 years	No	Yes. Dose adaptation scheme available for all ages from 3 months.	No
Ceftaroline [128]	• Complicated skin and soft tissue infections • Community-acquired pneumonia	Term neonates-18 years	Yes. 6 mg/kg every 8 hours (60 minute infusion time)	Yes. Dose adaptation scheme available for all ages from 2 years.	No
Ceftolozane/tazobactam [129]	• Complicated intra-abdominal infection • Complicated urinary tract infection • Acute pyelonephritis	Neonates >32 weeks and 7 days postnatal age to 18 years	Yes. 20/10 mg/kg every 8 hours (60 minute infusion time).	No	No
Meropenem-vaborbactam [130]	Data not available. The SPC states that 'Vaborem should not be used in children or adolescents under 18 years of age. This is because it is not known if the medicine is safe to use in these age groups.' A Pediatric Investigation Plan is available [131].				



SPC new β-lactams?

- SPC contains pediatric indications/doses ☺
- Including special subpopulations at risk of under/overdosing ☺
- Still incomplete ☹

3. β-lactam dosing strategies in children: TDM

- Dose adjustment based on measured drug concentrations
- Antimicrobial TDM
  - Historically: avoiding toxicity (vancomycin, AGs)
  - Recently: maximizing efficacy
- β-lactam TDM: gaining popularity (adults > children)

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Article | Open access | Published: 02 April 2024

Assessment of the practical impact of adjusting beta-lactam dosages based on therapeutic drug monitoring in critically ill adult patients: a systematic review and meta-analysis of randomized clinical trials and observational studies

Eszter Gulyás, István László Horváth, Marie Anne Engh, Stefania Bunduc, Fanni Dembrovszky, Péter Fehérvári, András Bánvölgyi, Dezső Csupor, Péter Hegyi & Gellért Balázs Karvaly ✉

Scientific Reports **14**, Article number: 7793 (2024) | Cite this article

TDM-guided beta-lactam treatment was associated with **improved clinical cure from infection** [odds ratio (OR): 2.22 (95% confidence interval (CI): 1.78–2.76)] and **microbiological eradication** [OR: 1.72 (CI: 1.05–2.80)], as well as a **lower probability of treatment failure** [OR: 0.47 (CI: 0.36–0.62)], but the heterogeneity of studies was remarkably high.

3. β-lactam dosing strategies in children: TDM

- Dose adjustment based on measured drug concentrations
- Antimicrobial TDM
  - Historically: avoiding toxicity (vancomycin, AGs)
  - Recently: maximizing efficacy
- β-lactam TDM: gaining popularity (adults > children)

Overall, **95% of patients had subtherapeutic anti-infective concentrations** and did not achieve the requisite pharmacodynamic exposure with current pediatric dosing recommendations.

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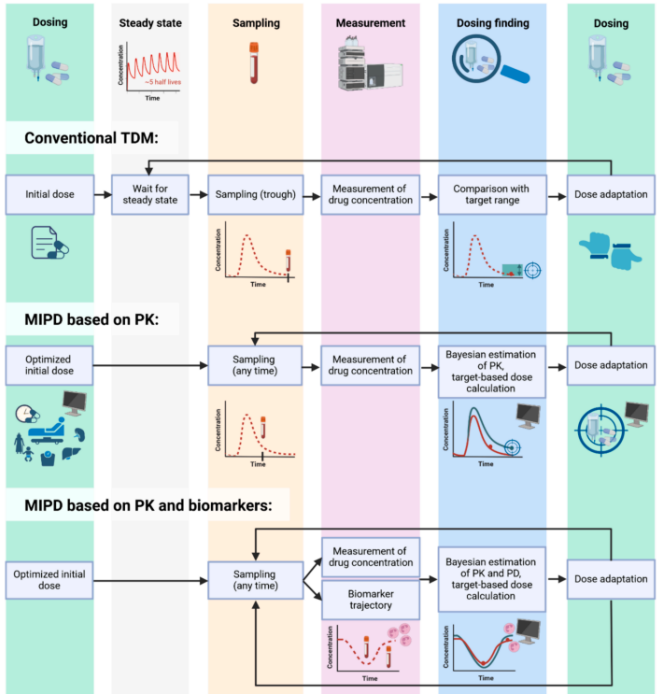
3. β-lactam dosing strategies in children: MIPD

- Emerging precision medicine tool (oncology, inflammatory disease, transplant medicine & infection)
- Dose adjustment based on popPK models + individual factors: *a priori & a posteriori*



Novy et al., 2023 (DOI: 10.3390/antibiotics12040681)

Feature	TDM	MIPD
Approach	Reactive	Pro-active
Delay for SS	+	-
Sampling	Rich, trough levels	Sparse, flexible timing
Dose adaption	Guidelines	Individualized
Data input	PK factors + MIC	PK & PD factors (biomarkers)

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3. β-lactam dosing strategies in children: MIPD

Evidence for MIPD clinical benefits for β-lactams on ICU?

- **Adults: 1 RCT (DOLPHIN trial) → ☹**
- Children: 1 retrospective cohort study

Intensive Care Med (2022) 48:1760–1771
https://doi.org/10.1007/s00134-022-06921-9

ORIGINAL

Model-informed precision dosing of beta-lactam antibiotics and ciprofloxacin in critically ill patients: a multicentre randomised clinical trial

Tim M. J. Ewoldt[1,2,3*], Alan Abdulla[2,3], Wim J. R. Rietdijk[2], Anouk E. Muller[3,4,5], Brenda C. M. de Winter[2,3], Nicole G. M. Hunfeld[1,2], Ilse M. Purmer[6], Peter van Vliet[7], Evert-Jan Wils[1,8], Jasper Haringman[9], Annelies Draisma[10], Tom A. Rijpstra[11], Attila Karakus[12], Diederik Gommers[1], Henrik Endeman[1] and Birgit C. P. Koch[2,3]

There is currently **no evidence for a clinical effect** of model-informed precision dosing (MIPD) of beta-lactam antibiotics or ciprofloxacin in critically ill patients. Other approaches will need to be explored. ☹

Not all ICU patients benefit … Specific populations?

ELSEVIER
International Journal of Antimicrobial Agents
Volume 62, Issue 4, October 2023, 106931

Short Communication

Which patients benefit from model-informed precision dosing of beta-lactam antibiotics and ciprofloxacin at the ICU?

Tim M.J. Ewoldt [a b c], Alan Abdulla [b c], Wim J.R. Rietdijk [b], Nicole Hunfeld [a b], Anouk E. Muller [c d e], Henrik Endeman [a], Birgit C.P. Koch [b c], DOLPHIN study group

Show more

SOFA score < 8 (mild/moderate organ dysfunction) = reduced 28-day mortality ☺

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3. β-lactam dosing in children: MIPD

Evidence for MIPD clinical benefits for β-lactams in ICU?

- Adults: 1 RCT (DOLPHIN trial)
- **Children: 1 retrospective cohort study → TDM/MIPD to prevent toxicity?**

We show a relationship between **estimated piperacillin AUC and highest Cmin** in the first 24 hours of piperacillin/tazobactam therapy and **piperacillin-associated AKI**, suggesting total piperacillin exposure early in the course is associated with AKI development. These data could serve as the **foundation for implementation of model-informed precision dosing to reduce AKI incidence in patients given piperacillin/tazobactam.**

4. Challenges & opportunities

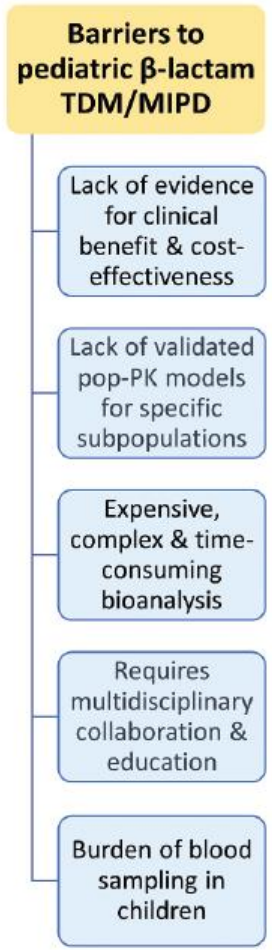

Figure 1. Barriers and future perspectives for pediatric β-lactam Therapeutic Drug Monitoring (TDM) and Model-Informed Precision Dosing (MIPD). Pop-pk: population pharmacokinetics; PK: pharmacokinetics; PD: pharmacodynamics; RCT: randomized controlled trial.

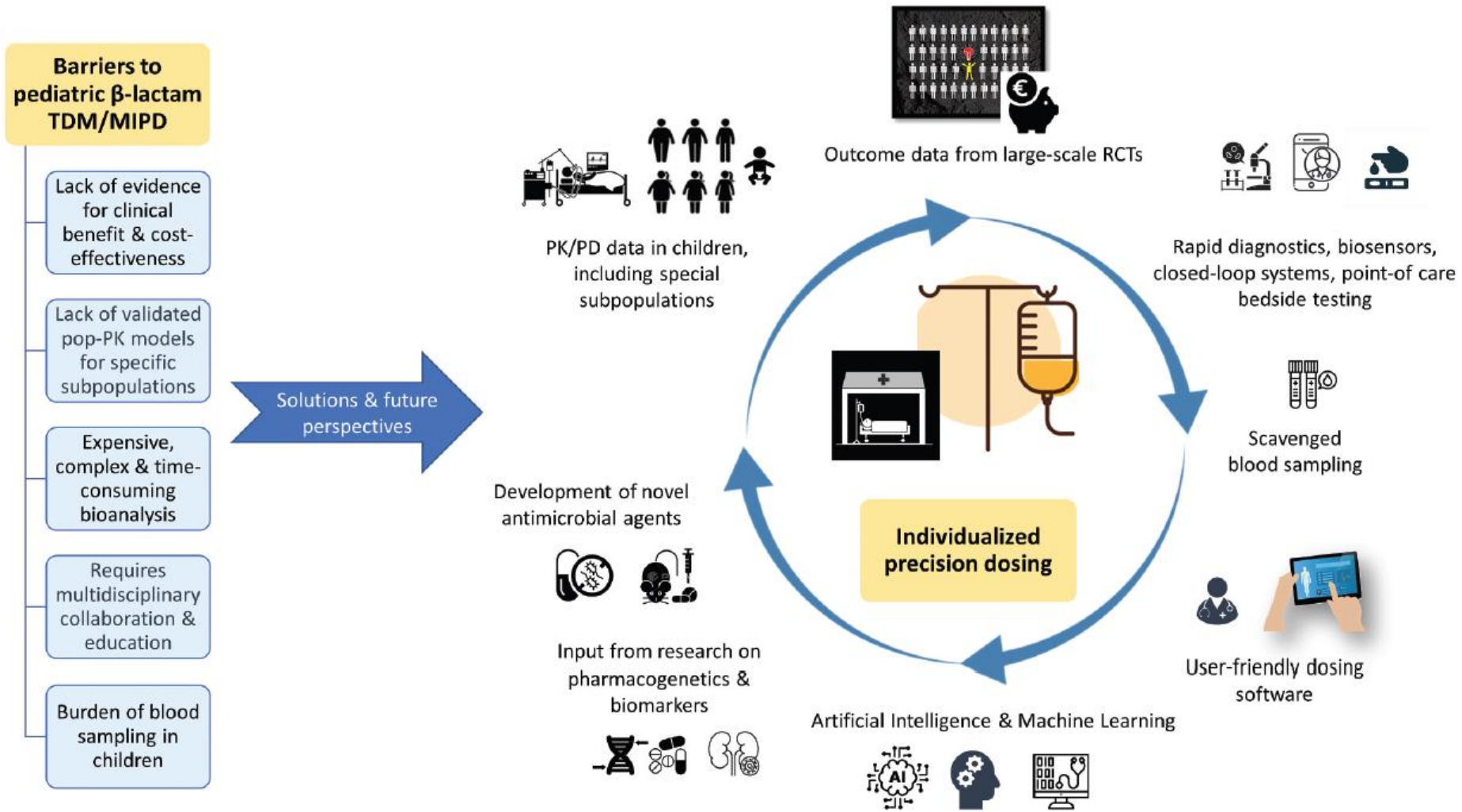

Figure 1. Barriers and future perspectives for pediatric β-lactam Therapeutic Drug Monitoring (TDM) and Model-Informed Precision Dosing (MIPD). Pop-pk: population pharmacokinetics; PK: pharmacokinetics; PD: pharmacodynamics; RCT: randomized controlled trial.

5. Conclusions & take-away messages

5. Conclusions & take-away messages

- β-lactams:
  - Renally cleared → GFR ~ drug exposure
  - Time-dependent activity → therapy optimization = maximize exposure time

- Fixed pediatric β-lactams doses = derived from extrapolation of adult data
  - Typically ok for older children with mild infections
  - Risk under/overdosing in very young and/or ill children (neonates, PICU)

- Improved & more individualized dose optimization strategies?
  - TDM - emerging. Who benefits the most?
  - MIPD - promising, but evidence is currently lacking

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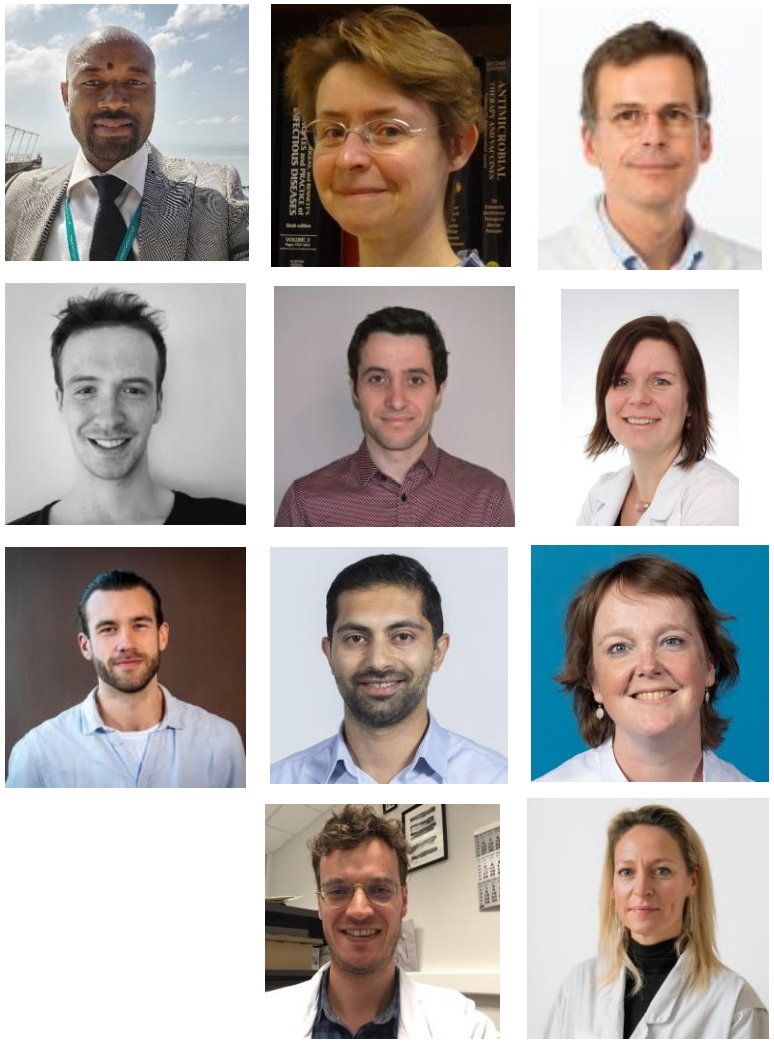
Thank you!



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