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REVIEW ARTICLE

Optimizing the Use of Antibiotic Agents in the Pediatric Intensive Care Unit: A Narrative Review

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Abstract

Antibiotics are one of the most prescribed drug classes in the pediatric intensive care unit, yet the incidence of inappropriate antibiotic prescribing remains high in critically ill children. Optimizing the use of antibiotics in this population is imperative to guarantee adequate treatment, avoid toxicity and the occurrence of antibiotic resistance, both on a patient level and on a population level. Antibiotic stewardship encompasses all initiatives to promote responsible antibiotic usage and the PICU represents a major target environment for antibiotic stewardship programs. This narrative review provides a summary of the available knowledge on the optimal selection, duration, dosage, and route of administration of antibiotic treatment in critically ill children. Overall, more scientific evidence on how to optimize antibiotic treatment is warranted in this population. We also give our personal expert opinion on research priorities.

Key Points

Optimizing antimicrobial treatment should focus on the optimal selection, dosage, and duration of antimicrobial treatment, via the optimal route of administration.

In critically ill children, little research has been conducted to increase the appropriate use of antibiotics.

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1 Introduction

The development of antibiotics has revolutionized modern medicine, not only by offering a cure for common potentially life-threatening communicable diseases such as community-acquired pneumonia, but also by facilitating surgical and oncologic therapies in which nosocomial infections are a major cause of morbidity and mortality [1].

Although potentially life-saving, antibiotic usage is not without problems. Adverse reactions, albeit most often mild, are a common reason for medical consultation, but more severe adverse reactions such as Stevens-Johnson syndrome may occur as well. Use of broad-spectrum antibiotics in an in-hospital setting is also strongly linked to *Clostridioides difficile* infections, a common reason for increased length of hospital stay (LOS), often in vulnerable patients [2]. The impact of broad-spectrum antibiotic use on the gut microbiome, with possible links to development of auto-immune diseases, is a hot topic in research [3]. These adverse effects are rarely discussed with patients prior to initiation of antibiotic treatment [4].

The most important adverse effect, however, is the occurrence of antibiotic resistance, both at a patient level (risk of developing life-threatening secondary infections caused by these organisms) and at a population level (spreading of colonization with resistant strains may reduce the effectivity of certain antibiotic drug classes in a defined population). Generally, antibiotic resistance is rising [5]. The increasing

use of carbapenems and glycopeptides (so called reserve antibiotics) may be attributed to increasing antibiotic resistance. Moreover, colonization with carbapenem-resistant Gram-negative bacteria in the gut microbiome has been documented to occur after only very brief exposure to these antibiotics [6].

Medical costs are soaring due to antibiotic resistance, with excess costs estimated to be as high as €85 trillion/year by 2050. It is considered to be one of the biggest global health threats, expected to result in 10 million attributable deaths by that year [7]. Tackling antibiotic resistance has become a priority for the World Health Organization (WHO) [8].

Multidrug-resistant Gram-negative (MDRGN) bacteria are the clinically most important resistant bacteria in children admitted to the Pediatric Intensive Care Unit (PICU), with extended-spectrum β-lactamase-producing Enterobacterales (ESBL-Ent), mainly *Escherichia coli* strains, increasingly causing severe infections [9–11]. They usually occur in children with chronic conditions, but may also be found in otherwise healthy children with recurrent infections or previous antibiotic exposure. Adequate antibiotic treatment for these children may only be possible once results of susceptibility tests are available. Carbapenem-resistant Enterobacterales (CRE), usually *Klebsiella* or *Enterobacter* species, are found in the same populations, usually in the PICU. Outbreaks with multidrug-resistant (MDR) *Acinetobacter* species have been documented in neonatal intensive care units (NICU) [12]. Microorganisms that are already intrinsically resistant (e.g., *Pseudomonas* species) may acquire resistance to multiple β-lactams, including carbapenems, causing major therapeutic problems in critically ill children, and also warranting draconic infection control measures to limit spread [13].

As for the Gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged in pediatric practice since 1990. Though incidence in the general population of the EU has decreased significantly between 2013 and 2016 [14], resistance to alternative antibiotic treatment is rising elsewhere [15].

Since infections occur in a large proportion of PICU patients, the use of broad-spectrum antibiotics is very common in this population. The largest point prevalence study so far, including 38 PICUs (both general and cardiac) in 23 countries, revealed antibiotic usage in 56% of PICU patients, of which the vast majority was treated with parenteral antibiotics and 50% with combination therapy [16].

Antibiotic stewardship (AS) encompasses all initiatives to promote responsible antibiotic usage. Its main goals are to guarantee adequate treatment of infections and to reduce inappropriate antibiotic use. This necessity has acquired a manifest place in medical thinking, firstly in adult medicine [17]. Yet, in critically ill children, inappropriate antibiotic prescribing ranges up to 60% (mainly overly broad spectrum and wrong dosage) and, as such, the PICU represents a major target environment for antibiotic stewardship programs (ASPs) [18].

AS is commonly defined as 'the optimal selection, dosage, and duration of antimicrobial treatment, via the optimal route of administration' that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance [19]. In this narrative review based on a literature search (MEDLINE and PubMed database) completed in June 2020, we sought to summarize recent advances and emerging perspectives for AS in the PICU.

2 Right Drug

2.1 General

When a clinically important infection is suspected, the first question is 'would this child require antibiotic treatment, and if so, which antibiotic class is to be chosen?'. Especially in young children with fever, in whom viral infections not requiring antibiotic treatment are common, the accuracy of clinical symptoms is poor [20].

The first goal of AS is to adequately treat serious bacterial infections (SBIs), comprising blood stream infections (BSIs), meningitis, pneumonia, and urinary tract infections, with aggressive empirical antibiotic therapy. In critically ill children with SBI, delayed empirical antibiotic therapy increases mortality and prolongs organ dysfunction. This risk increases significantly once antibiotic treatment is delayed for more than 3 h, and then again with every additional hour [21, 22]. However, when subsequent diagnostics cannot confirm infection and discontinuation of antibiotic treatment may be indicated, this often does not happen [23, 24].

Moreover, antibiotics are commonly prescribed or continued when viral disease is proven, and even in non-infectious diseases without evidence of bacterial infection, such as severe asthma [25]. However, the suspicion of a bacterial co-infection in proven viral disease [most often respiratory syncytial virus (RSV)] may warrant early antibiotic treatment, especially in critically ill infants < 3 months old [26]. Also, in these patients, timely discontinuation should be advocated when diagnostic evidence cannot reveal any sign of bacterial infection.

The role of the clinical laboratory is vital. Biomarkers may help distinguish patients with SBIs rapidly, guiding decision making on whether to start, continue, or discontinue antibiotic treatment. C-reactive protein measurement and white cell counting have been established for a long

time, with good sensitivity but poor specificity regarding bacterial infections [27]. The added value of serial measurement of procalcitonin (PCT) levels has been demonstrated in adults, where a strategy for early discontinuation of antibiotic treatment has shown efficacy [28]. The role of PCT in critically ill children is controversial. It may have an added value in distinguishing bacterial from non-bacterial infectious disease in young febrile infants [29]. In a PICU population, neither single nor serial measurements could predict presence or absence of bacterial infection with enough certainty to start or withhold antibiotic treatment [30]. PCT has been extensively studied in critically ill children after congenital heart surgery, where it failed to distinguish postoperative infection from inflammation [31].

Advances in molecular biology have the potential to shorten time to identification of pathogens and to radically improve AS. Rapid polymerase chain reaction (PCR) testing for respiratory viruses has significantly increased the diagnostic yield compared with immune fluorescence testing. However, the availability of positive PCRs for respiratory viruses in mechanically ventilated babies in the PICU does not appear to impact antibiotic prescribing practices, exposing different behavioral mechanisms determining prescription by PICU physicians [32]. In less ill hospitalized children with acute respiratory illness, introduction of a rapid respiratory panel seems to have more impact, with reduced antibiotic duration and LOS [33].

Molecular diagnostic tools identifying multiple infective agents have been developed not only in respiratory samples, but also in blood, cerebrospinal fluid (CSF), urine, and feces [34–36]. Rapid blood culture diagnostics, in which rapid multiplex PCR is performed on positive blood culture bottles, may result in earlier accurate diagnosis, shorter time to adequate antibiotic treatment, and earlier de-escalation of empirical treatment, especially when AS teams are involved, as documented in an RCT in a large mixed adult/pediatric and (P)ICU/non-(P)ICU population. However, impact on patient outcome could not be proven [37]. Specific pediatric data are scarce, with only a single study documenting a positive impact on antibiotic prescription patterns in *S. aureus* BSIs [38]. With new tests rapidly becoming available, the complexity of interpretation increases, warranting close communication between microbiologist and clinician in order to avoid unnecessary testing and to ensure that an adequate therapeutic response follows [39, 40].

When an SBI is suspected, empirical antibiotic therapy is selected based on which micro-organisms are presumed to have caused the infection. Practice guidelines for the choice of antibiotic drugs in common bacterial infectious emergencies (such as sepsis, pneumonia and meningitis) are rarely based on evidence but rather on clinical experience and observational studies [41–44]. Current knowledge regarding local antibiotic resistance is crucial. These may differ significantly between different regions, age groups, and healthcare centers. Institutional antibiotic resistance patterns need to be monitored as they should guide therapy [45]. Knowledge of the physicochemical properties of the antibiotic that allow drug penetration at the site of infection is crucial as well. For instance, antibiotics used for treatment of bacterial meningitis need to penetrate into the CSF.

Empirical therapy should account for the risk of antibiotic resistance, especially in hospital-acquired infections (HAI). Subsequently, antibiotic de-escalation (ADE) should be considered once microbiology results are available. ADE can be achieved in different ways: by replacing one antibiotic by another with a narrower spectrum, by reducing the number of antibiotics in case of combination therapy, or by discontinuation of antibiotics. No uniform definition of ADE is available [46]. Using this strategy, the aim is to reduce the antibiotic pressure and as such the selection of resistant bacteria. ADE is considered as a key intervention in ASPs [41] but it is only performed in a minority of adult ICU patients [47]. Important controversies regarding ADE do exist. Effects on bacterial resistance have not been demonstrated so far. Studies in adult patients have revealed that performing ADE was associated with an increase in antibiotic duration, which could be counterproductive when aiming for a reduction in antibiotic exposure [48]. PICU data are currently lacking.

The following sections focus on some common SBIs in PICU, both community and hospital acquired. A problem in all of these is the lack of uniform diagnostic criteria, leading to inconsistent diagnostics, categorization, and approaches [49, 50].

2.2 Community-Acquired Infections in the PICU

Infants younger than 3 months presenting with fever of unknown origin represent a group at increased risk for SBI. While awaiting results from diagnostic work-up and cultures, empiric antibiotic treatment is usually started early. The combination of IV ampicillin and gentamycin, or alternatively third-generation cephalosporins and ampicillin, provides good cover for the micro-organisms detected in a large prospective observational study [51].

For childhood bacterial meningitis, third-generation cephalosporins have proven their clinical efficiency for three decades [52]. Vancomycin is a valuable option for treatment of bacterial meningitis caused by resistant *Streptococcus pneumoniae* [53]. Other drug classes (carbapenems and fluoroquinolones, amongst others) have an adequate spectrum and meningeal penetration as well, but are less extensively studied.

Invasive group A streptococcal infections (mainly Streptococcal toxic shock syndrome and severe skin and soft

tissue infections) cause significant morbidity and mortality in previously healthy children. Most *Streptococcus pyogenes* species are susceptible to penicillin. However, prospective observational studies in a mixed pediatric/adult population have shown reduced mortality and morbidity when clindamycin was added to the β-lactam antibiotic treatment, and a further positive trend has been noted when immunoglobulin therapy was also used [54].

Community-acquired pneumonia (CAP) remains the leading cause of death in < 5-year-old children worldwide [55]. About 12–20% of children with CAP require PICU admission. Though viral disease is very common, antibiotic treatment is a cornerstone of treatment [56]. For those children requiring mechanical ventilation, delayed treatment with antibiotics is independently associated with adverse outcomes (longer duration of mechanical ventilation, increased PICU, and hospital LOS) [57]. Multiple guidelines for empirical antibiotic therapy exist, all with low levels of evidence. In regions with high susceptibility rates to penicillin for *S. pneumoniae*, amoxicillin remains the first-choice antibiotic [58]. Various randomized controlled trials (RCTs) comparing different antibiotic regimens have been conducted, all yielding similar efficacy outcomes for macrolides, amoxicillin, amoxicillin/clavulanic acid, and cephalosporins [59, 60]. As bacterial co-infection in children with influenza can lead to serious morbidity and is commonly caused by *S. aureus*, treatment with amoxicillin/clavulanic acid is recommended in this group of patients. Though the use of macrolides is advocated in atypical pneumonia in most guidelines, there is to date very little evidence to support this [61]. Altogether, very little research has been conducted in critically ill children.

2.3 Hospital-Acquired Infections in the PICU

The PICU environment has a high rate of HAI (up to 23%), due to frequent invasive procedures and use of medical devices (central lines, endotracheal tubes) and patient factors (immature immune system, immune deficiencies) [62]. They have a major impact on morbidity, LOS, and hospital costs [63]. The two most frequent forms of HAI are catheter-associated bloodstream infections (CA-BSI) and pneumonia [64–67]. Other HAI encountered in the PICU include surgical-site infections and catheter-associated urinary tract infections. Generally, incidence rates of HAIs in the PICU are decreasing, due to increased awareness and knowledge of prevention strategies [68].

Whenever CA-BSI is suspected, empirical treatment with broad cover for Gram-positives (*S. aureus* and coagulase-negative staphylococci are the most frequently reported pathogens [69]), and also, though less frequently found, Gram-negatives (notably also *Pseudomonas aeruginosa*), is started. If infection with MDRGN is likely, carbapenems are indicated. If *Candida* infection is likely (e.g., after long-duration antibiotic courses, immunosuppression, or multi-site candida colonization), empirical antifungal treatment is indicated [70].

Pneumonia, both community- and hospital-acquired, accounts for up to 50% of antibiotic use in PICUs [71]. Amongst hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) is the most common. Incidence is lower in pediatric than in adult patient series, but data are limited [72, 73]. The case definition of VAP is subject to debate, with both clinical signs (worsening ventilation conditions, fever, and appearance of purulent secretions) and laboratory findings (white cell counts and culture on respiratory samples) being important though imprecise diagnostic factors [74]. As colonization of an endotracheal tube occurs quickly, the mere presence of bacteria in surveillance cultures from endotracheal aspirates does not warrant antibiotic treatment [75]. Of note, > 30% of Enterobacterales in endotracheal aspirates may be MDR, with a clear link to previous antibiotic exposure of > 7 days [76]. Studies in adults revealed that only very recent cultures (from endotracheal aspirates taken ≤ 2 days before onset of VAP) are reliable in predicting the responsible pathogen [77].

Once VAP is diagnosed, antibiotic treatment should not be delayed [78]. Treatment for 'early' VAP (1–4 days after intubation) will focus on similar micro-organisms as in CAP, treatment for 'late' VAP (occurs more frequently, > 4 days after intubation) should cover *P. aeruginosa, Klebsiella pneumoniae/oxytoca, Enterobacter* spp, in addition to *S. pneumoniae* and *S. aureus*. Antibiotic resistance is a major problem in this group [69, 79].

HAP in non-ventilated patients may be acquired inside or outside the PICU and usually has a more benign course and is less frequently due to MDR organisms [80]. Adult guidelines with algorithms allowing tailored antibiotic treatment for these patients are available [81]. Pediatric guidelines are currently lacking.

3 Right Duration

3.1 General

When little evidence is available regarding the 'right drug', even fewer studies are available regarding the 'right duration' of treatment. Most guidelines are based on expert opinion. As occurrence of antibiotic resistance is related to the duration of antibiotic treatment, early discontinuation may offer an opportunity for AS [82]. The paradigm of 'once you start an antibiotic treatment course, you have to continue the full treatment duration to avoid emergence of antibiotic resistance' appears to be false [83]. However,

PICU physicians rarely consider shortening the duration of antibiotic therapy even when the child is getting better [24]. As described above, clinical laboratory support with serial biomarker testing and rapid molecular testing has the potential to alter not only the choice but also the duration of antibiotic therapy.

Electronic prescribing (EP) of medication has become common practice in PICUs. It has demonstrated increased medication safety by reducing prescription errors [84]. EP may include an 'auto-stop' strategy, allowing targeted antibiotics to be prescribed for a predefined duration before they have to be re-evaluated [85].

3.2 Community-Acquired Serious Bacterial Infections

Acute bacterial meningitis is treated with intravenous antibiotics for 7–21 days, with the exact duration depending on the responsible micro-organism and the clinical response. This duration is based on clinical experience and expert opinion rather than on evidence [42]. In a large multicenter RCT in children with acute purulent bacterial meningitis, either caused by *S. pneumoniae, Haemophilus influenzae* type b *or Neisseria meningitidis*, and with good clinical response after 5 days of intravenous ceftriaxone treatment, no difference in outcome could be seen when treatment was stopped compared with children subsequently treated for another 5 days [86].

For severe CAP, most guidelines recommend treatment for a minimum of 7 days [58, 87]. High quality RCTs comparing shorter courses with 'standard duration' are lacking [88]. For complicated CAP (empyema, necrotizing pneumonia), even less evidence is available and generally longer treatment courses are advocated.

3.3 Hospital-Acquired Serious Bacterial Infections

For CA-BSI, the goals of antibiotic treatment are to treat infection and to salvage the catheter if feasible. For long-term catheters, recommended duration depends on whether the catheter is removed and on the pathogen (range 5–14 days when catheter is removed vs 7–14 days if not). No RCTs are available, many data are derived from adult studies [89]. For short-term central venous catheters, salvaging the catheter may be less important and guidelines such as those issued by the Infectious Diseases Society of America (IDSA) support catheter removal as a first step. Antibiotic lock treatment, involving instilling an antibiotic solution into the central line with regular changing, can be seen as an adjunctive therapy in children who lack absolute criteria for line removal, especially for long-term catheters. Once again, only adult data are available [90].

For VAP, no specific pediatric data are available. In adult literature, a standard 8-day antibiotic course is equivalent to a 15-day course, with shorter courses considered safe upon guidance by clinical resolution or serial biomarkers (PCT) [28, 91]. A pragmatic approach for pediatric VAP would be to treat for 5 days with antibiotics in children with good initial response and 7–10 days if *P. aeruginosa* or MDRGN are isolated from cultures [92].

4 Right Dosage

Most antibiotics administered in the PICU are prescribed outside the terms of the product license (off-label) or even without market authorization (unlicensed use) [93]. The recommended dosing regimens for critically ill children are often empirically derived from adults, relatively 'healthy' and/or older children. Simple algorithms extrapolate these dosing schemes based on body weight, height or body surface area [94]. Although antibiotic use in these patients is one of the key interventions in their treatment, current knowledge on the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics in this population remains relatively limited. Many frequently used agents (e.g., ceftriaxone, ceftazidime, penicillin, flucloxacillin, metronidazole) even completely lack PK data in critically ill children. The PK studies that have been published report that conventional dosing strategies consistently fail to achieve the proper PK/PD targets [95, 96]. Specifically for β-lactam antibiotics, 95% of a PICU study population had sub-therapeutic concentrations [97].

A dosing strategy that 'fits all' does not exist in the critically ill child. When deciding on a dosing schedule in these patients, it is imperative to realize that maturation and pathophysiology significantly impact the PK and thus the time–concentration profiles of these antibiotics. The high level of inter-subject variability in PK characteristics emphasizes the need for clinicians to implement specific and personalized dosing strategies.

4.1 Pharmacokinetics in Critically Ill Children

Growth and development have an impact on drug absorption, distribution, metabolism, and excretion (ADME) processes in children. The developmental changes in the ADME processes are dynamic. Especially in the first 2 years of life, rapid maturation significantly influences PK processes [98, 99]. In addition to the maturational alterations, pathophysiological and treatment-induced changes in critically ill children can significantly impact drug disposition (Fig. 1) [95, 100–104]. The effect of these

changes on the concentration–time profiles of antibiotics depends on their physicochemical properties (Table 1).

Intravenous administration of antibiotics is often the preferred route in PICU patients to avoid compromised bioavailability due to impaired drug absorption. It is estimated that delayed gastric emptying occurs in 50% of critically ill children [105]. Additionally, splanchnic hypoperfusion due to shunting of the blood flow to the vital organs, disease- and therapy-induced cholestasis, and intestinal atrophy can contribute to a delayed and/or reduced antibiotic absorption [106–109].

Increased capillary permeability and the consequently augmented third spacing increase the volume of distribution (Vd) of hydrophilic drugs (e.g., β-lactams, aminoglycosides, glycopeptides). On the contrary, the distribution of lipophilic antibiotics (e.g., macrolides, fluoroquinolones) is little affected by these vascular changes [101, 104, 110]. Hypoalbuminemia is a common condition in critically ill patients, as a consequence of the increased capillary permeability and liver dysfunction [111]. It causes an increase in the unbound fraction of highly protein-bound antibiotics, which may lead to altered distribution and elimination [104, 110]. An elevated urea concentration and pH changes, commonly seen in critical illness, both can affect the ionized fraction of the antibiotic and the binding affinity of the antibiotic to plasma proteins, influencing the distribution and thus Vd [112]. The penetration of antibiotics into the tissues, the target site for most antibiotics, is governed by tissue perfusion, passive diffusion, transport mechanisms, lipid solubility, and protein binding [104]. Current data from microdialysis studies in critically ill adults suggest that the antibiotic penetration into the interstitial fluid in tissue is impaired when compared with healthy volunteers [113–115]. Reports on the tissue PK in critically ill children are still lacking.

Inflammation appears to downregulate hepatic drug metabolism [116]. In general, hepatic dysfunction impacts the clearance of lipophilic antibiotics, as they are mostly cleared after hepatic metabolization [103]. In the absence of significant organ dysfunction, the hyperdynamic circulation in a systemic inflammatory response (SIRS) leads to increased renal perfusion and consequently increased clearance of hydrophilic antibiotics. This 'augmented renal clearance' is a less well appreciated phenomenon in clinical practice, but can lead to significant under-dosing [117]. On the other hand, in the presence of renal insufficiency, antibiotics primarily eliminated via the kidneys will have a

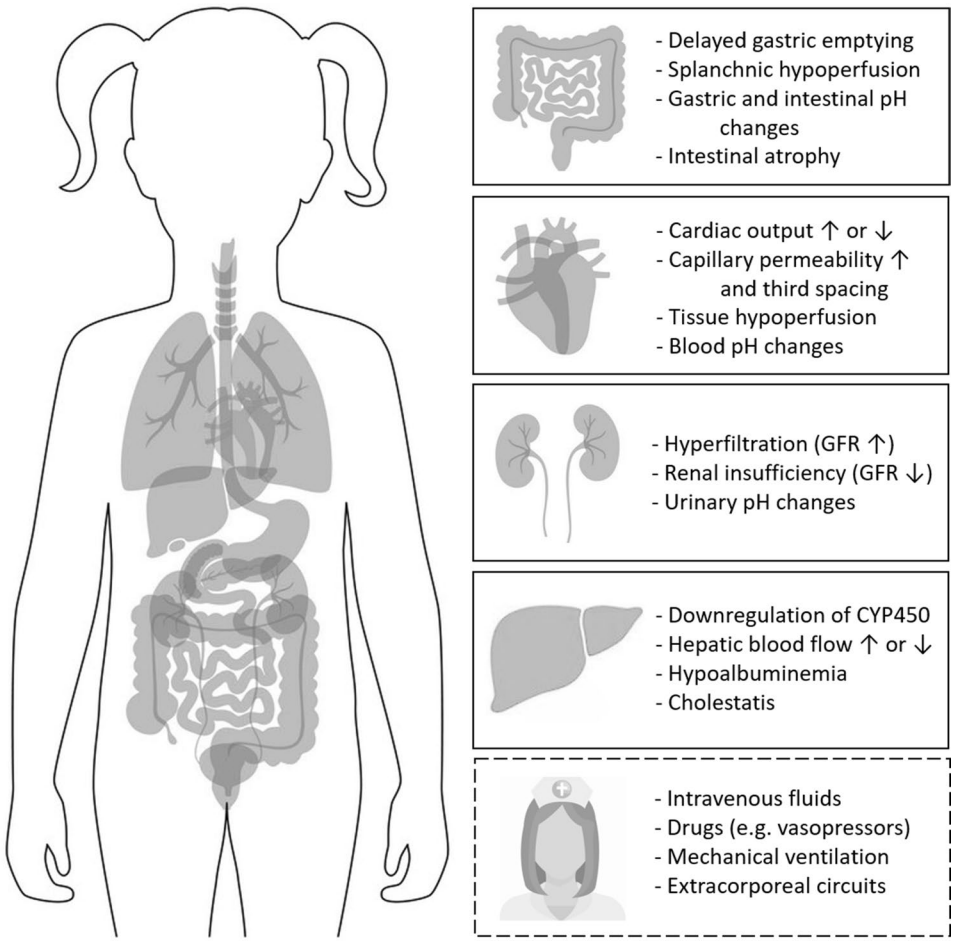

Fig. 1 Pathophysiological and treatment-induced alterations in critical illness that may impact antibiotic pharmacokinetics. *CYP450* cytochrome P450, *GFR* glomerular filtration rate

Table 1 The relationship between molecular and pharmacokinetic characteristics of antibiotics

	Hydrophilic antibiotics	Lipophilic antibiotics
PK in healthy conditions	Intracellular penetration: low	Intracellular penetration: good
	Vd: Low	Vd: High
	Cl: >> Renal	Cl: >> Hepatic
PK in critical illness	Vd: increased	Vd: Relatively unchanged
	Cl: increased (e.g., ARC) or decreased (e.g., renal dysfunction)	Cl: Unaffected or decreased depending on hepatic function and blood flow
PK in ECMO	Vd: increased	Vd: Increased or unaffected
	Cl: Unaffected or decreased (in renal function)	Cl: Likely decreased
PK in CRRT	Cl: Increased	Cl: unchanged or only mildly increased
Examples of antibiotic classes	β-Lactams, aminoglycosides, glycopeptides	Macrolides, fluoroquinolones

ARC augmented renal clearance, *Cl* clearance, *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *PK* pharmacokinetics, *Vd* volume of distribution

diminished clearance, leading to a prolonged half-life and potential toxicity [103, 104]. The administration of vasoactive drugs and intravenous fluid therapy can affect both antibiotic distribution and clearance, mainly through the resulting increase in cardiac output. Mechanical ventilation causes a decrease in cardiac output and hepatic and renal blood flow and thus potentially reduces the clearance of both hepatically and renally excreted antibiotics [118].

4.2 Special Patient Populations in the PICU: Extracorporeal Circuits

The use of extracorporeal circuits challenges the choice of the 'right dose' for the critically ill child even beyond the above-mentioned PK alterations. Extracorporeal membrane oxygenation (ECMO) and renal replacement therapy (RRT) are life-saving therapies with a very unique impact on drug disposition, depending on the treatment modality and system settings.

The ECMO system needs to be considered as an additional compartment when evaluating the PK of antibiotics. It causes an increase in the Vd of hydrophilic antibiotics, and results in decreased plasma concentrations due to hemodilution. The impact of hemodilution is expected to be largest in young children because of their low circulatory volumes. For lipophilic antibiotics, one of the drivers of the altered PK is drug sequestration in the circuit [119–121]. Renal dysfunction occurs in over 30% of patients on ECMO, leading to an altered elimination of renally excreted antibiotics [119, 120, 122]. The majority of the PK studies in ECMO were conducted in NICUs, but in recent years more data in older children and adults have become available. Antibiotic dosing recommendations in the presence of ECMO have been formulated [122]. In the case of vancomycin, for example, it is recommended to increase the initial dose and apply intensive therapeutic monitoring (TDM) in young patients due to the increase in Vd [122, 123].

RRT is available in multiple modalities that all have a different impact on drug clearance. In a PICU setting, continuous renal replacement therapy (CRRT) is the most common form of RRT. Antibiotics with low molecular weight, low plasma protein binding, low Vd, and renal clearance are predisposed to be eliminated from the body by CRRT [124]. CRRT-related clearance accounted for 63% of the total meropenem clearance in PICU patients [125]. For the frequently used antibiotics meropenem, piperacillin-tazobactam, and vancomycin, the effluent flow rate (net ultrafiltration + dialysate flow rate) appears to be the most reliable predictor of antibiotic clearance and should be taken into account when deciding on a dosing scheme [124, 126]. In contrast with ECMO, most studies on antibiotic PK in CRRT have been performed in critically ill adults and some antibiotic dosing recommendations have been formulated for this population [124]. To date, recommendations to guide antibiotic therapy during CRRT in children are not available.

4.3 Pharmacodynamics in Critically Ill Children

Antibiotics are distinct from other pharmacological therapies because the treatment is aimed at an infectious organism and not at any patient target per se. The PD characteristics of antibiotics relate drug concentrations to their ability to kill the pathogen and suppress the emergence of resistance. The minimum inhibitory concentration (MIC), which in vitro is the lowest concentration of the antibiotic required to inhibit visible growth of the organism, is the most widely used PD measurement to describe the potency of an antibiotic agent. Different antibiotic classes appear to demonstrate different kill characteristics on bacteria and thus, depending on the class, different PK/PD targets represent optimal

bactericidal activity (Fig. 2). Three main targets are defined: ratio of the area under the drug concentration–time curve over MIC (AUC/MIC), time during which the concentration remains above the MIC (T>MIC) and ratio of the peak concentration over MIC (C_{max}/MIC) [127].

4.4 Strategies for Optimized Dosing in the PICU

4.4.1 Extended and Continuous Infusions

Extended and continuous infusions may be a beneficial strategy when optimizing PK/PD target attainment of time-dependent antibiotics. For β-lactam antibiotics, the minimum T>MIC should be 40–70%, depending on the class of β-lactam antibiotic. Some clinical studies even suggest that higher exposures may be necessary to treat more severe infections [128]. In the case of piperacillin-tazobactam, PK studies in critically ill children determined that the traditional four doses per day, 30-min administration schedule often failed to maintain adequate plasma concentrations [129–132]. Monte Carlo simulations showed the need for more frequent, extended or continuous infusions to attain the target of T>MIC of 50%. Extended and continuous infusions of other β-lactam antibiotics (e.g., meropenem, cefotaxime) in a PICU setting have been observed to maximize the PK/PD target attainment as well [96]. In the case of vancomycin, an AUC/MIC dependent antibiotic, a recent RCT in young infants comparing continuous and intermittent infusions demonstrated continuous infusions to be associated with earlier and improved target attainment [133]. Additionally, lower total daily doses and fewer dose adjustments were required to achieve therapeutic levels with continuous vancomycin infusions. Also, in older children, continuous vancomycin infusions appeared to be beneficial as they reached or exceeded the desired target concentration within 24–48 h in the majority of the patients, after target concentrations could not be reached during intermittent therapy in the same patients [134].

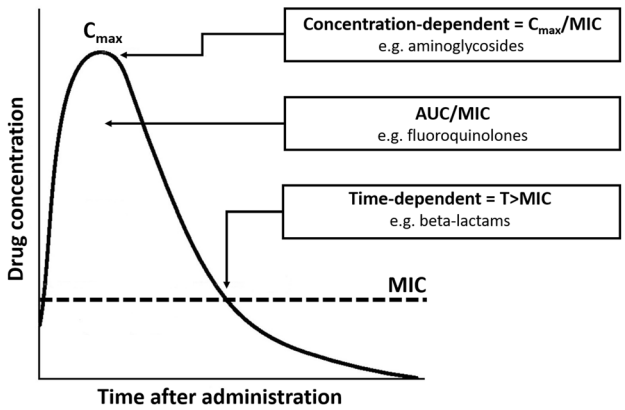

Fig. 2 Pharmacokinetic/pharmacodynamic parameters of antibiotics. *AUC* area under the curve, C_{max} peak drug concentration, *MIC* minimum inhibitory concentration, *T* time

Extended and continuous infusions have practical implications for clinical practice. When initiating an antibiotic therapy, a loading dose, adapted to the expected increase in Vd in the critically ill patient, is required to rapidly achieve target concentrations ("hit hard, hit early") [135, 136]. Another potential pitfall is the incomplete administration of the drug due to the contribution of infusion-line dead space volume [135, 137]. Infusion volume and pump characteristics should be considered when deciding on a dosing scheme. It is recommended to use syringe pumps with a dead volume less than 2 ml and to consider flushing the infusion line after completion of the administration. Other practical issues to take into account are drug stability at room temperature and drug–drug incompatibilities which sometimes may require the presence of a separate infusion line for the extended or continuous administration of the antibiotic [135].

Even though extended infusions improve the PK/PD target attainment of time dependent antibiotics, to date clinical trials have failed to show a clinical outcome benefit of this strategy in critically ill children or adults [138].

4.4.2 Therapeutic Drug Monitoring

TDM relies on the accurate and timely measurement of plasma antibiotic concentrations and the availability of a defined therapeutic range for the antibiotic to individualize the patient's dosing schedule during therapy. Historically, TDM has been used as a cautionary measure to prevent toxicity rather than to optimize antibiotic efficacy. For aminoglycosides and glycopeptides, TDM has become part of general practice with proven beneficial effect on clinical outcome. At this time, measurement of peak and trough concentrations are advised for aminoglycosides, starting from the first dose. Vancomycin intermittent dosing is individualized based upon the measured trough concentration, a practical surrogate marker for the AUC. During continuous infusions of vancomycin, a blood sample can be taken at any time once steady state is achieved [139, 140].

More recently, the use of TDM in other antibiotic classes has gained popularity, especially in specific patient populations (e.g., critical illness) [141–143]. Traditionally, β-lactam antibiotics were not considered for TDM because of their low toxicity and proven efficacy of empiric regimens. Nonetheless, in the current context of more heterogeneous patient populations with complex alterations in PK and the global burden of antibiotic resistance, TDM of β-lactam antibiotics is becoming more widespread [141, 144].

4.4.3 Model-Informed Precision Dosing

Model-informed precision dosing (MIPD) is an innovative approach that combines the knowledge from mathematical models describing the drug PK/PD behavior and individual TDM measurements to personalize antibiotic treatment. MIPD allows prescribers to determine the starting dose before any TDM sample is taken. When TDM measurements become available, MIPD will combine the information from the PK/PD model and individual patient PK characteristics to further personalize the dosing regimen during treatment [145–147]. The main advantages of this approach are that target concentrations can be achieved earlier in the course of the drug therapy when compared with classical TDM, and that it can predict future drug concentrations. Additionally, TDM samples do not have to be collected at steady state. Although MIPD sounds attractive as a strategy, there are several hurdles that hinder implementation on a large scale (e.g., software issues, training of personnel, the need for richly sampled prior PK data, selection of the appropriate model) [145, 146].

When reviewing the case of vancomycin, it is clear that abundant data on the PK in different populations and many population PK models have been published [148]. However, prospective studies investigating the clinical benefit of the application of MIPD are far less available. Limited data in neonates and critically ill adults have shown that MIPD improved the PK/PD target attainment of vancomycin [149, 150]. Application of MIPD for vancomycin in a pediatric teaching hospital, including patients admitted to the PICU, showed similar results [151].

5 Optimal Route: Intravenous to Oral Switch Therapy

The major concern of clinicians in making the intravenous to oral (IV-to-PO) switch of an antibiotic in the PICU is a fear for reduced bioavailability in oral versus intravenous formulations. However, for a large group of antibiotics it is proven that, if the circumstances are right, essentially the same amount of drug is found in the blood when given intravenously or orally [152]. The few studies that have investigated the bioequivalence, efficacy, and safety of an early IV-to-PO antibiotic switch in eligible adults ICU patients demonstrated a shorter ICU LOS, no increase in mortality, and lower costs of antibiotic therapy [153]. Nevertheless, we should remain cautious in critically ill patients, as was illustrated by anecdotal PK data on IV-to-PO switch of moxifloxacin in an adult ICU [154].

The Australasian Society for Infectious Diseases has issued evidence-based recommendations for optimal IV and total antibiotic duration and criteria for IV-to-PO switch for a number of specific pediatric infections [155]. They did not report on critical illness specifically, but based on their recommendations some general guidance for clinical decision making can be formulated (Table 2). Data on the outcome of early IV-to-PO switch of antibiotics in critically ill children are lacking.

In general, an early IV-to-PO antibiotic switch is an important AS intervention. Yet the question remains how applicable this intervention is in a PICU setting. This patient population is by definition not 'clinically stable' and is often at risk for impaired antibiotic absorption. Additionally, for certain severe infections no appropriate oral antibiotic exists (e.g., meningitis). However, in some cases an IV-to-PO switch is indeed possible in PICU patients and it should be a standard consideration while reviewing an individual patient's treatment regimen.

6 Future Perspectives

What seems to be an easy-to-achieve measure, 'the right drug in the right dose for the right duration', has been proven to be quite difficult to implement. As described above, rapid diagnostics have revolutionized diagnostic support.

Table 2 General principles guiding intravenous to oral switch of antibiotics (adapted from McMullan et al. [155])

Clinical condition
Clinically stable without signs of severe sepsis (fever alone need not prevent switch)
Ability to absorb oral antibiotics
Able to tolerate oral medication (not vomiting/nausea or nil per os)
No impairment to absorption (e.g., mucositis, altered gut motility)
Older than 28 days (<28 days not an absolute contraindication, but absorption variable)
Availability of an appropriate oral antibiotic
Antibiotic treats the identified or expected organism
Antibiotic available in appropriate or palatable pediatric formulation
Antibiotic has sufficient penetration of affected tissues

Correct interpretation of test results is challenging, however, and the specific benefits of biomarkers such as PCT and of rapid PCR assays in PICU patients need to be clarified further. In the PICU population, inflammation is not always related to infection. Sepsis-mimicking syndromes, such as hemophagocytic lymphohistiocytosis, macrophage activation syndrome, cytokine release syndrome, and autoimmune disorders, are increasingly recognized. It is crucial to discriminate between bacterial infection and these inflammatory syndromes, as the latter require different therapeutic approaches with immune modulatory therapy. New insights and research into new sets of biomarkers can be expected.

Research on common bacterial infectious emergencies should focus on duration of therapy, as this may be a key factor to decrease antibiotic pressure. The impact of interventions such as ADE on clinical outcome and on antibiotic resistance patterns needs to be clarified as well.

More research into 'right dosage' is required of antibiotics in critically ill children as dosage schedules may need a significant overhaul. In particular, knowledge on the impact of critical illness on antibiotic disposition at the site of infection (e.g., CSF, bronchial epithelial lining fluid) warrants further study. Instead of using fixed PK/PD target values, more sophisticated models incorporating the full time-course of bacterial growth and killing are the next step in finetuning antibiotic PK/PD targets. Outcome data on morbidity and mortality of proposed strategies to optimize dosing are required as well, as an improved PK/PD target attainment may not necessarily translate into a clinically and economically measurable benefit.

The majority of antibiotic prescriptions are made in district hospitals, where the resources and skills to invest in an ASP may be lacking. Most PICUs have an outreaching function; responsible antibiotic prescribing could be integrated into an outreach program by providing clinical guidelines and education. To achieve adequate training, however, insights into behavioral aspects of antibiotic prescribing should be further explored.

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