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DOSING AND APPROPRIATE DURATION OF INTRAVENOUS ANTIBIOTIC FOR PEDIATRIC

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Abstract:

The effective management of infections in pediatric patients necessitates the careful consideration of various factors, including the proper choice of antibiotics, optimal dosage, and duration of treatment. This approach aims to optimize the effectiveness of the medicines while minimizing any potential adverse effects. An essential aspect of achieving optimal dosing is a comprehensive comprehension of the pharmacokinetics and pharmacodynamics of the medications that are now accessible. The utilization of pharmacokinetic/pharmacodynamic (PK/PD) principles in dosing techniques can be advantageous in tailoring antibiotic dosages to ensure efficient eradication of bacteria in patients with modified pharmacokinetics or illnesses caused by organisms that are less sensitive or resistant. The objective of the present review is to examine the optimal duration and dose regimen for intravenous antibiotic therapy in the pediatric population.

A methodology for diluting antimicrobial agents in a healthcare facility has been developed specifically for the pediatric population. The purpose of this protocol is to ensure the proper administration of intravenous drugs in various healthcare settings, including inpatient units, emergency departments, and pediatric intensive care units (PICUs). The elements taken into account encompass the necessary diluent specifications and monitoring parameters, following a comprehensive evaluation of manufacturer labeling, primary literature, and drug information databases.

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INTRODUCTION:

Antimicrobials are frequently given as intravenous (IV) drugs. Children suffering from sepsis are typically given intravenous antibiotics. They may be administered as a bolus push, a gradual IV push, or as intermittent or continuous infusions, depending on the child's state and the infection for which it is prescribed, and with proper regard for the pharmacokinetics and pharmacodynamics of the provided antimicrobia [1]. Several difficulties are better addressed by evidence-based policies, procedures, and practices, in addition to the use of best practice recommendations to guide safe use and enhance therapeutic outcomes. Childhood is distinct in that it is characterized by rapid growth, maturity, and development; the ability to handle active medications varies during childhood, as acknowledged in developmental pharmacology [2]. The degree of dosage modifications necessary during the pediatric age group could be more than 50-fold different between the neonate and the teenager. Fluid management is vital in severely unwell patients [3]. The majority of antibiotic dilution recommendations are geared toward adults. There are very few pediatric IV drug administration recommendations [4,5].

While antibiotic cautious usage is clearly required in all paediatric settings, adequate medication selection and dose optimisation are equally necessary to optimize bacterial infection treatment. Understanding pharmacokinetic/pharmacodynamic (PK/PD) principles may enable for the selection of the best treatment to treat a given bacterial pathogen while employing the optimal dose schedule to eliminate the infection, limit toxicity, and reduce bacterial resistance development [5].

Aminoglycosides and fluoroquinolones are two primary kinds of antibiotics used in pediatrics that kill bacteria in a concentration-dependent manner. Other medications that work in this manner include ketolides, daptomycin, and metronidazole [6]. Concentration-dependent medications have the greatest bactericidal activity at the highest concentrations and a PAE, reducing bacterial growth after concentrations fall below the organism's MIC. These features enable dosage regimens that attempt to maximize concentration (high doses) while taking advantage of the medications' lasting effects (extended-interval dosing). This method of optimizing concentration-dependent antibiotics not only promotes optimal efficacy but may also avoid the development of resistance and undesirable responses. Because aminoglycosides are the most commonly used concentration-dependent antibiotics in children, optimal dosing for this class will be explored in details.

REVIEW:

Fluid resuscitation, as part of fluid management, may be required in critically unwell children to maintain intravascular volume. Unfortunately, this frequently results in fluid overload3, with devastating consequences for children admitted to the PICU [7]. These children would be given a variety of IV drugs. Fluid restriction might benefit from reducing the volume of diluent for each medicine, including antimicrobials. This method, however, is not applicable to medications marketed as premixed infusions. Depending on the individual drug recommendation, antimicrobials may be provided via IV push, intermittent IV infusion, and/or continuous IV infusion. Intravenous antimicrobial push has the benefit of a low fluid volume, which might be very beneficial for fluid-restricted patients. Furthermore, the speedier administration time may bring advantages in the emergency room, allowing for a shorter time-to-first-dose. In the event of a drug or fluid shortage, such as the current lack of small-volume parenteral solutions, IV push delivery may be of interest. The need of the antibiotic dilution technique for children who require fluid restriction is underlined here.

Antimicrobial actions are often classified as either concentration- or time-dependent [8]. Concentration-dependent medications kill bacteria at rising concentrations, whereas time-dependent drugs kill

bacteria at increasing concentrations; the latter are most effective when exposure is sustained. Some medications also exhibit persistent or post-antibiotic effects (PAE), which relate to the continuing suppression of bacterial growth after drug removal, which varies depending on the mechanism of drug action, the pathogen, and how the drug is administered [9,10]. Thus, antibiotics can be classified into three types based on optimal bactericidal conditions (**Table 1**): concentration-dependent killing with moderate-to-persistent PAEs, time-dependent killing with minimal-to-no persistent bactericidal effects, and time-dependent killing with prolonged persistent effects [11]. Depending on the mechanism of antibacterial activity, the PK/PD indices that correlate with clinical efficacy varies. Understanding which category best describes the action of an antibiotic allows for sensible dose modifications to maximize activity.

PK/PD correlations have already been identified using in vitro or animal infection models [12] and confirmed in adult patient trials [13]. PK/PD endpoint studies in paediatric populations are frequently inadequate. Nonetheless, the mechanism of action and PK/PD parameters that correlate with efficacy for the treatment of certain infections in adults should be the same in children. There are three primary PK/PD parameters that are frequently described as clinical targets for antibiotic exposure because they have been shown to correlate with clinical efficacy for different antibiotic classes: the maximum serum concentration (C_{max}) to MIC ratio (C_{max}/MIC) for concentration-dependent drugs; the percentage of the dosing interval above the MIC ($T_{>MIC}$) for time-dependent drugs with minimal-to-no persistent effects; and the ratio of the area under the curve (AUC) to the area under the curve (A Because drug molecules attached to plasma proteins are not free to act on bacteria, PD measures frequently relate to the free fraction of drug in serum [14]. In the following sections, we will go over each of the antimicrobial effect categories in further detail, using particular examples to show how PK/PD information might affect dose optimisation in paediatric clinical practice [15].

TABLE 1: Pattern of activity of different antibacterial drugs and their associated pharmacokinetic/pharmacodynamic (PK/PD) targets

Mechanism of bactericidal effects based on in vitro data	**Antibiotic class**	**PK/PD parameter(s) associated with efficacy**	**Goal of dosing regimen**
Concentration- dependent killing with moderate-to-persistent bactericidal effects	Aminoglycosides Fluoroquinolones Metronidazole Daptomycin Ketolides	C_{max}/MIC AUC_{0-24}/MIC	**Maximise concentration**: increase dose
Time-dependent killing with minimal-to-no persistent bactericidal effects	β-Lactams: Penicillins Cephalosporins Carbapenems Aztreonam Erythromycin	$T_{>MIC}$	**Maximise the duration of exposure**: increase duration of infusion or frequency of administration
Time-dependent killing with moderate-to-prolonged persistent bactericidal effects	Macrolides Tetracyclines Glycopeptides Clindamycin Linezolid [b]	AUC_{0-24}/MIC	**Maximise drug exposure**: increase dose, frequency of administration or duration of infusion

Cmax, maximum serum concentration; MIC, minimum inhibitory concentration; AUC0–24, area under the concentration–time curve over a 24-h period; T>MIC, percentage of the dosing interval above the MIC.

Aminoglycosides:

Aminoglycosides, which are derived from Streptomyces spp., have been administered to paediatric patients for over six decades. There is a substantial body of literature available that discusses the clinical value, mechanisms of action, pharmacokinetics and pharmacodynamics, and toxicity of the subject [16]. Gentamicin is often regarded as the most suitable aminoglycoside for the paediatric population, despite its classification as a relatively minor constituent within the extensive and diverse group of aminoglycosides. The mechanism of action of aminoglycosides involves their irreversible binding to the 16S ribosomal RNA of the 30S subunit of bacterial ribosomes, resulting in the inhibition of protein synthesis. The occurrence of peak serum concentrations is routinely observed at the conclusion of intravenous (i.v.) infusions. This enables the direct assessment of C_{max} after infusion, as well as the evaluation of the distribution phase, during which the drug disperses from the plasma into the tissues. These drugs exhibit a wide range of antibacterial activity against Gram-negative bacteria, and they also show synergistic effects against certain Gram-positive organisms.

The initial discovery of the correlation between enhanced patient outcomes and elevated Cmax/MIC ratios for aminoglycosides was documented by Moore et al. [17]. Their study revealed a heightened response in adult individuals with Gram-negative infections when the Cmax/MIC ratio ranged from 8 to 10. The PK/PD target mentioned in this study has been replicated in multiple additional studies conducted on adult populations [17,18]. It is frequently employed as a basis for developing personalized PK dosing protocols for pediatric patients. While the conventional method of administering aminoglycosides involves numerous daily doses, it has been found that best dosage strategies involve administering high amounts once daily [19,20]. Extended-interval dosing capitalizes on the concentration-dependent bactericidal action of the medications and is clinically supported by the significant post-antibiotic effect (PAE) and leukocyte augmentation, hence reducing bacterial re-growth following a decrease in serum concentration below the minimum inhibitory concentration (MIC) [12]. Extended-interval dosing is a therapeutic approach that also tackles the pharmacodynamic phenomenon referred to as adaptive resistance, which involves the development of temporary resistance by bacteria to the bactericidal effects of medications. This process facilitates the thorough elimination of medications, providing sufficient duration for the targeted bacteria to revert to a susceptible state, hence reducing the likelihood of difficulties arising from the emergence of resistance.

The administration of aminoglycosides is restricted due to concerns related to nephrotoxicity and ototoxicity. These limitations are particularly relevant when treating clinically important infections caused by multidrug-resistant (MDR) pathogens. The occurrence of nephrotoxicity is associated with drug buildup, which is a result of the medication binding to the brush edges of renal cells [21]. The tissues exhibit greater absorption efficiency when exposed to low sustained concentrations compared to high intermittent levels [20]. Ototoxicity arises from the generation of reactive oxygen species, commonly known as free radicals, which inflict harm onto the hair cells located in the cochlear and vestibular regions [22]. The irreversible nature of ototoxicity and the reversible nature of nephrotoxicity, although predominantly reversible, can result in extended hospital stays and heightened healthcare expenses for both pediatric and adult patients [23]. The implementation of personalized pharmacokinetic (PK) dosing has demonstrated a decrease in the occurrence of nephrotoxicity [24,25].

The comprehensive documenting of variations in pharmacokinetic/pharmacodynamic (PK/PD) characteristics for aminoglycosides in pediatric populations facilitates the implementation of dose optimization strategies. Dosing techniques in preterm newborns are primarily influenced by pharmacokinetic (PK) concerns. The population under consideration exhibits immature renal function, which results in a deceleration of drug clearance. Consequently, the anticipated half-life of the medicine is extended from a range of 2 to 3 hours to a range of 8 to 12 hours. If no adjustments are made to the dose interval, there is a possibility of increased trough concentrations, which in turn could elevate the risk of toxicity. Premature newborns also demonstrate decreased peak concentrations due to their comparatively larger volume of distribution (Vd) [26]. Pharmacokinetic (PK) models provide evidence for the administration of higher dosages at reduced frequency, such as every 24-48 hours, in this particular population [19].

When administering gentamicin for neonatal sepsis, it is recommended to achieve peak serum

concentrations of greater than 8-10 µg/mL when treating organisms with a minimum inhibitory concentration (MIC) of 1 µg/mL or less. Additionally, the goal is to maintain trough concentrations below 0.5-1 µg/mL before re-dosing [19,20]. This case serves as a notable illustration of the efficacy of individualized dose optimization, since the customization of treatment leads to enhanced outcomes through the mitigation of toxicity and the reduction of healthcare expenditures [21]. Clinicians frequently acquire these concentrations subsequent to the administration of the third to fourth dose, allowing for the patient's levels to near steady-state values. Nonetheless, this method has the potential to cause delays in making essential adjustments to medication dosages when treating confirmed illnesses. The utilization of suitable population pharmacokinetic (PK) models and Bayesian adaptive control allows for the customization of dose regimens after the clinical necessity for an extended antibiotic treatment is established. This approach aims to optimize the therapeutic effectiveness of the medication while minimizing the risk of adverse effects [21].

Patients diagnosed with cystic fibrosis (CF) also have advantages from extended-interval medication, albeit with distinct rationales compared to neonates. The primary objective of aminoglycoside therapy in individuals diagnosed with cystic fibrosis (CF) is to effectively address the presence of Gram-negative microorganisms, namely targeting Pseudomonas aeruginosa. There are three reasons why higher doses are required in patients with CF. Firstly, bacteria present in patients with CF often exhibit reduced susceptibility to antibacterial agents due to repeated exposure to antibiotics over a prolonged period of time. Secondly, patients with CF have a higher total body clearance and larger volume of distribution compared to other patients, necessitating higher doses to attain equivalent serum concentrations. Lastly, achieving high concentrations in pulmonary infections is more challenging than in serum. These factors collectively contribute to the need for higher doses in CF patients [22]. The utilization of extended-interval dosing of aminoglycosides enables medical professionals to provide substantial dosages, attain elevated peak concentrations, and optimize effectiveness against organisms that exhibit greater resistance. Extended-interval dosage additionally provides ample time for the drug to be fully eliminated from the body before subsequent administration, thus diminishing the probability of nephrotoxicity. Research has indicated that the optimal dose method for patients with cystic fibrosis (CF) is once-daily dosing [23]. This approach has been officially recommended by the Cystic Fibrosis Foundation as the preferred dosing strategy. While the C_{max}/MIC ratio has been identified as the preferred pharmacokinetic/pharmacodynamic objective for achieving clinical effectiveness in the management of bronchopneumonia in individuals with cystic fibrosis [26], a definitive peak to MIC ratio has not yet been determined.

β-Lactam antibiotics:

β-Lactam antibiotics are frequently used in the field of paediatrics due to their comparatively favorable safety profile. These medications are utilized in the treatment of both common and serious illnesses in the paediatric population. To illustrate the optimization of PK/PD features of β-lactam antibiotics based on the site of infection, we shall compare their application in acute otitis media and bacteraemia [27].

The predominant causative agents of acute otitis media in babies and children are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. The development of resistance to β-lactams in Streptococcus pneumoniae is mostly attributed to modifications in penicillin-binding proteins. However, it is possible to counteract this resistance by administering β-lactam antibiotics in a manner that is dependent on the dosage. Due to the escalating incidence of resistant Streptococcus pneumoniae, there is a growing necessity for higher dosages of penicillins. The susceptibility of S. pneumoniae isolates to intravenous (i.v.) penicillin is indicated by a minimum inhibitory concentration (MIC) of less than 2 µg/mL. For oral penicillin, the MIC is less than 0.06 µg/mL. In the case of non-meningitis infections, the MIC for i.v. cephalosporins is equal to or less than 1.0 µg/mL [27]. The average probability of achieving bacteriological cure ranges from 80% to 85% when the time over the minimum inhibitory concentration ($T_{>MIC}$) is between 40% and 50%. When the $T_{>MIC}$ is increased to 60% to 70%, the likelihood of bacteriological cure approaches 100% [28]. Fortunately, the middle ear possesses a substantial network of capillaries and a limited quantity of interstitial fluid, facilitating the efficient permeation of antibiotics. This phenomenon gives rise to delayed reactions to fluctuations in serum concentrations, leading to diminished peak levels and elevated trough values [28]. The administration of higher dosages of amoxicillin twice daily has been found to effectively saturate the antibiotic in the middle ear and overcome resistance. As a result, the

recommended dosing regimen for treating penicillin-resistant S. pneumoniae is now 75-90 mg/kg/day [29,30]. The administration of a solitary intramuscular dose of ceftriaxone at a concentration of 50 mg/kg results in middle ear fluid concentrations of 9.5 μg/mL after 72 hours and 4.8 μg/mL after 96 hours. This dosage regimen ensures a sustained period of time during which the concentration of the drug exceeds the minimum inhibitory concentration (MIC) by 100%, even for strains of S. pneumoniae that are resistant to ceftriaxone [31].

In the context of managing bacteraemia or other severe infections, the absence of an additional compartment for antibiotic saturation necessitates reliance on the concentration of unbound medication in the bloodstream to determine clinical effectiveness. In the case of patients who are severely ill or have impaired immune systems, it may be necessary to optimize the efficacy of treatment by maximizing the rate of pathogen eradication across the whole duration of the dosing schedule. Continuous or longer infusions of medication may provide advantages compared to the conventional approach of intermittent dosing. The administration of β-lactam antibiotics through extended or continuous intravenous infusion has the potential to prolong the duration during which the drug concentration exceeds the minimum inhibitory concentration (MIC) of the targeted organism. This method of drug administration may offer advantages over intermittent administration, particularly when dealing with pathogens that exhibit high MIC values. The notion was supported by a systematic evaluation of adult randomised clinical trials undertaken by Kasiakou et al. [32]. Furthermore, the utilization of Monte Carlo simulations was employed to investigate the effects of different drug regimens (cefepime, ceftazidime, imipenem/cilastatin, meropenem, and piperacillin/tazobactam) on children aged 2 years and 12 years, who were subjected to various levels of P. aeruginosa with different minimum inhibitory concentrations (MICs). The findings of this study indicate that achieving the desired therapeutic outcome becomes more challenging when higher MICs are present, particularly when intermittent dosing is utilized as opposed to prolonged or continuous infusion [33]. The use of extended-infusion β-lactams has been found to be advantageous in reducing death rates, shortening hospital stays, and lowering hospital expenses in adult patients [34]. However, there is a dearth of research that demonstrate the clinical superiority of this approach in pediatric populations. Despite the lack of evidence from a recent systematic review regarding the regular use of extended or continuous infusions in paediatric patients [35], it is necessary to conduct future well-designed prospective clinical trials to assess the potential benefits of such infusions. These trials should focus on improving outcomes in paediatric patients and optimizing the attainment of pharmacokinetic/pharmacodynamic targets.

In order to effectively combat bacterial infections, it is crucial for β-lactam antibiotics to sustain free concentrations above the MIC of the targeted organism. However, it is worth noting that certain antimicrobial agents that operate based on time-dependent principles exhibit supplementary antibacterial action even when serum concentrations fall below the MIC threshold. The antimicrobials encompassed within this classification are the macrolides, tetracyclines, clindamycin, linezolid, and vancomycin. For instance, the pharmacokinetic-pharmacodynamic (PK-PD) parameter known as the post-antibiotic effect (PAE) of vancomycin exhibits variability based on the specific organism being targeted. Specifically, the PAE duration for Staphylococcus aureus ranges from 0.7 hours to 2.6 hours, while for Staphylococcus epidermidis it ranges from 4.3 hours to 6.5 hours [36]. The $AUC0–24/_{MIC}$ ratio is the PK/PD metric that is most strongly linked to the effectiveness of this class of antibiotics, owing to its moderate-to-persistent suppressive effects [36]. In this discussion, we will examine two specific antibiotics, namely vancomycin and linezolid, as illustrative instances of this category. Our focus will be on their respective applications in combating drug-resistant Gram-positive infections, with an emphasis on highlighting the differences between them.

Vancomycin:

Vancomycin, a glycopeptide, has been commercially accessible for utilization since 1958 [37]. The utilization of clinical applications was widespread throughout the 1950s, primarily driven by the introduction of staphylococci that produce penicillinase. Presently, there has been a resurgence in its frequent implementation owing to the prevalence of meticillin-resistant Staphylococcus aureus (MRSA). Improved clinical outcomes have been observed in people with MRSA infections when the area under the concentration-time curve from 0 to 24 hours (AUC0–24) divided by the minimum inhibitory concentration (MIC) is greater than 400 [38]. The Infectious Diseases Society of America (IDSA) has established current clinical practice guidelines for the treatment of MRSA infections. These guidelines suggest the use of dosage regimens that incorporate the

pharmacokinetic/pharmacodynamic (PK/PD) aim mentioned in reference [39]. It is recommended to initiate intravenous administration of vancomycin at a dosage of 15 mg/kg per dose every 6 hours in children who have serious or invasive infections caused by methicillin-resistant Staphylococcus aureus (MRSA). This dosage regimen is advised in order to achieve the desired therapeutic outcome for MRSA isolates with a minimum inhibitory concentration (MIC) of 1 µg/mL or less. Nevertheless, there is a dearth of data regarding the association between improved outcomes in children and the achievement of an AUC0–24/MIC >400.

The evaluation of achieving an AUC0–24/MIC >400 has been conducted in various pharmacokinetic models for pediatric populations. The study conducted by Frymoyer et al. (year) examined a cohort of children ranging from 2 to 12 years of age. The researchers aimed to estimate the area under the concentration-time curve from 0 to 24 hours divided by the minimum inhibitory concentration (AUC0–24/MIC) for vancomycin daily dosages of 40 mg/kg/day and 60 mg/kg/day [40]. The authors of this study discovered that doses of 40 mg/kg/day were improbable to result in an AUC0–24/MIC value greater than 400 when the minimum inhibitory concentration (MIC) was equal to or greater than 1 µg/mL. However, achieving an AUC0–24/MIC value greater than 400 was more feasible with doses of 60 mg/kg/day [41]. This conclusion was further supported by a Monte Carlo simulation, which indicated that 58-66% of children would attain AUC0-24/MIC >400 with doses of 40 mg/kg/day. Additionally, doses beyond 60 mg/kg/day resulted in 88-98% of children achieving this target, provided that the MIC was ≤1 µg/mL [42]. The attainment of a target AUC0–24/MIC >400 in clinical practice may pose challenges, as evidenced by the study conducted by Chhim et al. In their investigation, it was seen that only 40% of the 96 children who received a dosage of 60 mg/kg/day vancomycin were able to obtain the desired AUC0–24/MIC >400 [43].

According to the current guidelines of the Infectious Diseases Society of America (IDSA), it is recommended to aim for trough values ranging from 15 to 20 µg/mL in adult patients who have invasive methicillin-resistant Staphylococcus aureus (MRSA) infection. This recommendation is based on the correlation between trough values in this range and an area under the concentration-time curve from 0 to 24 hours divided by the minimum inhibitory concentration (AUC0–24/MIC) more than 400 for MRSA isolates with a minimum inhibitory concentration (MIC) of 1 µg/mL or lower [44]. Trough concentrations ranging from 15 to 20 µg/mL are frequently selected for pediatric patients, despite the scarcity of supporting evidence for this approach. According to Frymoyer et al. and Le et al., there is a suggestion that lower troughs would be sufficient in the case of youngsters [45]. In a study conducted by Frymoyer et al., population pharmacokinetic (PK) modeling and simulation were utilized to determine the therapeutic drug monitoring (TDM) targets for children. The results indicated that maintaining trough concentrations between 7-10 µg/mL resulted in an area under the concentration-time curve from 0 to 24 hours (AUC0-24) to minimum inhibitory concentration (MIC) ratio more than 400 in over 90% of the pediatric population. This target was attained when a dosage of 15 mg/kg was administered every 6 hours, assuming the MIC value was 1 µg/mL [46]. In contrast, Le et al. employed population-based pharmacokinetic (PK) modeling and Monte Carlo simulation to demonstrate that a dosage regimen of 60-70 mg/kg/day administered in divided doses every 6 hours resulted in the attainment of the desired AUC0-24/MIC >400 in 75% of simulated patients across various MIC values. It was shown that an AUC0-24/MIC >400 corresponded to trough concentrations of 8-9 µg/mL [46]. According to a study conducted at Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio, it was shown that only 67% of children were able to attain an AUC0-24 more than 400 when their trough concentrations ranged from 8-10 µg/mL. This indicates that lower trough concentrations may be suitable for minimum inhibitory concentrations (MICs) below 1 µg/mL, but may not be sufficient for MICs equal to or greater than 1 µg/mL [46].

CONCLUSION:

Hospitalized juvenile patients are particularly vulnerable to experiencing adverse events related to pharmaceutical errors. This is due to the fact that they constitute a distinct patient population, for whom healthcare practitioners are more susceptible to making mistakes in dosage or selecting inappropriate drugs. This statement emphasizes the observation that the responsibilities of clinical pharmacists have evolved beyond the mere tasks of dispensing and preparing medications. They have now assumed a crucial position as integral members of the healthcare team, engaging in activities such as suggesting modifications to existing drug therapy, optimizing drug dosage, and preventing medication errors.

A comprehensive understanding of pharmacokinetic/pharmacodynamic (PK/PD)

concepts is necessary in the context of prescribing antibiotics for pediatric patients, especially in cases involving severe illnesses and certain subgroups of children with modified pharmacokinetic profiles. While regular dose regimens may suffice for the majority of children, it is crucial to identify those individuals who would derive the greatest advantage from alternative dosing procedures. Furthermore, since paediatricians increasingly participate in the fight against multidrug-resistant (MDR) organisms, which were previously only a concern for adult patients, the application of pharmacokinetic/pharmacodynamic (PK/PD) principles in antibiotic dosing may enable the ongoing use of commonly prescribed antibiotics. This approach would help preserve newer antibiotic medicines for patients who genuinely have no alternative therapeutic alternatives available to them.

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