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INDIAN ACADEMY OF PEDIATRICS



IAP Specialty Series on

RATIONAL ANTIMICROBIAL PRACTICE IN PEDIATRICS

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THIRD EDITION



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Pharmacokinetics and Pharmacodynamics of Antimicrobials

4 Chapter

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INTRODUCTION

Optimizing outcomes for infected patients requires attention to three interconnected factors, namely, patient, pathogen, and drug. While patient and pathogen are uncontrollable factors, the choice of the drug and the way it is administered are modifiable. Against the backdrop of increasing antimicrobial resistance coupled with a poor antimicrobial pipeline, treatment of serious infections has become increasingly challenging. The situation is further aggravated in critically ill patients where resistant organisms are common and in whom pathophysiological change results in alteration of pharmacokinetics (PK) of antimicrobials. This has led to a growing interest in the understanding of PK/pharmacodynamics (PD) parameters and their clinical utility in improving outcomes and minimizing the risk of resistance. This chapter outlines the fundamentals of antimicrobial PK-PD and a few concepts regarding their application in clinical practice, namely, the role of therapeutic drug monitoring (TDM) and prolonged infusion of beta-lactams.

BASICS OF PHARMACODYNAMICS AND PHARMACOKINETICS

Pharmacodynamics describes the effect of the drug on the body and the microorganisms while PK describes the plasma time-concentration course of the drug. It is well known that for a drug to achieve its effect (PD), it has to achieve a certain concentration at the site of the infection via the plasma (PK) (Fig. 1). Looking at the PK-PD together links drug exposure to the antimicrobial and clinical effects after administration of the drug to a patient.

The typical course of a drug after oral administration is illustrated in Figure 2. The drug achieves its maximum concentration (C_{max}) at a particular time point (T_{max}) and is metabolized and finally eliminated from the body depending on its half-life. The "area under the curve (AUC)" represents the total body exposure to the drug. When this is plotted on the same graph as the

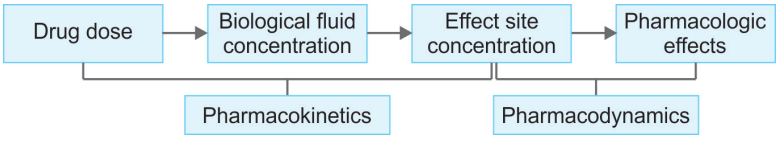

Fig. 1: The relationship between pharmacokinetics-pharmacodynamics (PK-PD) of drugs.

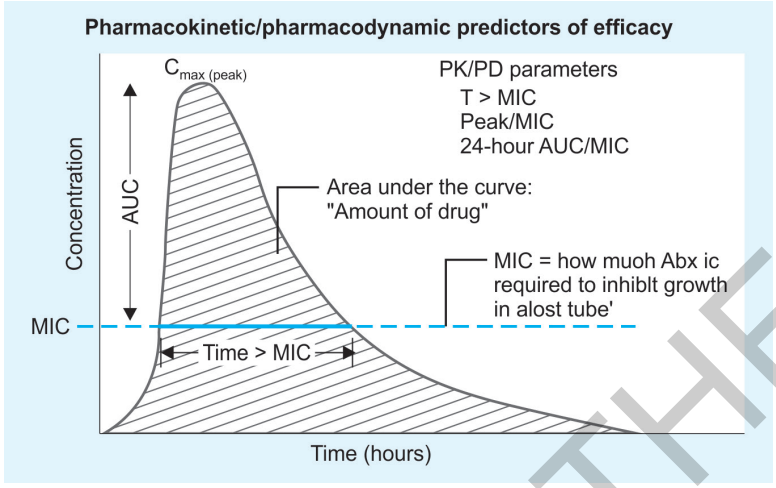

Fig. 2: Plasma time concentration curve of a drug and various pharmacokinetics-pharmacodynamics (PK-PD) parameters.
(AUC: area under the curve; C_{max}: maximum concentration; MIC: minimum inhibitory concentration; T>MIC: time above MIC)

minimal inhibitory concentration (MIC) of the drug against a particular organism, we begin to understand the concept of PK-PD of antibacterial agents.

TYPES OF ANTIBACTERIAL EFFECTS

There are three PD properties of antibiotics that best describe killing activity—these are concentration-dependence, time-dependence, and persistent effects. The rate of killing is determined by either the effect of increasing concentrations (concentration-dependent) or length of time necessary to kill (time-dependent) and persistent suppression of bacterial growth following antibiotic exposure (postantibiotic effect). Using these parameters, antibiotics can be divided into three categories: (1) concentration-dependent killing with moderate-to-persistent bactericidal effects, (2) time-dependent killing with no or minimal persistent bactericidal effects, and (3) time-dependent killing with prolonged persistent effects. PK-PD parameters are interrelated and these are influenced by dose adjustments. Unlike other drugs, it is important to recognize that an organism's MIC strongly influences the likelihood of PK-PD target attainment.

Concentration-dependent Killing with Moderate-to-Persistent Bactericidal Effects

Antibiotics belonging to this group exhibit maximum bactericidal activity at the highest concentration and have a persistent effect in suppressing bacterial growth after the concentration drops below the MIC of the organism. These properties allow a dosing regimen that aims to maximize the concentration by giving a large dose and to keep an extended interval dosing due to the advantage of prolonged effect. Concentration-dependent killing is determined by how much greater is the C_{max} above the MIC and from this, the C_{max} to MIC ratio is calculated. The minimum ratio should be 10; the greater the ratio, the greater is the kill power of the antimicrobial agent. An excellent example of this is the aminoglycoside class of drugs which produce similar

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or better results when the total dose is given as a once-daily injection versus twice or thrice daily. The other common examples are fluoroquinolones and colistin.

Colistin is increasingly being used to treat multidrug resistant gram-negative infections. With a better understanding of PK-PD of colistin, dosing recommendations have been updated from 1–2 million units (MU) three times a day to initiating treatment with a loading dose. Colistin exhibits concentration-dependent killing and is rapidly bactericidal at concentrations above the MIC. Clinical cure rates of 82% was achieved in adults by using a loading dose of 9 MU followed by 4.5 MU as a maintenance dosage every 12 hours. The loading dose may go up to 12 MU. The logic behind administering the loading dose is because almost two-third of colistin administered as its prodrug colistimethate sodium is excreted unchanged by the kidneys soon after administration. The loading dose should be administered intravenously over 1–2 hours, followed by the first maintenance dose after 12 hours. Recently, a small study in seven children with carbapenem-resistant gram-negative infection aged 46 days–14 years suggests that a loading dose of 150,000 units/kg up to a max of 9 MU followed by a maintenance dose of 75,000 units/kg up–4.5 MU every 12 hours could provide desired plasma concentrations of more than 1 mg/L. However, further studies should be conducted in critically ill children to confirm these results.

Time-dependent Killing with no or Minimal Persistent Bactericidal Effects

On the other hand, some antibiotics demonstrate "time-dependent killing" which means that the efficacy is dependent on how long in the dosing interval the concentration of the drug remains above the MIC levels. For antibiotics in this class, concentrations at four times the MIC are sufficient to kill the organisms and killing is not improved at higher concentrations. Hence, the key PK-PD parameter associated with efficacy is time above MIC (T>MIC) and thus, more frequent administration of antibiotics is often needed. Beta-lactams, such as penicillins, cephalosporins, and carbapenems have this property. Cephalosporins, which have a slow rate of killing require a T>MIC of 60–70% of the dosing interval for maximum efficacy; less time is acceptable for penicillins (50%) and carbapenems (40%), which have faster rates of killing.

Studies have shown that the bacteriological efficacy is greater than 80% in such cases. In children with otitis media, bacteriological cure rates of 80–85% were observed when the serum concentrations exceeded the MIC for 40–50% of the dosing interval and increased to nearly 100% when it was 60–70% of the dosing interval. Table 1 shows the probability of achieving the PK-PD target of piperacillin-tazobactam (P-T) against *Escherichia coli* and *Klebsiella pneumoniae*,

TABLE 1: Probability of attaining pharmacokinetics-pharmacodynamics (PK-PD) targets of piperacillin-tazobactam with different dosing intervals.

Regimen	*Probability of attaining PK-PD target measures*				
	30%	*40%*	*50%*	*60%*	*70%*
Escherichia coli					
3.375 g every 4 hours	0.96	0.92	0.9	0.86	0.77
3.375 g every 6 hours	0.91	0.86	0.73	0.50	0.28
Klebsiella pneumoniae					
3.375 g every 4 hours	0.77	0.72	0.65	0.57	0.48
3.375 g every 6 hours	0.69	0.57	0.43	0.29	0.16

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which are extended-spectrum beta-lactamase-producing phenotypes. For example, giving P-T at a dose of 3.375 g every 6 hours had a 73% probability of achieving concentrations greater then MIC against *E. coli* for 50% of the dosing interval. This increased to 90% if the same dose was given every 4 hours. For beta-lactam antibiotics, increasing the dose to increase C_{max} more than four times the MIC does not usually result in achieving greater killing.

Time-dependent Killing with Prolonged Persistent Effects

The time-dependent antimicrobials have additional antibacterial activity after serum concentrations have dropped below the MIC. Efficacy of these antibiotics depends on the total exposure of the organism to the drug and PK-PD parameter associated with efficacy for this category of antibiotics is AUC_{0-24}/MIC ratio. Antimicrobials belonging to this category are macrolides, tetracyclines, clindamycin, linezolid, and vancomycin.

In adults with methicillin-resistant *Staphylococcus aureus* (MRSA) infections being treated with vancomycin, an AUC_{0-24}/MIC of more than 400 has been associated with improved clinical outcomes. However, data in children linking improved outcomes with attainment of an AUC_{0-24}/MIC of more than 400 is lacking. For children with serious or invasive MRSA infections, initiating intravenous (IV) vancomycin 15 mg/kg/dose every 6 hours is recommended as a means of reaching the goal to eradicate isolates with a MIC of less than or equal to 1 mg/mL. It was found in a study that an AUC_{0-24}/MIC of 80–120 and T>MIC of more than 85% of the dosing interval were associated with successful treatment of bacteremia, lower respiratory tract infection, and skin and soft tissue infection in debilitated adult patients. Studies have demonstrated that more frequent doses (every 8 hours) are required for children less than 12 years of age to achieve appropriate exposure.

The other example is azithromycin whose efficacy depends primarily on the total exposure of the organism to the drug and AUC_{0-24}/MIC being more than 100.

Table 2 summarizes the types of killing of antibacterial agents.

TABLE 2: Types of killing for different antibacterial agents.

Pattern of activity	*Antibiotics*	*Goal of therapy*	*PK-PD parameter*
Concentration-dependent killing and prolonged persistent effects	Aminoglycosides Fluoroquinolones Daptomycin Ketolides	Maximize concentrations; increase dose	C_{max}/MIC (should be >10) and AUC_{0-24}/MIC (should be >125)
Time-dependent killing with no or minimal persistent bactericidal effects	Carbapenems Cephalosporins Erythromycin penicillin	Maximize duration of exposure; increase duration of infusion or increase frequency of administration	T>MIC (at least 40% of the dosing interval for carbapenems; 50% for penicillins; and 60–70% for cephalosporins)
Time-dependent killing with moderate-to-prolonged persistent effects	Azithromycin Clindamycin Oxazolidinones Tetracyclines Vancomycin	Maximize amount of exposure; increase dose, frequency of administration or duration of infusion	AUC_{0-24}/MIC (>400 for vancomycin and 80–120 for linezolid)

(C_{max}: maximum concentration; MIC: minimum inhibitory concentration; PK-PD: pharmacokinetics-pharmacodynamics; T>MIC: time above MIC)

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AUGMENTED RENAL CLEARANCE IN CRITICALLY ILL PATIENTS

Critically ill patients undergo physiological changes that can alter drug PK. Traditionally, dose adjustments of antimicrobials have been done based on the renal impairment in these patients. However, augmented renal clearance (ARC) has recently begun to be recognized as an alteration in kidney function that can led to accelerated drug elimination and suboptimal drug levels. Around 20–65% of critically ill patients have ARC. Younger age group, polytrauma, and severity of illness have been identified as risk factors.

Augmented renal clearance is a fairly new concept and does not have a standard definition. However, according to broad consensus, ARC is defined as a creatinine clearance (CrCl) of more than 130 mL/minute/1.73m^2. The normal glomerular filtration rate (GFR) in young adults is approximately 125 mL/min/1.73m^2. The mechanism of ARC is not well defined. However, the combination of systemic inflammation coupled with a physiological renal function reserve has been accepted as a possible mechanism for ARC. It has been postulated that systemic inflammatory response syndrome (SIRS), an activation of the immune system could be associated with ARC. The release of inflammatory mediators leads to decrease vascular resistance and increase in cardiac output. This together with intensive fluid therapy and use of inotropic drugs may increase renal blood flow and the GFR. The concept of renal function reserve refers to the capacity of the kidneys to increase GFR in response to certain physiological and pathological stimuli. This would explain the association of ARC and risk factors, such as young age and polytrauma.

It can influence the PK profile of antimicrobial drugs that are renally cleared, such as beta-lactams, vancomycin or aminoglycosides. Enhanced drug clearance leads to shorter half-life, lower C_{max}, and smaller AUC, thereby compromising their efficacy. There are several studies that have shown that the ARC has been significantly and consistently related to subtherapeutic beta-lactam and vancomycin levels. However, the impact of ARC on clinical outcome has not been studied adequately.

An increase in antimicrobial clearance can have negative consequences, but could be overcome with alternative dosing strategies that optimize drug exposure, such as higher daily dose, continuous/extended infusions or loading dose. Further studies are warranted in critically ill patients to explore the dosage adjustment based on the ARC.

CAPSULE SUMMARY

- Augmented renal clearance is defined as a creatinine clearance of (CrCl of >130 mL/minute/1.73 m^2.
- Around 20–65% of critically ill patients have ARC.
- Younger age group, polytrauma, and severity of illness have been identified as risk factors.
- Augmented renal clearance can influence the PK profile of antimicrobial drugs that are renally cleared, such as beta-lactams, vancomycin or aminoglycosides.

THERAPEUTIC DRUG MONITORING

Measurement of the concentration of a specific drug in serum or plasma in a designed interval is known as TDM. This is considered important for antibiotics wherein a strong relationship has been demonstrated between drug concentrations and clinical efficacy and/or toxicity, and more so if the drug shows high PK variability. TDM guides in customizing the optimal dosage of an antibiotic in a particular patient. In other areas where TDM is also useful are drug–drug interactions, compliance, and therapy cessation monitoring. Several methods have been used for

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measuring serum concentrations of antimicrobial agents, including bioassay, high-performance liquid chromatography (HPLC), and mass spectrometry.

Antimicrobial drugs, such as aminoglycosides, vancomycin, and some azole antifungals (voriconazole and posaconazole) show both significant PK variability and potential toxicity in the patients and in these cases, TDM is a valuable tool for the safe use of these drugs.

Aminoglycosides, such as gentamicin, amikacin, and tobramycin are commonly used antibiotics in children. Irreversible ototoxicity and nephrotoxicity in the form of renal tubular damage are associated with aminoglycosides. These antibiotics are excreted by the kidneys with a lot of interindividual variability. Hence, to prevent this toxicity from happening, TDM is performed at trough level which should be less than 2 mg/mL.

There is a challenge using vancomycin in the neonatal and pediatric patient populations due to the necessity for achieving a high concentration to maintain effective antimicrobial activity and its adverse effects profile. This drug is also renally cleared with significant inter-individual variability. Over the last decade, the recommended pediatric vancomycin dosages have increased as the conventional dosing regimens in children resulted in low initial trough concentrations, thereby leading to treatment failure. The pediatric-specific guidelines from the Infectious Diseases Society of America (IDSA) recommend targeting trough concentration more than 15 mg/mL in critically ill children and more than 10 mg/mL for all pediatric patients. In 2011, the adult guideline by the IDSA was revisited and pediatric-specific guidance was included. However, the authors acknowledged that their recommendation for a target trough concentration of 15–20 mg/mL in critically ill children required additional study and was supported by moderate evidence from respected authorities and expert opinions. In this context, TDM gives clinicians the opportunity to assess whether the drug dose is achieving the expected serum concentration or not. Critically abnormal serum trough concentrations should be followed by an appropriate dosing modification.

Voriconazole is a triazole antifungal administered both orally and intravenously with a high oral bioavailability. It is metabolized in the liver by the cytochrome (CY) P450 system and thus demonstrates significant interindividual variability. It is also susceptible to many drug–drug interactions. In case of voriconazole, concentration-effect, and concentration-toxicity relationships are consistently reported. In a prospective randomized controlled trial, outcomes in patients undergoing TDM (who had plasma concentration maintained between 1.0 mg/L and 5.5 mg/L) were significantly better (81%) than those in the non-TDM group (57%). It is, therefore, recommended to target a trough concentration of more than 1 mg/L for both prophylaxis and treatment of invasive fungal diseases. To reduce the risk of toxicity (visual disturbances, liver dysfunction, skin reactions, and neurotoxicity), the dosage should be adjusted to keep serum concentration less than 5.5 mg/L. The serum trough concentration should be measured within 7 days of initiation of therapy, or following dose adjustment.

In addition, there has been increased interest regarding the application of TDM for drugs used for tuberculosis and for beta-lactam drugs as well. Beta-lactam TDM would be helpful in patients who are critically ill, obese, elderly, cystic fibrosis or infected due to pathogens with high MICs.

CAPSULE SUMMARY

- Therapeutic drug monitoring refers to the measurement of the concentration of a drug in serum or plasma.
- It helps in customizing the dosage of an antibiotic for a patient.
- It is a valuable tool for antimicrobial drugs, such as aminoglycosides, vancomycin and some azole antifungals, all of which have both significant PK variability and potential toxicity.

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CONTINUOUS/EXTENDED INFUSION

In clinical practice beta-lactams antibiotics are very commonly used to treat various bacterial infections. Efficacy of these drugs is dependent on how long the concentrations of the drug remain above the MIC levels for the pathogen in the dosing interval (Fig. 3). This can be achieved either by shortening the dosing interval or prolonging the infusion time of the drug. Intermittent dosing regimens are associated with a high peak and low trough. Hence, the serum concentrations falls below the MIC and regrowth of bacteria occurs. So a better strategy is continuous infusion or extended infusion. When the infusion is prolonged for the entire dosing interval, then it is called as continuous infusion whereas when the infusion given for 40–50% of the dosing interval (3–4 hours), then it is known as extended infusion. The total daily milligram per kilogram dose of beta-lactam antibiotics used in continuous or extended infusion dosing is same as used for intermittent infusions. A strategy of administering high dose coupled with prolonged infusion should be adopted for patients infected with organisms having high MICs. However, the first dose should always be given as a bolus to ensure therapeutic levels are achieved quickly.

Evidence of better tissue penetration with continuous infusion into the lungs, subcutaneous tissue, and intra-abdominal tissue has been documented. There were potential clinical benefits associated with prolonged beta-lactam infusion in hospitalized adult patients as per a large meta-analysis comprising 29 studies. Prolonged infusion was associated with a reduction in mortality and improvement in clinical success rates compared with intermittent boluses. Studies have also suggested that giving meropenem as an infusion over 4 hours as against bolus doses reduces the risk of failure; a retrospective Japanese study also showed a significant difference

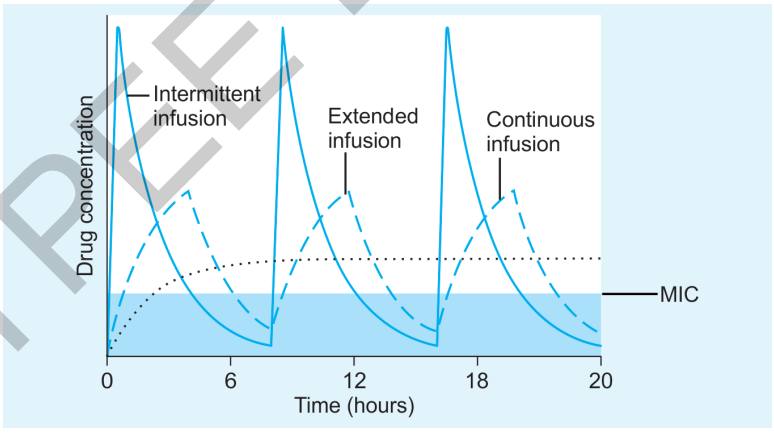

Fig. 3: Time above the minimum inhibitory concentration (MIC) for intermittent, extended and continuous infusion of time-dependent drugs. Extended or continuous infusion of time-dependent drugs can improve the percentage of the dosing interval time above MIC (T>MIC), particularly when treating infections with elevated MICs. Intermittent infusion (solid line), extended infusion (dashed line), and continuous infusion (dotted line) are compared with the time that each dosing regimen is below the MIC, highlighted by the grey area. Curves were generated using the same total daily dose and consistent pharmacokinetic parameters for each regimen.
Source: Downes KJ, Hahn A, Wiles J, et al. Dose optimisation of antibiotics in children: application of pharmacokinetics/pharmacodynamics in paediatrics. Int J Antimicrob Agents. 2014;43(3):223-30.

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in mortality. However, in children, there is need for a large, multicenter randomized controlled trial to determine whether there is a clinical benefit of this dosing strategy beyond the PK-PD advantages.

Despite the advantages, practical concerns associated with prolonged infusion should be taken into consideration. Some of these include the limited stability of beta-lactams at room temperature, availability of pump or infusion devices, limited IV access, compatibility issues with other drugs, and patient mobility. Therefore, the use of prolonged infusion should be considered based on patient factors and a clinical setting wherein the benefits outweigh the inconveniences.

Based on available evidence, prolonged infusion dosing of beta-lactam antibiotics in pediatric patients should be considered on a case-by-case basis. Patients who will benefit include those with serious gram-negative infections, such as meningitis, pneumonia, bacteremia, etc. those infected with pathogens with high MIC, and those with repeated exposure to antibiotics. Infants and children have increased clearance of beta-lactams compared to adults and, hence, may benefit from a prolonged infusion strategy.

CAPSULE SUMMARY

- The PK-PD characteristics of beta-lactams make them a suitable candidate for prolonged infusion.
- The infusion can be prolonged for the entire dosing interval (continuous infusion) or it can be extended to 40–50% of the dosing interval (3–4 hours).
- Continuous or extended infusion dosing of beta-lactam antibiotics is the same as the total daily milligram per kilogram dose used for intermittent infusions.

CONCLUSIONS

There are several proof-of-concept studies that have suggested that the application of PK-PD principles to the use of antibiotics results in improved efficacy and decreases the risk of resistance since the exposure to the antimicrobials is not suboptimal. However, one parameter that is important in this PK-PD relationship is the MIC of the offending pathogen. As newer antimicrobial agents are developed, investigating the PK-PD relationship has become an integral part of the drug development process. Knowledge of PK-PD principles is crucial when prescribing antibiotics in children, particularly when treating serious infections. Identifying the patients who will benefit the most from nontraditional dosing strategies is important. The foundation of antimicrobial stewardship is judicious antibiotic prescribing and an important component of this is PK-PD dose optimization.

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RATIONAL ANTIMICROBIAL PRACTICE IN PEDIATRICS

Treatment of infections is the most common clinical problem faced by pediatricians. Rational prescribing practices are crucial to ensure good clinical outcomes at low treatment costs with minimum risk of adverse effects and development of antimicrobial resistance. The book comprehensively discusses rational approach to antimicrobial therapy in Indian children.

The book is divided into four sections. The first section deals with basics of microbiology, as well as clinical pharmacology of antimicrobial drugs. The second section discusses basics of rational antimicrobial therapy and use of antimicrobials in various clinical settings from head to toe including central nervous system, respiratory tract, gastrointestinal tract, skin and soft tissue, bone and joint, etc. as well as treatment of tuberculosis, fungi, viruses, helminths, malaria and human immunodeficiency virus (HIV). The third section discusses antimicrobial therapy through various case scenarios to help the readers apply the principles discussed in their own clinical practices. The fourth section is a ready reckoner for antimicrobial doses, preparations, side effects and drug interactions.

Antimicrobial therapy is a very dynamic subject owing to new clinical data, evolving antimicrobial resistance and advent of new drugs. Hence, all chapters in this new edition have been revised to reflect these changes. The new edition also includes new chapters on antimicrobial resistance, basics of antimicrobial therapy including escalation and de-escalation, new drugs in the pipeline, intra-abdominal infections, brucellosis, rickettsial disease and infective endocarditis. All chapters have been written and revised by well-known academicians and an effort has been made to include the latest information and guidelines. It is hoped that this book will be a useful resource for both postgraduates and practicing pediatricians in India and South Asia.

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