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Current Scenario and Various Mechanisms of Antibiotic Resistance in Pediatric Infections – A Narrative Review

Mamta Naagar[1], Tanishq Gupta[2], Nishtha Loona[3], Karan Goel[4], Manish Kumar Maity[*5]

[1]Department of Pharmacy Practice, Geeta Institute of Pharmacy, Geeta University, Naultha - 132145, Panipat, Haryana, India

[2]Department of Psychiatry, Maharishi Markandeshwar College of Medical Sciences and Research, Sadopur - 134007, Ambala, Haryana, India

[3]Department of Dermatology, Punjab Institute of Medical Sciences, Jalandhar – 144006, Punjab, India

[4]Department of Pharmacology, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university), Mullana - 133207, Ambala, Haryana, India

[*5]Department of Pharmacy Practice, Chandigarh College of Pharmacy, Chandigarh Group of Colleges (CGC) - Landran, Mohali – 140307, Punjab, India

***Corresponding Author:**

Dr. Manish Kumar Maity

Email ID: manishkumarmaity@gmail.com

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ABSTRACT

The threat posed by antibiotic resistance to public health is critical, particularly with regard to children. Data from the World Health Organisation indicates that infections with bacteria resistant to several drugs result in 700000 fatalities annually, of which 200000 are infant mortality. There are several facets to this growing problem that are unique to children. For example, the dearth of pediatric-specific data and studies contributes to the harmful overuse and abuse of antibiotics (for incorrect diagnosis and indications, or at improper dose). Due to the constantly changing nature of this age group, there is an additional problem: the population's biochemical characteristics and pharmacokinetic profiles are rather diverse, making it difficult to codify in an age or weight dependent dosage due to the partially age dependent changes of a developing system of cytochromes. The paediatric population is particularly negatively impacted by congenital deformities that frequently necessitate recurrent hospital stays as well as medical and surgical interventions starting at a very early age, as well as the contraindications of tetracyclines and fluoroquinolones. MRSA, VRSA, ESBL producing Enterobacteriaceae, carbapenem resistant Enterobacteriaceae, and the concerning colistin resistance are emerging risks for paediatric patients. Reversing the trend of uncomplicated illnesses leading to baby deaths in the very likely post-antibiotic era will need immediate intervention.

Keywords: *multidrug resistance, antibiotic resistance, infections, antimicrobial stewardship*

INTRODUCTION

Antimicrobial resistance (AMR) is currently one of the biggest global risks to public health and should be given top consideration by all healthcare providers and organisations. In order to put the threat posed by AMR into perspective, the World Health Organisation (WHO) calculated that infections with multidrug resistant (MDR) bacteria cause 700000 fatalities globally annually, of which over 200000 are infant mortality [1]. Up to 30% of all cases in Europe may have MDR infections in paediatric patients [2]. 90% of newborns hospitalised in ICUs with sepsis in the Middle East had resistant bacteria [3], 83% of children in some parts of South East Asia have *E. Coli* resistant to first-line antibiotics [4], 66% of neonatal sepsis and meningitis in Sub-Saharan Africa were found to be caused by antibiotic-resistant bacteria [5], and 20% of paediatric patients receiving colistin to treat already-MDR Gramme negative bacteria developed resistance [6]. Multidrug-resistant organisms (MDROs) are becoming more common and they are linked to a high rate of morbidity and mortality in those who are impacted. MDR bacterial infections are more challenging to treat and are associated with more severe and protracted illness, which results in longer hospital stays (20% longer duration of stay) and worse outcomes, increasing mortality in MDR hospital-acquired infections by up to 40% [7-10]. This has a financial burden as well, with an estimated 2.39 billion

dollars being spent on treating MDR infections in the USA alone [11,12]. This has a significant influence on healthcare systems. There is a risk to our future from this troubling state of affairs, which has many interrelated and varied origins. Despite the fact that Alexander Fleming had alerted the scientific and medical world in 1945 to the dangers of antibiotic misuse, an age of antibiotic abuse in veterinary, pastoral and agricultural activities as well as human medicine began following World War II. The main cause of the emergence of bacterial resistance was this overuse [13, 14]. Furthermore, unneeded, unsuitable, or suboptimal prescriptions—which have been seen in 30% to 60% of antibiotic regimens given to both inpatients and outpatients in certain studies—contributed to the emergence of some MDR strains of bacteria [15,16]. The already rapid natural selection of MDROs is being sped further by these behaviours. If we take into account the amount of time that passes between the release of a new antibiotic onto the market and the emergence of MDROs for that medication, we can see that vancomycin has the longest duration of resistance (almost 16 years) among antibiotics. However, this period is reduced to just two years for penicillin and even to one year for ceftaroline and daptomycin, which are more modern drugs [17, 18]. This is especially true for children, who are frequently exposed to common infections and as a result to a selective antimicrobial pressure after the perinatal period. Without immediate action, we are heading towards a post-antibiotic era where common infections may once again be fatal. This is especially true for babies who haven't been born for a week or less, since their gastrointestinal tracts contain communities of multidrug-resistant bacteria, most likely via exposure to mother and ambient germs during and right after delivery [19, 20]. As to the WHO's assessment, drug-resistant illnesses may result in 10 million yearly fatalities if this trend is not reversed by 2050. This would entail an estimated $300 billion in losses to the gross domestic product and an annual cost to healthcare systems. By encouraging antimicrobial stewardship and preventing antibiotic overuse in all fields, we can lessen its cost on our society. We reviewed the state of paediatric AMR, new threats to it, and possible countermeasures since these were strong reasons.

1. **Causes of antibiotic resistance in Pediatric Populations -** Since children are more likely to contract infections of all kinds, from the less common meningitis to the more common urinary tract infections, children are known to take antibiotics more frequently than any other class of medication.

   1.1. Misuse of antibiotics - The primary factor contributing to the current rise in antibiotic resistance is inappropriate antibiotic usage [21, 22]. Lack of understanding of the microorganisms linked to various diseases as well as the pharmacokinetic and pharmacodynamic properties of the various antibiotic classes is the main cause of inappropriate antibiotic usage. These characteristics have a significant impact on medication selection, dosage accuracy, posology, and treatment course length. Furthermore, especially in outpatient treatment, antibiotics are still often recommended for incorrect diagnoses, such as viral infections [23-25]. For the first time, a multicenter retrospective cohort research provided comprehensive data on antibiotic usage in hospitalised neonates and children in 2012 to the Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) group. Analyses were conducted on almost 17000 paediatric hospital admissions in 226 institutions across 41 countries, of which 6499 inpatients received at least one antibiotic. They revealed that large rates of ESBL-producing or carbapenem-resistant Gram-negative bacteria were present in several areas, which may account for the excessive usage of broad-spectrum antibiotics in such areas. The high rate of empirical broad-spectrum antibiotic usage would suggest that part of this medication isn't necessary. Levy et al. also discovered this improper usage in paediatric wards and intensive care units (PICUs), which they linked to a failure to stop or de-escalate therapy [26]. Despite this, effective de-escalation of carbapenems has been documented in settings with lower resources and less consideration for de-escalation, as well as less frequent use of bacteriological cultures [27]. Additionally, the ARPEC study discovered that amikacin was used far more frequently in neonates admitted to hospitals in Western Europe, Southern Europe, Asia, and Latin America, and that meropenem was administered to Asian population on a startlingly large scale. On the other hand, hospitalised children (older than 28 days) showed a notable geographical variation in the prescription of antibiotics. The majority of children in Western Europe, Africa, Australia, and North America were still prescribed older narrow-spectrum antibiotics, such as gentamicin, amoxicillin, sulfamethoxazole/trimethoprim, and benzylpenicillin. Children were given more broad-spectrum antibiotics, mostly carbapenems and third-generation cephalosporins, in Asia, Eastern and Southern Europe, North and South America. It would appear that rich nations prefer to prescribe new-generation antibiotics, which have a wider range, whereas resource-constrained settings favour the empirical application of older, narrow-spectrum antibiotics.

   1.2. Dose Inappropriateness in young age - Pharmacological therapies that are suitable in terms of prescription, safety, posology, and effectiveness profiles should be provided to the paediatric population. This is particularly true when one considers the significant paediatric heterogeneity in pharmacokinetics (PK), which is partially dependent on age. There is a dearth of high-level evidence and strictly paediatric guidelines due to the lack of pediatric-specific clinical trials on antibiotics and the common practice of extrapolating adult pharmacokinetic and pharmacodynamics (PD) data, either fully or partially, to the paediatric population (with weight or body surface area as the only discerning indicator). To provide the highest quality of treatment to this significant group, dose-finding and safety paediatric studies remain essential, even in the face of the useful tool that is extrapolating pharmacological effectiveness data to the paediatric population. Extrapolation as a practice and a dearth of

pediatric-specific clinical studies on antibiotics frequently result in antibiotic misuse, over- or under-dosage, and a corresponding risk of toxicity as well as the emergence of pediatric-specific antibiotic-resistant bacterial strains. Specifically, the wide range of paediatric age groups—from preterm to neonates, from babies and children to adolescents—contributes to the complicated diversity of PK. Although age-related physiologic development persists throughout infancy and adolescence, neonates and babies exhibit the most notable variations when compared to adults. This is especially true in light of kidney function, which has been shown to be highly varied and age-dependent: during the first two weeks of life, the glomerular filtration rate rises fast, and then it climbs gradually until 8–12 months of age, when adult values are achieved [28]. Furthermore, throughout the first year of life, tubular secretion matures from an immature state at birth to an adult function. There is a direct correlation between the developmental variability of kidney function and the wide range of medication clearance observed during childhood. There have been suggestions for ways to reduce paediatric dosage, avoid moral dilemmas, and deal with particular paediatric challenges while conducting studies on this group [29]. When dealing with such a particular age range, there are additional practical considerations that need to be made. Indeed in recent years developmental pharmacology has made significant strides, offering more precise insights into how maturation affects antibiotic absorption, excretion and effects. However, further research is required to fully comprehend PK and PD in the paediatric population in order to prescribe antibiotics in a way that meets the highest standards of care, particularly for kids with underlying medical issues. For this group in particular, the population pharmacokinetic–pharmacodynamics technique works well since it only needs a small number of samples per patient at flexible periods [29]. It describes the distinctions between individuals as well as the typical behaviour of a homogenous community. Regulatory bodies have generally supported the use of the population PK–PD technique on this population, and the Food and Drug Administration (FDA) and European Medicines Agency (EMA) Guidance Documents provide extensive details on this approach [30, 31]. Physiologically based pharmacokinetic (PBPK) model is another suggested strategy to characterise drug absorption, effects, and PK in this group; it is a potential tool to help paediatric first-dose investigations [32]. The physiological processes of child development are combined with adult PK data in this model. To do this, adult PK parameters and pediatric-specific data on the anatomical, physiological, and biochemical variables from birth to 18 years of age are needed. It has been suggested that PBPK models be used in paediatric clinical trial design and to facilitate children's first-time dosing [33, 34]. Further study on the development of drug metabolising enzymes, transporters, receptor systems, and disease course is still desperately needed, even with the recent advancements in developmental pharmacology. The growing body of information regarding paediatric developmental physiology will enable more accurate, safe and effective pharmacological prescriptions for children.

1.3. Contraindications among children – It is also important to remember that many antibiotics have specific age-related contraindications, which limits the variety of antimicrobial treatments available for illnesses. For example, due to safety concerns, fluoroquinolones are still mainly avoided in pediatric medicine. These drugs have caused inflammation and disturbance of weight-bearing joints, which have shown irreversible detrimental effects on cartilage formation in young animals [35, 36]. Since these occurrences have been clearly shown in several pediatric trials comparing fluoroquinolones to non-fluoroquinolone therapies, the use of fluoroquinolones in treating children has been restricted due to the possibility of these severe arthropathies. The tendency of fluoroquinolones to induce bacterial resistance is another issue with their usage. Fluoroquinolone resistance patterns have been considerably worse in the last 25 years in adults, and with continued usage, they may pose a serious risk to children as well. Despite this, fluoroquinolones have been effectively used to treat a range of pediatric illnesses, including exacerbations of cystic fibrosis. However, the majority of the research supporting the use of fluoroquinolones in children comes from small, uncontrolled trials or retrospective investigations. The pros and cons of this antibiotic treatment need to be carefully considered. Fluoroquinolones were advised by the American Academy of Pediatrics (AAP) in 2006, but only in three main situations:

(a) FDA-approved indications;

(b) MDROs without a safe or effective alternative; and

(c) Oral fluoroquinolone sensitivity when intravenous treatment is the sole choice.

Pediatric patients with lower respiratory tract infections, pneumonia, sinusitis, gastrointestinal infections, acute otitis media or Mycobacterium infections may be evaluated for them [37]. Tetracyclines are an example of another family of antibiotics that is mainly ignored in pediatric medicine. When tetracyclines were initially released in 1948, there were already some concerns about tooth discolouration in children, according to a study conducted in 1956 [38]. Since this occurrence is more likely to happen during the tooth-calcification process, which is finished by the age of eight [39], children younger than eight years old should generally avoid using this class of antibiotics. Tetracyclines have been effectively used in older children to treat respiratory infections, acne, malaria, and community-acquired *S. aureus* resistant to methicillin (MRSA). Notably, tetracycline-induced photosensitivity is another side effect that should be noted. This often appears as a photosensitive rash that resembles severe sunburn. While tooth discolouration is a good enough reason to steer clear of prescribing these

antibiotics for young children whenever feasible, phototoxicity can pose a serious risk. When using tetracycline is necessary, there is little evidence to support the idea that using doxycycline, a tetracycline with a reduced calcium binding capacity, and reducing the overall dose and duration of exposure can lessen the risk of tooth discolouration. Tetracycline should be used for pediatric infections when the advantages exceed the potential drawbacks, according to the American Academy of Pediatrics (AAP). They recommend giving doxycycline since it has a lower risk of tooth staining with fewer frequent posology intervals and is indicated for rickettsial infections, cholera and anthrax [40].

1.4. Biofilms and Chronic Conditions: Two Contemporary Issues that Predispose to Infection - Because the bacteria stick to the injured tissue or implanted medical device, biofilms are linked to recurrent infections that are persistent and have an innate resistance to antibiotic treatment. Instead of using aggressive virulence, bacteria in biofilms survive by adopting a tenacious survival strategy. Although biofilm infections are seldom lethal, they can persist for months or even years and are frequently unaffected by antibiotic therapy. Since biofilm infections need large antibiotic dosages over extended periods of time, treatment of these illnesses frequently fails. Antimicrobial resistance mechanisms that are now understood, including target mutations, enzyme modifications, and efflux pumps, do not appear to be connected to the defense mechanisms of bacteria within biofilms. Indeed bacteria that are released from biofilm typically exhibit antibiotic sensitivity, indicating that the unique environment this cell film produces may confer an innate resistance to antibiotics. Three basic theories might account for this phenomenon, since most occurrences of antibiotic-resistant biofilm infections remain unexplained by conventional antibiotic resistance mechanisms. Three theories explain antibiotic resistance: the first postulates that the antibiotic may enter the biofilm slowly or incompletely [41], the second is dependent on a changed chemical microenvironment within the biofilm [42], and the third theory is that a subpopulation of bacteria within a biofilm may change into "persister cells," which are highly protected phenotypes. A subset of bacterial cells known as persister cells is momentarily resistant to antibiotics. They frequently exhibit sluggish or stopped development and can resume growth following extreme stress. They are connected to an elevated risk of AMR and recurrent, persistent bacterial infections [43]. Children have been observed to be great biofilm hosts. Medical devices ranging from basic central venous catheters to intricate heart defect patches and ventriculoperitoneal shunts are administered to them. Almost impenetrable by antibiotics, these devices can be a dangerous haven for germs and biofilms. These might put people at risk for chronic infections, which occasionally can only be completely cured by taking the device out and replacing it. In general, biofilms are linked to a significant percentage of pediatric infections—even when there is no biomedical equipment present. Children with recurrent middle ear and upper respiratory infections have also had biofilms discovered in their nasopharynx, which may help to explain why antibiotic treatment often proves ineffective in these situations [44]. Biofilms in particular have been identified as the cause of recurrent acute otitis media and otitis media with effusion. This finding may be explained by the fact that otitis media with effusion is highly recurrent, frequently presents with a negative culture despite positive molecular research for pathogens, and is frequently antibiotic-resistant. Furthermore, compared to children with no underlying medical condition or children with acute rhinosinusitis, children with chronic rhinosinusitis are more likely to develop biofilms. In fact, mature biofilms were discovered in 95% of the adenoids removed from these children [45]. Chronic diseases like cystic fibrosis (CF) are linked to significant morbidity and early mortality because of recurrent acute and chronic infections. These infections can arise from the specific pathophysiology of the disease, or they can result from frequent and extended hospital stays because the long-term use of multiple antibiotics raises the risk of multidrug resistance (MDR). Because various bacteria employ type VI secretion systems to mediate interbacterial competition, pediatric CF patients appear to host distinct opportunistic infections than adult CF patients [46]. This may help to explain the rise of AMR and has an effect on the use of antibiotics in both adult and pediatric CF patients.

1.5. Emerging Threats - A list of microorganisms for which new antimicrobials are desperately required was recently released by the WHO [47]. This stems from the finding that, in stark contrast to the alarming growth in resistance diseases, the R&D pipeline for novel antibiotics is gradually depleting. Research and development (R&D) on oral formulations for community-acquired illnesses with high morbidity, such as drug-resistant Enterobacteriaeceae, Neisseria gonorrhoeae, and Salmonella typhi, is desperately needed for the pediatric population. In adult patients, MRSA strains were initially recognized as a danger in the 1960s. Before the 1990s, MRSA infections in children were rare. At that time, resistant strains of the virus were identified in infections in adults and children without a history of predisposing factors or contact with healthcare facilities [48]. Consequently, community-acquired MRSA (CA-MRSA) and healthcare-acquired MRSA (HA-MRSA) started to spread simultaneously [49]. When treating CA-MRSA, trimethoprim-sulfamethoxazole and clindamycin are frequently utilized. While resistance to trimethoprim/sulfamethoxazole is rare, resistance to clindamycin has grown over the last 10 years [49]. The injection of mupirocin ointment into anterior nares has been used, frequently in conjunction with chlorhexidine baths, to assist remove MRSA carriage and restrict its spread. However, since these practices began, resistance to both mupirocin and chlorhexidine has arisen [50]. Though the first strain of vancomycin-intermediate susceptible Staphylococcus aureus (VISA) was isolated from a

surgical wound of a Japanese child in 1997, whose infection did not respond well to long-term vancomycin therapy, vancomycin has long been thought of as the last resort for treating MRSA infections [51]. Since then, the therapy of anti-MRSA bacteria has been clouded by vancomycin resistance, particularly for the children whose treatment options—daptomycin and linezolid—remain limited. Daptomycin binds surfactant, causing its deactivation; hence it is useless for treating lung infections [52].

Children's ESBL-Ent infections have significantly increased in the United States, and this rise has been linked to the proliferation of E. coli strains that produce MDR ST131 CTX-M [54]. There is a lot of variation in the acquisition of ESBL-Ent based on the ESBL genotype, organism, age, healthcare exposure, and country. International research conducted in hospital environments has shown that ESBL-Ent colonization is on the rise; risk factors for this group include low birth weight, extended mechanical ventilation, use of antibiotics, and shorter gestational age [55]. While neurological illnesses may be a predisposing risk typical of the pediatric population, outside of the newborn age, risk factors for ESBL-Ent infections are similar to those of adults, including antibiotic usage, chronic clinical problems, healthcare access and recurrent infections [56, 57]. Piperacillin-tazobactam, ceftazidime-avibactam, cefepime, aminoglycosides, tigecycline, fosfomycin, and carbapenems are among the therapeutic choices for ESBL-Ent; however, their safety profiles and sometimes ambiguous dose recommendations restrict their use in youngsters. Furthermore, in order to prevent misuse of carbapenems, techniques for sparing them should be considered first. If at all feasible, a step-down approach should be used following empirical therapy. Reduced susceptibility to carbapenems may result from downregulated porins, ESBL synthesis, or the β-lactamases carbapenemases, which hydrolyze penicillins (cephalosporins, carbapenems, and monobactams). Pediatric populations' resistance to carbapenems has been reported to have increased rapidly in recent decades. The 2013 CDC study addressed this concern as urgent, noting that hospitalized children with bloodstream CRE infection had a 50% death rate [16]. Particularly for the Enterobacter species, there was a notable rise in CRE frequency in some pediatric groups from 0% in 2000 to 4.5% in 2012, particularly in intensive care units [58]. There are few therapeutic options for CRE and even fewer for pediatric patients: Due to its safety profile, tigecycline use is carefully considered for individuals under the ages of 18 years. The pediatric population should take colistin and other polymyxins at the recommended dosage; oral fosfomycin can be used for CRE bladder infections, but dosing guidelines are only available for older children and adolescents [59]. Furthermore, ESBL-Ent and carbepenemase-producing bacteria are considered to be real MDROs because they frequently have additional plasmid-transmitted genes that confer resistance to aminoglycosides, sulfonamides and fluoroquinolones [60].

Clinicians were forced to reevaluate outdated, underutilized antibiotics like fosfomycin and more intriguingly colistin in the mid-1990s due to the emergence of multidrug resistant (MDR) Gram-negative bacteria and a decline in the manufacturing of new antimicrobials targeted against them [61]. Due to concerns of nephrotoxicity and neurotoxicity, colistin was soon supplanted in the 1970s with safer, more modern parenteral antibiotics [62]. When colistin was reintroduced in clinical pediatrics as salvage therapy for hard-to-treat MDR Gram-negative infections, patterns of resistance were for the first time noticed and reported. Prior to this, resistance to colistin had hardly been documented, and resistance mechanisms remained unknown [63]. Although there have previously been reports of a chromosomally encoded resistance to colistin, throughout the last ten years, more information has been provided on intrinsic mutations or adaptive mechanisms, as well as the identification of the mcr-1 gene that confers resistance by plasmid transfer [64]. In summary, since colistin is one of the very few medications that effectively combat carbapenem-resistant Gram-negative bacteria; its activity needs to be maintained. To do this, it should only be used in extremely few clinical practice circumstances, taking into account its complex PK and restricted therapeutic window, particularly when it comes to pediatric patients.

2. **Future Perspective -** Implementing an antimicrobial stewardship plan in acute care, long-term care, and outpatient care settings is a necessary first step towards controlling antimicrobial resistance (AMR). The definition of antimicrobial stewardship is "coordinated interventions designed to promote the selection of the optimal drug regimen, including dosing, duration of therapy, and route of administration, in order to improve and measure the appropriate use of antibiotic agents" [65]. Therefore, the following measures need to be taken in a pediatric setting to prevent the onset of AMR and reverse the current trend :
    (a) The establishment of an institutionalized team of experts composed of pediatricians, clinical pharmacologists, infectious disease specialists, and microbiologists who can develop local recommendations, offer guidance on the use of antibiotics, and carry out educational activities;
    (b) Monitoring and checking (i.e, auditing) local antimicrobial prescriptions on a regular basis;
    (c) Pharmacodynamics and pharmacokinetic-guided dosage, taking into account the child's physiological development processes.

Regarding the final issue, precise dosage is crucial in children, particularly when it comes to antimicrobial therapy. Clinical practice should incorporate the use of software that can predict the appropriate dosage based on the characteristics of the specific drug, changes in pharmacokinetic and pharmacodynamic properties during development according to the maturation stage, and the real clinical state of the newborn, infant, or child. Accordingly, it is advised to work "into finding markers

correlated to maturation-related changes in pharmacokinetics, making individualization of the dose possible between individuals, as well as within an individual over time" in the EMA Guidelines on the role of pharmacokinetics in the development of medicinal products in the pediatric population [66]. Antibiotic overuse and abuse are mostly caused by empirical treatments: 50% of antibiotic therapy is initiated incorrectly and without a proper diagnosis of the causative agent [13]. Antimicrobial susceptibility testing (AST) must be completed promptly and accurately in order to prevent the spread of antimicrobial resistance (AMR) and to select the appropriate antimicrobial medication at the appropriate time. A prompt diagnosis is crucial for the proper management of infectious diseases. As of the now, technological advancements are encouraging the use of fresh diagnostic instruments for quick AST. Validation is being done on apparatus and procedures utilizing nucleic acid amplification that combine mass spectrometry with biosensor-based AST. Furthermore, third-generation whole genome sequencing (WGS) technologies are available in the majority of sophisticated diagnostic facilities and may be used to swiftly detect infections and screen for genes related to medication susceptibility [67]. For antimicrobials to be managed optimally, a fast analysis that can determine the etiological agent and provide answers for susceptibility testing is necessary. In order to get the proper concentrations and prevent the establishment and spread of antibiotic resistance, it is also crucial to determine the optimal antimicrobial dosage based on customized pharmacokinetic characteristics. This is especially true when it comes to pediatrics, where pharmacokinetic variability needs to be carefully taken into account and intervention time is crucial.

A few novel antibiotics, such ceftaroline [68,69] and ceftazidime/avibactam [70], have been licensed for use in pediatric patients as part of the clinical arsenal to combat multidrug-resistant infections. Additional clinical studies are required to validate the efficaciousness of other new antibiotics, such as ceftolozane/tazobactam [71], tedizolid [72], and dalbavancin [73], which are exhibiting intriguing results in the pediatric population. Specifically, pharmacokinetics investigations should be conducted in addition to safety and effectiveness trials to identify the optimal dosing regimen for different age groups rather than assuming adult doses. This will enable us to use the right dosage, preventing the development of new resistances and protecting the limited number of new weapons we have available. Furthermore, even for outdated medications those are resurfacing in wards as a potential defense against MDR infections, the scientific community as a whole ought to be dedicated to doing pharmacokinetic research in pediatric populations. Furthermore, it is imperative to firmly urge pharmaceutical companies to involve children in clinical studies related to the pharmacological development of novel antibiotics.

DISCUSSION AND CONCLUSION

Antibiotic resistance poses a global concern, increasing the likelihood of a post-antibiotic period in which easily curable illnesses would once again claim the lives of children. From a comprehensive viewpoint, the causes include specific pediatric difficulties such the evolving nature of this heterogeneous population, the paucity of trials on children, the irresponsible prescribing of antibiotics for incorrect diagnoses, and the restricted alternatives. Since the advent of antibiotics into medicine, a relatively new issue has arisen that requires innovative solutions. These could include the establishment of new clinical teams to prescribe antibiotics in wards, the use of software that can analyze numerous factors and return a specific medication and dosage, the use of rapid antimicrobial susceptibility tests to guide empirical therapy, the promotion of the use of novel antibiotics, and the preference for including children in trials for both old and new medications.

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