RESEARCH PAPER

ANTIMICROBIAL STEWARDSHIP IN NEONATAL AND PEDIATRIC CARE: BALANCING INFECTION CONTROL AND RESISTANCE

DR. BENU MOIRANGTHEM[1*], DR. S.S PRASAD[2], DR. ADITI GUPTA[3]

[1]Junior Resident 3, Department of Paediatric, MM Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India

[2]Professor and HOD, Department of Paediatric, MM Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India

[3]Junior Resident 3, Department of Paediatric, MM Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India

***Corresponding Author: DR. BENU MOIRANGTHEM, Junior Resident 3, Department of Paediatric, MM Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India**

Email: benumoirangthem@gmail.com

ABSTRACT

Antimicrobial stewardship (AMS) has become a cornerstone of modern neonatal and pediatric healthcare due to the increasing prevalence of antimicrobial resistance (AMR) and the widespread use of antibiotics in hospitalized children and neonates. Neonates admitted to neonatal intensive care units (NICUs) and critically ill pediatric patients frequently receive empirical broad-spectrum antibiotics because of the high risk of sepsis and the often non-specific clinical presentation of infections. However, unnecessary or prolonged antimicrobial exposure contributes to the emergence of multidrug-resistant organisms, disruption of the developing microbiome, increased healthcare costs, and adverse clinical outcomes. AMS programs aim to optimize antimicrobial therapy through evidence-based prescribing, appropriate drug selection, dosage optimization, timely de-escalation, and limitation of treatment duration. Recent advances, including rapid molecular diagnostics, antimicrobial surveillance systems, electronic decision-support tools, and biomarker-guided therapy, have improved the ability to distinguish bacterial infections from non-infectious conditions and facilitate rational antibiotic use. Effective stewardship requires multidisciplinary collaboration among pediatricians, neonatologists, microbiologists, pharmacists, infection-control specialists, and nursing staff. This review summarizes the principles of antimicrobial stewardship in neonatal and pediatric settings, discusses current resistance patterns, highlights rational prescribing strategies, and explores emerging technologies and future directions that may enhance infection management while minimizing antimicrobial resistance.

Keywords: Antimicrobial stewardship, neonatal intensive care unit, pediatric infections, antibiotic resistance, antimicrobial resistance, rational prescribing, neonatal sepsis, pediatric antimicrobial therapy, infection control, antibiotic optimization.

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INTRODUCTION

Antimicrobial agents have transformed the management of infectious diseases and continue to be among the most frequently prescribed medications in neonatal and pediatric healthcare. The substantial decline in morbidity and mortality associated with bacterial infections over the past century has been largely attributed to the availability and effective use of antibiotics. In neonatal intensive care units (NICUs) and pediatric wards, antimicrobial therapy remains indispensable for the management of sepsis, pneumonia, meningitis, urinary tract infections, and numerous other potentially life-threatening infections. Despite these benefits, the increasing and often inappropriate utilization of antibiotics has significantly accelerated the emergence of antimicrobial resistance (AMR), which is now recognized as one of the most serious global public health challenges of the twenty-first century.[1]

Neonates and children represent a uniquely vulnerable patient population in whom the diagnosis of infection is frequently difficult because clinical manifestations are often subtle, nonspecific, or rapidly evolving. Consequently, empirical broad-spectrum antimicrobial therapy is commonly initiated before microbiological confirmation becomes available. Although this approach is frequently lifesaving, unnecessary or prolonged antibiotic exposure may disrupt the developing gut microbiome, increase the incidence of adverse drug reactions, facilitate colonization by multidrug-resistant organisms, and contribute to rising healthcare expenditures.[2,3] The extensive use of antibiotics in NICUs is particularly concerning, as preterm and low-birth-weight infants are highly susceptible not only to severe infections but also to the harmful consequences associated with excessive antimicrobial exposure.[4]

Antimicrobial resistance has become a critical healthcare challenge across both developed and developing nations. Pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Gram-negative bacilli, and multidrug-resistant *Pseudomonas aeruginosa* are increasingly encountered in neonatal and pediatric healthcare environments.[5] Infections caused by these resistant organisms are associated with prolonged hospital stays, therapeutic failures, increased healthcare costs, and higher mortality rates. Furthermore, the slow pace of new antimicrobial drug development highlights the urgent necessity of preserving the effectiveness of currently available agents through rational and evidence-based prescribing practices.[6]

Antimicrobial stewardship (AMS) has emerged as a comprehensive and evidence-based strategy designed to optimize antimicrobial utilization while ensuring the best possible clinical outcomes for patients. The principal goals of AMS include selecting the most appropriate antimicrobial agent, dose, route of administration, and duration of therapy; minimizing unnecessary antibiotic exposure; reducing adverse drug events; and limiting the development and spread of antimicrobial resistance.[7] Within neonatal and pediatric populations, stewardship interventions must be adapted to age-specific pharmacokinetic and pharmacodynamic characteristics, developmental physiology, disease epidemiology, and local antimicrobial susceptibility patterns.[8]

Successful antimicrobial stewardship programs require coordinated multidisciplinary collaboration involving pediatricians, neonatologists, infectious disease specialists, clinical pharmacists, microbiologists, infection prevention teams, nursing personnel, and hospital administrators. Core stewardship strategies include prospective audit and feedback, formulary restriction and preauthorization, implementation of evidence-based treatment guidelines, optimization of diagnostic testing, timely de-escalation of therapy according to microbiological results, and continuous surveillance of antimicrobial consumption and resistance patterns.[9] Recent advances in rapid molecular diagnostics, biomarker-guided treatment approaches, electronic prescribing platforms, and antimicrobial utilization monitoring systems have further strengthened clinicians' ability to make timely, precise, and informed therapeutic decisions.[10]

In an era characterized by escalating antimicrobial resistance, achieving an appropriate balance between effective infection management and responsible antibiotic prescribing has become a fundamental objective of neonatal and pediatric healthcare. Antimicrobial stewardship serves as a critical framework for improving patient outcomes, preserving the long-term efficacy of existing antimicrobial agents, minimizing the emergence of resistant pathogens, and ensuring sustainable infection management for future generations.[11]

METHODOLOGY

This narrative review was conducted through a comprehensive search of peer-reviewed literature available in PubMed, Scopus, Web of Science, the Cochrane Library, Google Scholar, publications of the World Health Organization (WHO), reports from the Centers for Disease Control and Prevention (CDC), and international pediatric infectious disease guidelines. The search strategy employed keywords both individually and in combination, including antimicrobial stewardship, neonatal sepsis, pediatric infections, antibiotic resistance, neonatal intensive care unit (NICU), pediatric intensive care unit (PICU), rational antibiotic prescribing, antimicrobial surveillance, rapid diagnostics, and pediatric antimicrobial therapy. Eligible studies included English-language publications involving neonates, infants, children, and adolescents, encompassing randomized controlled trials, cohort studies, systematic reviews, meta-analyses, clinical practice guidelines, and expert consensus statements published between 2015 and 2025. Studies exclusively involving adult populations, non-peer-reviewed reports, case reports with limited generalizability, and duplicate publications were excluded. Relevant articles were screened for methodological quality and relevance to the review objectives. Data were extracted and synthesized qualitatively to provide a comprehensive overview of current evidence on antimicrobial stewardship interventions, antibiotic utilization patterns, emerging resistance mechanisms, surveillance strategies, rapid diagnostic technologies, and future directions for optimizing antimicrobial use in neonatal and pediatric healthcare settings.

Literature Review

Burden of Antibiotic Use in Neonatal and Pediatric Settings

Antibiotics continue to be among the most commonly prescribed medications in neonatal and pediatric healthcare and remain fundamental to the prevention and treatment of bacterial infections across both hospital and community settings. While their therapeutic value is unquestionable, accumulating evidence indicates that antibiotic utilization in children is frequently excessive, particularly within neonatal intensive care units (NICUs), where empirical antimicrobial therapy is routinely initiated for suspected sepsis before definitive microbiological confirmation is obtained.[12] Numerous investigations have reported that a large proportion of hospitalized neonates receive empirical antibiotics during the first few days of life despite subsequently negative blood culture results, reflecting the considerable diagnostic uncertainty that surrounds neonatal infections.[13] The combination of ampicillin and gentamicin remains the standard empirical regimen for suspected early-onset neonatal sepsis because of its broad activity against common neonatal pathogens, established efficacy, and acceptable safety profile.[14]

Several factors contribute to the high burden of antibiotic prescribing in neonatal and pediatric practice. These include the nonspecific nature of clinical manifestations such as respiratory distress, temperature instability, lethargy, feeding intolerance, and apnea; difficulties in distinguishing bacterial infection from noninfectious conditions; delays in obtaining culture results; limited access to highly sensitive rapid diagnostic technologies; and concerns regarding the potentially catastrophic consequences of untreated sepsis.[15] In addition, medicolegal considerations and the desire to avoid missing serious infections often encourage precautionary prescribing behavior. Clinicians are frequently compelled to initiate antimicrobial therapy promptly because delayed treatment in critically ill neonates and children has been associated with worse clinical outcomes and increased mortality.[16] As a result, many infants and children continue receiving antibiotics despite the absence of microbiological evidence of bacterial infection, leading to prolonged antimicrobial exposure and unnecessary drug utilization. Recent systematic reviews have demonstrated an increasing dependence on broad-spectrum antimicrobial agents in NICUs and pediatric intensive care units (PICUs), reflecting a clinical tendency to prioritize immediate therapeutic intervention over diagnostic certainty in order to reduce the likelihood of missed invasive infections.[17] These prescribing practices highlight the critical need for effective antimicrobial stewardship programs capable of ensuring timely treatment while simultaneously reducing unnecessary antimicrobial exposure and limiting the emergence of resistance.

Impact of Excessive Antibiotic Exposure

Microbiome Disruption

The neonatal period represents a crucial phase of physiological development during which the infant microbiome is established and undergoes rapid maturation. The gastrointestinal microbial community plays an essential role in immune regulation, nutrient metabolism, maintenance of intestinal barrier integrity, and protection against pathogenic microorganisms. Exposure to antibiotics during this sensitive developmental window can profoundly alter microbial composition, reduce microbial diversity, and induce persistent dysbiosis.[18] Disturbance of the normal intestinal microbiota has been associated with a wide range of adverse health consequences that may extend well beyond infancy. Growing evidence suggests that early antibiotic exposure contributes to an increased risk of necrotizing enterocolitis (NEC), one of the most serious gastrointestinal emergencies affecting preterm infants, through disruption of beneficial microbial colonization and promotion of intestinal inflammation.[18]

Furthermore, antibiotic-induced dysbiosis has been associated with a greater incidence of allergic disorders, including atopic dermatitis, food allergies, allergic rhinitis, and asthma, as well as other immune-mediated diseases.[19] Long-term observational studies have also reported associations between early-life antibiotic exposure and an increased risk of childhood obesity, metabolic syndrome, insulin resistance, inflammatory bowel disease, and alterations in neurodevelopmental outcomes.[19] These findings underscore the extensive and potentially lifelong consequences of microbiome disruption during critical developmental stages and emphasize the importance of limiting unnecessary antibiotic administration whenever clinically appropriate to preserve microbial diversity and promote optimal health outcomes.

Development of Antimicrobial Resistance

Among the most serious consequences of excessive antibiotic utilization is the emergence and dissemination of antimicrobial resistance (AMR). Repeated or prolonged exposure to antimicrobial agents creates selective pressure that favors the survival, proliferation, and transmission of resistant microorganisms while eliminating susceptible bacterial populations.[20] This evolutionary process has contributed substantially to the growing prevalence of multidrug-resistant pathogens within NICUs, PICUs, and pediatric inpatient units worldwide. Resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Gram-negative bacilli, and multidrug-resistant *Pseudomonas aeruginosa* are increasingly implicated in healthcare-associated infections among children.[20]

The clinical and economic consequences of antimicrobial resistance are considerable and include therapeutic failure, prolonged hospitalization, increased utilization of intensive care services, higher healthcare costs, greater dependence on reserve antimicrobial agents, and elevated mortality rates.[21] In addition, infections caused by resistant pathogens frequently require prolonged treatment courses, complex supportive interventions, invasive procedures, and extensive infection-control measures, thereby imposing a substantial burden on healthcare systems globally. Contemporary estimates indicate that antimicrobial resistance is responsible for millions of deaths and disability-adjusted life years worldwide each year and poses a significant threat to numerous advances in modern medicine, including neonatal intensive care, organ transplantation, cancer chemotherapy, and major surgical interventions.[21] These challenges reinforce the urgent need for comprehensive antimicrobial stewardship initiatives focused on optimizing prescribing practices, reducing inappropriate antibiotic exposure, and safeguarding the effectiveness of existing antimicrobial agents for future generations.

Common Pathogens in Neonatal and Pediatric Infections

Neonatal Infections

Neonatal infections continue to represent a major cause of morbidity and mortality worldwide, particularly among preterm and low-birth-weight infants. The spectrum of causative organisms varies according to geographic location, healthcare environment, and the timing of infection onset. Common pathogens implicated in neonatal sepsis and other invasive neonatal infections include Group B *Streptococcus* (GBS), *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and *Pseudomonas aeruginosa*.[31] Early-onset neonatal sepsis is most commonly associated with vertical maternal transmission of GBS and *E. coli*, whereas late-onset sepsis is more frequently linked to healthcare-associated pathogens such as CoNS, *Klebsiella* species, and *S. aureus*.[32] The growing prevalence of antimicrobial resistance among neonatal pathogens has complicated empirical treatment strategies and underscores the importance of continuous surveillance of local microbiological epidemiology and susceptibility patterns.[33]

Pediatric Infections

In older infants and children, the etiological profile of infectious diseases differs according to age group, immunization status, underlying medical conditions, and the anatomical site of infection. Commonly encountered pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* species, and *Mycoplasma pneumoniae*.[34] *Streptococcus pneumoniae* remains a leading cause of community-acquired pneumonia, acute otitis media, sinusitis, and bacterial meningitis, whereas *Haemophilus influenzae* continues to contribute to respiratory tract infections despite the success of widespread vaccination programs.[35] *Escherichia coli* is the predominant pathogen responsible for pediatric urinary tract infections, while *Salmonella* species remain important causes of enteric fever and invasive gastrointestinal disease in many low- and middle-income countries.[36] In addition, atypical pathogens such as *Mycoplasma pneumoniae* are increasingly recognized as significant causes of respiratory tract infections among school-aged children and adolescents.[37] An understanding of local pathogen prevalence, resistance profiles, and epidemiological trends is essential for selecting appropriate empirical antimicrobial therapy, minimizing unnecessary broad-spectrum antibiotic exposure, and improving patient outcomes through evidence-based stewardship practices.[38]

Current Resistance Patterns

Recent international surveillance studies have documented a concerning increase in antimicrobial resistance among pathogens responsible for neonatal and pediatric infections, creating substantial challenges for clinical management and infection-control practices.[39] The rising prevalence of resistant microorganisms has reduced the effectiveness of many commonly prescribed empirical therapies and increased dependence on broad-spectrum and reserve antimicrobial agents. Resistance among Gram-negative organisms has become particularly problematic within neonatal intensive care units (NICUs) and pediatric intensive care units (PICUs), where vulnerable patients often require prolonged hospitalization, invasive procedures, and repeated antimicrobial exposure.[40]

Major resistance mechanisms include the production of extended-spectrum β-lactamases (ESBLs), which confer resistance to penicillins and third-generation cephalosporins; carbapenemase production resulting in carbapenem resistance; aminoglycoside-modifying enzymes causing aminoglycoside resistance; and the emergence of multidrug-resistant Enterobacterales exhibiting resistance to multiple antimicrobial classes simultaneously.[41] Contemporary surveillance data from neonatal sepsis cohorts have reported aminoglycoside resistance rates ranging from 20% to 45%, third-generation cephalosporin resistance rates between 15% and 35%, and a growing burden of carbapenem-resistant Gram-negative organisms, which now account for a significant proportion of neonatal and pediatric Gram-negative infections worldwide.[42] These resistant pathogens are associated with delays in appropriate therapy, prolonged hospitalization, increased healthcare expenditures, greater resource utilization, and higher mortality rates.[43]

Resistance among Gram-positive organisms has also evolved considerably, with increasing reports of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate *Staphylococcus aureus* (VISA), and resistant *Enterococcus* species in both community-acquired and healthcare-associated infections.[44] MRSA remains an important cause of skin and soft tissue infections, pneumonia, bloodstream infections, osteoarticular infections, and surgical site infections in children, whereas vancomycin-resistant enterococci substantially limit therapeutic options for severe invasive disease.[44] The emergence of multidrug-resistant Gram-positive pathogens further complicates empirical treatment decisions and highlights the importance of ongoing microbiological surveillance. Recent surveillance reports from international health organizations continue to demonstrate substantial resistance rates among common bacterial pathogens worldwide, emphasizing the urgent need for strengthened antimicrobial stewardship initiatives, enhanced infection-prevention strategies, and robust resistance-monitoring programs to preserve the effectiveness of existing antimicrobial therapies.[45]

Principles of Antimicrobial Stewardship

Antimicrobial stewardship (AMS) comprises a coordinated series of interventions designed to optimize antimicrobial prescribing while ensuring optimal clinical outcomes and minimizing the emergence and spread of antimicrobial resistance.[46] One of the core principles of AMS is the appropriate initiation of antibiotic therapy. Antimicrobial agents should be prescribed only when a bacterial infection is considered likely on the basis of clinical assessment, laboratory findings, and available diagnostic evidence. Empirical treatment should follow established clinical guidelines, and microbiological investigations—including blood cultures and other relevant specimens—should be obtained whenever feasible before antibiotic administration.[39] This approach minimizes unnecessary antibiotic exposure among patients with viral illnesses or noninfectious conditions.

Another fundamental stewardship principle is appropriate antimicrobial selection. Clinicians should select the most suitable antimicrobial agent based on local antibiogram data, suspected site of infection, patient age, allergy history, previous antimicrobial exposure, and pharmacokinetic and pharmacodynamic properties of the drug.[46] Preference for narrow-spectrum antibiotics whenever clinically appropriate helps minimize disruption of the normal microbiota and reduces selective pressure favoring antimicrobial resistance. Dose optimization is equally important and involves adjusting antimicrobial dosing according to body weight, gestational age, postnatal age, renal and hepatic function, severity of illness, and pathogen susceptibility patterns.[47] Appropriate dosing maximizes therapeutic efficacy while minimizing toxicity and avoiding subtherapeutic exposure that may facilitate resistance development.

A key stewardship strategy is antimicrobial de-escalation, whereby broad-spectrum empirical therapy is narrowed or discontinued once microbiological culture results and antimicrobial susceptibility data become available.[40] De-escalation reduces unnecessary exposure to broad-spectrum agents and preserves their effectiveness for future clinical use. In addition, optimization of treatment duration has emerged as an increasingly important component of modern AMS programs. Accumulating evidence suggests that shorter antibiotic courses are effective for many neonatal and pediatric infections and achieve clinical outcomes comparable to prolonged regimens while reducing adverse events, antimicrobial exposure, healthcare costs, and resistance selection.[48] Collectively, these stewardship principles support rational antimicrobial use and improve patient safety throughout neonatal and pediatric healthcare settings.

Core Components of Pediatric AMS Programs

Successful pediatric antimicrobial stewardship programs require strong institutional commitment and a comprehensive multidisciplinary framework. Leadership support is considered the cornerstone of effective stewardship implementation and includes the provision of dedicated personnel, financial resources, information technology infrastructure, and administrative oversight.[46] Without sustained organizational commitment, long-term stewardship success and sustainability remain difficult to achieve.

Effective AMS programs depend upon multidisciplinary collaboration involving pediatricians, neonatologists, infectious disease specialists, clinical pharmacists, microbiologists, infection-prevention professionals, epidemiologists, nursing staff, and healthcare administrators.[47] Each discipline contributes specialized expertise that supports evidence-based prescribing, interpretation of microbiological data, clinician education, and quality-improvement initiatives. Prospective audit and feedback is among the most effective stewardship interventions and involves systematic review of antimicrobial prescriptions followed by individualized recommendations to prescribing clinicians. Numerous studies have demonstrated that this strategy significantly reduces inappropriate antibiotic use, improves prescribing quality, and decreases healthcare costs without negatively affecting patient outcomes.[40]

Another important stewardship intervention is formulary restriction and preauthorization, in which selected broad-spectrum or high-cost antimicrobial agents require approval from infectious disease specialists or stewardship teams before use.[47] This strategy helps prevent inappropriate utilization of reserve antibiotics and encourages adherence to institutional treatment guidelines. Furthermore, surveillance and reporting constitute essential components of AMS programs and include continuous monitoring of antimicrobial consumption, resistance patterns, prescribing behaviors, and clinical outcomes.[45] Regular dissemination of surveillance findings enables healthcare institutions to identify opportunities for improvement, assess stewardship effectiveness, and implement targeted interventions based on local epidemiological data.

Diagnostic Stewardship

Diagnostic stewardship complements antimicrobial stewardship by promoting the appropriate use of diagnostic investigations to improve clinical decision-making and reduce unnecessary antibiotic exposure.[48] Accurate and timely diagnosis is fundamental for distinguishing bacterial infections from viral illnesses and noninfectious conditions and for facilitating targeted antimicrobial therapy. Diagnostic stewardship strategies include obtaining blood cultures before initiating antimicrobial therapy, ensuring appropriate specimen collection techniques to minimize contamination, implementing standardized sepsis-evaluation pathways, and optimizing the use of laboratory, microbiological, and molecular diagnostic tests.[39] These interventions improve diagnostic accuracy, support evidence-based prescribing, and reduce inappropriate antimicrobial utilization.

Biomarkers

C-Reactive Protein (CRP)

C-reactive protein (CRP) is among the most extensively utilized inflammatory biomarkers in neonatal and pediatric clinical practice. Although CRP lacks absolute specificity for bacterial infections and may be elevated in various inflammatory conditions, serial CRP measurements provide valuable information for assessing treatment response and guiding antimicrobial management decisions.[49] Repeated CRP assessments can assist clinicians in determining whether ongoing antibiotic therapy remains necessary, particularly in neonates and children who demonstrate clinical improvement and have negative microbiological cultures. The incorporation of CRP-guided protocols into neonatal sepsis management strategies has been associated with significant reductions in unnecessary antibiotic exposure while maintaining patient safety and favorable clinical outcomes.[49] Consequently, CRP remains an important adjunctive tool within antimicrobial stewardship programs aimed at optimizing antibiotic utilization and minimizing excessive antimicrobial exposure.

Procalcitonin (PCT)

Procalcitonin (PCT) has emerged as one of the most promising biomarkers for antimicrobial stewardship because serum concentrations rise rapidly in response to bacterial infections and decline promptly as infection resolves.[50] Numerous randomized controlled trials and systematic reviews have demonstrated that PCT-guided treatment algorithms facilitate earlier discontinuation of antibiotics during neonatal sepsis evaluations and significantly reduce overall antimicrobial exposure without adversely affecting treatment success, relapse rates, or mortality.[50] Furthermore, incorporation of PCT-based protocols into stewardship initiatives has been associated with reductions in antibiotic duration, hospital length of stay, healthcare expenditures, and antimicrobial-related adverse effects. The growing body of evidence supporting PCT-guided management highlights its value as an objective tool for enhancing diagnostic accuracy and promoting judicious antibiotic use in neonatal and pediatricpopulations.[51] Collectively, biomarker-guided antimicrobial strategies represent an important advancement in stewardship practice by improving therapeutic precision while reducing unnecessary antibiotic administration.

Stewardship in NICUs

Antimicrobial stewardship within neonatal intensive care units (NICUs) has become an increasingly important priority because neonates—particularly premature and low-birth-weight infants—are among the highest consumers of antibiotics in healthcare settings.[52] Concerns regarding neonatal sepsis frequently lead clinicians to initiate empirical antimicrobial therapy immediately after birth, even in situations where the actual probability of infection is relatively low. Because the clinical manifestations of neonatal sepsis are often nonspecific and overlap considerably with noninfectious conditions, healthcare providers commonly adopt a precautionary approach that may inadvertently contribute to excessive antimicrobial utilization.[53]

To address this challenge, modern stewardship programs increasingly emphasize evidence-based evaluation of early-onset sepsis (EOS) through structured risk-stratification models incorporating maternal risk factors, perinatal history, physical examination findings, and laboratory parameters. Neonatal sepsis risk calculators have demonstrated substantial effectiveness in reducing unnecessary antibiotic exposure without increasing rates of missed infection, treatment failure, or adverse clinical outcomes.[54] By accurately identifying infants at genuinely increased risk of infection, these predictive models facilitate more selective use of empirical therapy while maintaining patient safety.

A fundamental component of NICU stewardship is the implementation of antibiotic “time-outs,” involving structured reassessment of antimicrobial therapy at predetermined intervals, commonly at 24, 36, and 48 hours following treatment initiation.[55] During these evaluations, clinicians review microbiological findings, inflammatory markers, and the infant’s clinical condition to determine whether continuation of antibiotic therapy remains justified. Such systematic reassessment prevents unnecessary prolongation of empirical treatment and encourages evidence-based decision-making. Particular emphasis is placed on the management of culture-negative sepsis, a frequent clinical scenario in which infants continue receiving antibiotics despite sterile blood cultures. Current stewardship recommendations support discontinuation of antimicrobial therapy when cultures remain negative, clinical status improves, and inflammatory biomarkers normalize.[56] Multiple studies have demonstrated that adherence to these principles significantly reduces cumulative antibiotic exposure, antimicrobial-associated complications, hospital length of stay, and healthcare costs without increasing mortality, recurrent infection, or treatment failure.[52] These findings reinforce the importance of integrating stewardship principles into routine neonatal practice to achieve an optimal balance between effective infection management and prevention of antimicrobial resistance.

Stewardship in Pediatric Intensive Care Units

Antimicrobial stewardship in pediatric intensive care units (PICUs) presents unique challenges because critically ill children frequently require immediate empirical treatment for severe infections while simultaneously facing a heightened risk of antimicrobial overuse.[57] Consequently, stewardship efforts within PICUs focus not only on the initiation of therapy but also on ensuring continued appropriateness throughout the entire treatment course. One of the most effective interventions is the daily multidisciplinary review of antimicrobial therapy, during which clinicians evaluate ongoing indications for treatment, microbiological findings, therapeutic response, and opportunities for regimen optimization. Regular reassessment facilitates identification of de-escalation opportunities, enabling transition from broad-spectrum empirical regimens to narrower pathogen-directed therapies once culture and susceptibility results become available.[57]

Another important stewardship strategy is intravenous-to-oral antimicrobial conversion. Patients demonstrating clinical improvement can often be safely transitioned from intravenous antibiotics to equally effective oral formulations. This practice reduces catheter-associated complications, enhances patient comfort, shortens hospitalization, and decreases healthcare expenditures.[58] In addition, accumulating evidence supports shorter treatment durations for many pediatric infections—including community-acquired pneumonia, urinary tract infections, and selected intra-abdominal infections—with outcomes comparable to those achieved using longer courses while substantially reducing cumulative antimicrobial exposure. Continuous resistance surveillance within PICUs further enables clinicians to tailor empirical treatment recommendations according to local epidemiological trends and antimicrobial susceptibility profiles.[59] More recently, machine-learning–based clinical decision-support systems have emerged as innovative tools capable of analyzing complex clinical datasets to identify opportunities for antimicrobial optimization, predict therapeutic responses, and support individualized prescribing decisions in critically ill children.[60] These technological advances have considerable potential to enhance stewardship effectiveness while maintaining high standards of patient care.

Recent Advances in Management

The escalating global threat of antimicrobial resistance has accelerated the development of innovative diagnostic and stewardship technologies designed to improve antimicrobial utilization and clinical outcomes in neonatal and pediatric populations. Advances in molecular diagnostics, biomarker-guided treatment algorithms, electronic clinical decision-support systems, surveillance networks, and artificial intelligence have fundamentally transformed the diagnosis and management of infectious diseases.[61] These innovations facilitate earlier pathogen identification, more accurate antimicrobial selection, reduced unnecessary antibiotic exposure, and more effective implementation of stewardship strategies across healthcare settings.

Rapid Molecular Diagnostics

Rapid molecular diagnostic technologies have revolutionized infectious disease management by substantially reducing the time required for pathogen identification and antimicrobial susceptibility assessment.[62] Conventional culture-based methods often require 24–72 hours or longer to yield definitive results, compelling clinicians to rely on broad-spectrum empirical therapy during this interval. Contemporary diagnostic platforms—including multiplex polymerase chain reaction (PCR) assays, real-time PCR systems, next-generation sequencing (NGS), and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry—enable rapid detection of bacterial, viral, and fungal pathogens directly from clinical specimens.[62] These technologies facilitate earlier initiation of targeted therapy, reduce diagnostic uncertainty, improve antimicrobial selection, and minimize unnecessary broad-spectrum antibiotic exposure. Furthermore, rapid diagnostics support timely de-escalation decisions, reduce hospital length of stay, and contribute substantially to antimicrobial stewardship objectives by promoting precision-based infection management.[61]

Biomarker-Guided Stewardship

Biomarker-guided antimicrobial stewardship has emerged as an effective approach for improving diagnostic accuracy and reducing unnecessary antibiotic exposure among neonates and children. Biomarkers provide objective information regarding the presence, severity, and progression of infection, thereby supporting evidence-based therapeutic decisions. Combined utilization of procalcitonin (PCT), C-reactive protein (CRP), and emerging cytokine-based approaches has demonstrated superior diagnostic performance compared with reliance on clinical findings alone.[56] Procalcitonin-guided algorithms have consistently been associated with earlier discontinuation of antibiotics in neonatal sepsis evaluations and reduced overall treatment duration without compromising patient safety. Similarly, serial CRP monitoring assists clinicians in assessing therapeutic response and determining appropriate timing for antibiotic discontinuation in clinically improving patients.[61] Cytokine biomarkers such as interleukin-6 and interleukin-8 are increasingly being investigated because of their potential to detect infection at earlier stages and improve diagnostic sensitivity. Collectively, biomarker-guided strategies contribute to shorter antibiotic courses, lower healthcare expenditures, and improved stewardship outcomes across pediatric healthcare settings.

Electronic Clinical Decision Support Systems

Electronic clinical decision-support systems (CDSS) have become valuable instruments for strengthening antimicrobial stewardship programs by integrating evidence-based recommendations directly into routine clinical workflows.[55] These computerized platforms provide real-time prescribing guidance, individualized dosage recommendations, automated drug-interaction alerts, and predefined stop orders that encourage periodic reassessment of antimicrobial therapy. Decision-support systems may also integrate local antibiogram data, patient-specific characteristics, microbiological findings, and institutional treatment guidelines to assist clinicians in selecting the most appropriate antimicrobial regimen. Studies consistently demonstrate that electronic stewardship interventions improve guideline adherence, reduce inappropriate antimicrobial utilization, enhance dosing accuracy, and facilitate timely de-escalation of therapy.[59] As healthcare systems continue expanding electronic health record adoption, integration of advanced decision-support capabilities is expected to further improve stewardship effectiveness and patient outcomes.

Antimicrobial Surveillance Networks

Comprehensive antimicrobial surveillance is fundamental for understanding resistance trends and guiding stewardship initiatives. National, regional, and international surveillance programs systematically collect and analyze microbiological and antimicrobial utilization data from healthcare institutions, generating valuable insights into pathogen distribution and resistance patterns.[45] Modern surveillance networks support resistance mapping, institutional antibiogram development, outbreak detection, and benchmarking of antimicrobial utilization practices across healthcare facilities.[59] These data enable clinicians to make evidence-based empirical prescribing decisions and assist policymakers in designing targeted interventions to address emerging resistance threats. Surveillance information additionally facilitates evaluation of stewardship effectiveness and identification of areas requiring further improvement. By providing timely epidemiological intelligence, antimicrobial surveillance networks play a central role in optimizing antimicrobial utilization and mitigating resistance development at local, national, and global levels.

Artificial Intelligence and Predictive Analytics

Artificial intelligence (AI) and predictive analytics represent some of the most promising emerging technologies in antimicrobial stewardship and pediatric critical care. Recent advances in machine-learning methodologies enable sophisticated analysis of large clinical datasets, electronic health records, microbiological information, and epidemiological trends to support complex clinical decision-making.[60] AI-driven tools can assist clinicians by predicting sepsis risk, identifying patients who may safely discontinue antibiotics, forecasting local resistance patterns, and recommending individualized antimicrobial regimens based on patient-specific characteristics. In addition, predictive algorithms may facilitate earlier recognition of clinical deterioration, improve risk stratification, and promote more precise antimicrobial prescribing practices. Preliminary evidence suggests that AI-assisted stewardship interventions can reduce inappropriate antibiotic utilization while maintaining favorable clinical outcomes.[61] As these technologies continue to evolve and undergo validation in pediatric populations, they are expected to become increasingly important components of future antimicrobial stewardship programs, enhancing both efficiency and effectiveness within neonatal and pediatric healthcare settings.

Future Directions

The future of antimicrobial stewardship in neonatal and pediatric care will be shaped by advances in precision medicine, diagnostic technologies, digital health innovations, microbiome science, and global collaborative efforts aimed at combating antimicrobial resistance (AMR). As resistance rates continue to rise and the pipeline of new antimicrobial agents remains limited, healthcare systems must increasingly adopt innovative, evidence-based strategies that optimize antibiotic use while preserving therapeutic effectiveness for future generations. Emerging technologies and personalized approaches are expected to transform how infections are diagnosed, treated, monitored, and prevented across neonatal and pediatric healthcare settings.

Precision Medicine

Precision medicine is anticipated to play a pivotal role in the next generation of antimicrobial stewardship programs. Traditional antibiotic prescribing is largely based on population-level treatment guidelines and empirical risk assessment; however, advances in genomics and molecular medicine are enabling more individualized therapeutic approaches. Future antimicrobial strategies may incorporate host genomics, pharmacogenomics, and immune profiling to guide treatment decisions tailored to each patient's unique biological characteristics. Genetic variations affecting drug metabolism, distribution, efficacy, and toxicity could be identified before treatment initiation, allowing clinicians to select the most appropriate antimicrobial agent and dosage while minimizing adverse effects. Furthermore, characterization of individual immune responses may help distinguish bacterial infections from viral or inflammatory conditions, reducing unnecessary antibiotic exposure and improving diagnostic accuracy. Such personalized approaches have the potential to enhance treatment outcomes while supporting more judicious antimicrobial use.

Advanced Point-of-Care Diagnostics

One of the most promising developments in pediatric infectious disease management is the emergence of highly sensitive and rapid point-of-care diagnostic technologies. Current microbiological methods often require several hours to days for pathogen identification and susceptibility testing, leading clinicians to rely on empirical broad-spectrum therapy. Future bedside diagnostic platforms are expected to identify bacterial, viral, and fungal pathogens within minutes through advanced molecular techniques, biosensors, microfluidics, and nanotechnology-based systems. Rapid determination of antimicrobial resistance genes and virulence markers may further facilitate immediate targeted therapy. By reducing diagnostic uncertainty, advanced point-of-care diagnostics can substantially decrease unnecessary empirical antibiotic administration, shorten treatment delays, improve antimicrobial selection, and enhance stewardship outcomes in both neonatal and pediatric settings.

Machine Learning Integration

Artificial intelligence (AI) and machine learning technologies are likely to become integral components of antimicrobial stewardship programs in the coming years. These systems can analyze vast amounts of clinical, laboratory, microbiological, pharmacological, and epidemiological data in real time to support complex clinical decision-making. Machine learning algorithms may assist healthcare providers by predicting sepsis risk, estimating the probability of bacterial infection, forecasting antimicrobial resistance patterns, recommending optimal empirical therapy, and identifying patients eligible for early antibiotic discontinuation. Predictive analytics may also improve resource allocation, optimize antimicrobial utilization, and enhance patient stratification according to infection risk. As validation studies continue and integration with electronic health records expands, AI-driven stewardship tools are expected to improve both efficiency and precision in pediatric antimicrobial management.

Microbiome-Based Therapeutics

Growing recognition of the critical role of the microbiome in human health has generated considerable interest in microbiome-targeted therapeutic interventions. Antibiotic exposure during early life can significantly disrupt microbial diversity and alter immune system development, potentially contributing to long-term adverse health outcomes. Future stewardship strategies may incorporate microbiome-preserving approaches designed to minimize collateral damage associated with antimicrobial therapy. These interventions could include targeted probiotics, prebiotics, synbiotics, fecal microbiota transplantation, engineered microbial therapeutics, and microbiome restoration therapies following antibiotic treatment. By maintaining or restoring microbial balance, such approaches may reduce susceptibility to opportunistic infections, inflammatory diseases, and antimicrobial-resistant colonization while supporting overall health and immune function.

Novel Antimicrobials

The continued emergence of multidrug-resistant pathogens highlights the urgent need for new therapeutic options beyond conventional antibiotics. Ongoing research is exploring a variety of innovative antimicrobial strategies, including the development of novel antibiotic classes with unique mechanisms of action, agents targeting bacterial virulence factors, and compounds capable of overcoming existing resistance mechanisms. Additionally, **bacteriophage therapy**, which utilizes viruses that specifically infect and destroy bacteria, has re-emerged as a promising alternative for treating resistant infections. Other experimental approaches include **antimicrobial peptides**, monoclonal antibodies, immune-enhancing therapies, and host-directed treatments that strengthen natural defense mechanisms rather than directly targeting pathogens. These innovative therapies may provide valuable alternatives for managing infections caused by highly resistant organisms and could significantly expand the therapeutic arsenal available to pediatric clinicians.

Global Stewardship Collaboration

Given the transnational nature of antimicrobial resistance, effective stewardship increasingly requires coordinated international collaboration. Future efforts will likely emphasize the expansion of global surveillance networks, standardized antimicrobial stewardship frameworks, harmonized prescribing guidelines, and multinational research initiatives. Enhanced data sharing among countries will facilitate early detection of emerging resistance threats, monitoring of antimicrobial consumption patterns, and evaluation of stewardship interventions across diverse healthcare systems. International organizations, governments, academic institutions, and healthcare providers must continue to work collaboratively to strengthen infection prevention programs, improve access to diagnostics, promote responsible antimicrobial use, and support the development of new therapeutic agents. Such coordinated global action will be essential for mitigating the growing burden of AMR and ensuring the continued effectiveness of antimicrobial therapy for children worldwide.

Collectively, these future developments have the potential to revolutionize antimicrobial stewardship in neonatal and pediatric care by enabling more precise diagnosis, individualized treatment, optimized antimicrobial utilization, preservation of microbial health, and improved management of resistant infections. Continued investment in research, innovation, surveillance, and international cooperation will be critical to achieving sustainable progress in the fight against antimicrobial resistance and safeguarding the efficacy of antimicrobial agents for future generations.

DISCUSSION

Antimicrobial stewardship (AMS) has become a fundamental strategy for combating the growing threat of antimicrobial resistance (AMR) in neonatal and pediatric healthcare. The evidence reviewed in the present study underscores the delicate balance clinicians must achieve between providing prompt and effective treatment for potentially life-threatening infections and minimizing unnecessary antimicrobial exposure. In neonatal and pediatric settings, antibiotics are frequently initiated empirically because delays in the treatment of sepsis may lead to rapid clinical deterioration, multiorgan dysfunction, and increased mortality.[63] Nevertheless, accumulating evidence suggests that a substantial proportion of antimicrobial prescriptions in neonatal intensive care units (NICUs) and pediatric intensive care units (PICUs) are administered without subsequent confirmation of bacterial infection, resulting in avoidable antimicrobial exposure and increased selective pressure favoring resistant pathogens.[64] Multiple observational studies have demonstrated that prolonged empirical antibiotic therapy in cases of culture-negative sepsis is associated with adverse outcomes, including disruption of normal microbial colonization, increased vulnerability to opportunistic infections, and emergence of multidrug-resistant organisms.[64] These observations strongly support stewardship strategies that emphasize timely reassessment of therapy and early discontinuation of antibiotics when ongoing treatment is no longer clinically justified.

A particularly concerning finding across recent literature is the accelerating rise in antimicrobial resistance among pathogens responsible for neonatal and pediatric infections. Gram-negative bacteria, especially extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, *Klebsiella pneumoniae*, multidrug-resistant *Enterobacter* species, and carbapenem-resistant Enterobacterales, have become increasingly prevalent across diverse healthcare settings worldwide.[65] Resistance to commonly prescribed empirical agents—including ampicillin, gentamicin, and third-generation cephalosporins—has been documented in numerous surveillance studies, creating significant challenges for clinicians and narrowing available therapeutic options.[66] The emergence of carbapenem-resistant pathogens is particularly alarming because carbapenems are frequently reserved as last-line agents for severe Gram-negative infections. Similar concerns have been reported for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, and other resistant Gram-positive pathogens that contribute substantially to healthcare-associated infections in children.[67] The increasing burden of antimicrobial resistance has been linked to prolonged hospitalization, increased healthcare costs, greater dependence on intensive care resources, and elevated mortality rates, highlighting the urgent need for comprehensive and sustainable stewardship interventions globally.

The review further emphasizes the profound impact of antimicrobial exposure on the developing neonatal microbiome. Early microbial colonization is essential for immune system maturation, metabolic regulation, maintenance of intestinal integrity, and protection against pathogenic organisms. Excessive or prolonged antibiotic exposure during infancy can significantly alter microbial diversity, resulting in persistent dysbiosis and disruption of normal host–microbe interactions.[68] Emerging evidence suggests that such alterations may increase susceptibility to necrotizing enterocolitis, allergic diseases, asthma, obesity, inflammatory bowel disease, and other chronic health conditions later in life.[68] Recognition of these long-term consequences has strengthened the rationale for minimizing unnecessary antibiotic exposure and has encouraged incorporation of microbiome-preserving strategies into modern stewardship frameworks. Future interventions aimed at restoring microbial balance, including microbiome-targeted therapies, may further enhance stewardship outcomes and contribute to improved long-term pediatric health.

Successful antimicrobial stewardship programs require a comprehensive, multidisciplinary approach involving pediatricians, neonatologists, infectious disease specialists, clinical pharmacists, microbiologists, infection-prevention personnel, nurses, and healthcare administrators. Numerous studies have consistently demonstrated that interventions such as prospective audit and feedback, formulary restriction, evidence-based guideline implementation, antimicrobial review rounds, and clinician education can significantly reduce inappropriate prescribing while maintaining or improving clinical outcomes.[69] Diagnostic stewardship has likewise emerged as a critical component of effective AMS programs. Appropriate collection of microbiological specimens, reduction of specimen contamination, optimization of laboratory testing, and implementation of standardized diagnostic protocols improve diagnostic accuracy and facilitate evidence-based treatment decisions.[70] Furthermore, incorporation of biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) into clinical decision-making algorithms has enabled earlier discontinuation of antimicrobial therapy and shorter treatment durations without compromising patient safety or treatment efficacy.[71]

Technological innovations are increasingly reshaping the field of antimicrobial stewardship. Rapid molecular diagnostic platforms—including multiplex polymerase chain reaction (PCR), next-generation sequencing (NGS), and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry—allow more rapid pathogen identification and facilitate earlier transition from empirical to targeted antimicrobial therapy.[72] Electronic prescribing systems and computerized clinical decision-support tools further strengthen stewardship efforts by providing real-time recommendations regarding antimicrobial selection, dose optimization, drug interactions, and automatic review or stop orders.[73] More recently, artificial intelligence and machine-learning technologies have shown promising potential for predicting sepsis risk, identifying candidates for early antibiotic discontinuation, forecasting resistance trends, and supporting individualized antimicrobial prescribing based on patient-specific clinical characteristics.[74] Although these technologies remain under ongoing evaluation, their integration into routine pediatric healthcare practice may substantially improve antimicrobial utilization, diagnostic precision, and overall healthcare efficiency in the future.

Despite substantial progress, several barriers continue to impede widespread implementation of pediatric antimicrobial stewardship programs, particularly in low- and middle-income countries. Limited laboratory capacity, inadequate access to rapid diagnostic technologies, insufficient surveillance infrastructure, shortages of trained infectious disease professionals, and inconsistent adherence to treatment guidelines can all compromise stewardship effectiveness.[75] Moreover, considerable variability in local pathogen epidemiology and antimicrobial susceptibility patterns necessitates development of region-specific stewardship strategies rather than exclusive reliance on universal prescribing recommendations. Strengthening antimicrobial surveillance systems, expanding educational and training initiatives, improving access to diagnostic technologies, and promoting international collaboration will be essential for overcoming these challenges and achieving sustainable improvements in antimicrobial utilization worldwide.

Overall, the evidence reviewed clearly demonstrates that antimicrobial stewardship represents one of the most effective approaches for preserving antibiotic effectiveness, improving patient outcomes, and limiting the spread of antimicrobial resistance in neonatal and pediatric healthcare. Through the integration of rational prescribing practices, diagnostic stewardship, microbiological surveillance, emerging technologies, and multidisciplinary collaboration, healthcare systems can successfully balance the need for prompt treatment of serious infections with the imperative of responsible antimicrobial use. Continued investment in research, innovation, professional education, and global stewardship initiatives will remain essential to safeguarding the effectiveness of antimicrobial therapy and ensuring optimal healthcare outcomes for future generations of children.

CONCLUSION

Antimicrobial stewardship has emerged as an essential strategy for preserving the effectiveness of antibiotics in neonatal and pediatric healthcare. The increasing prevalence of antimicrobial resistance, coupled with frequent empirical antibiotic use in NICUs and pediatric settings, necessitates careful optimization of antimicrobial therapy. Effective stewardship programs promote evidence-based prescribing, dose optimization, timely de-escalation, and appropriate treatment duration while maintaining patient safety and clinical efficacy. Advances in rapid diagnostics, biomarker-guided management, surveillance systems, and artificial intelligence offer promising opportunities to improve antibiotic utilization and reduce unnecessary exposure. Multidisciplinary collaboration among clinicians, pharmacists, microbiologists, infection-control teams, and healthcare administrators remains fundamental to successful stewardship implementation. Future efforts should focus on precision medicine approaches, enhanced resistance surveillance, innovative antimicrobial therapies, and global stewardship initiatives. Through sustained commitment to rational antimicrobial use, healthcare systems can effectively balance infection control needs with the urgent imperative to combat antimicrobial resistance and protect future pediatric populations.

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