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Challenges of Antibiotic Stewardship in the Pediatric and Neonatal Intensive Care Units

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The goals of antimicrobial stewardship programs (ASPs) are to optimize antimicrobial prescribing habits in order to improve patient outcomes, reduce antimicrobial resistance, and reduce hospital costs. Multiple society-endorsed guidelines and government policies reinforce the importance of ASP implementation. Effective antimicrobial stewardship can impact unique patients, hospitals, and societal antibiotic-resistance burden. The role and subsequent success of these programs has largely been reported in the adult population. Pediatric and neonatal intensive care units present unique challenges for traditional antimicrobial stewardship approaches. The purpose of this review article is to explore the challenges of appropriate antibiotic use in the pediatric and neonatal intensive care units and to summarize strategies ASPs can use to overcome these challenges. These problems include non-specific disease presentations, limited evidence for definitive treatment durations in many pediatric infections, fewer pediatric-trained infectious disease physicians, and applicability of intensive laboratory obtainment, collection, and interpretation. Additionally, many ASP implementation studies evaluating the efficacy of ASPs exclude the PICU and NICU. Areas of focus for pediatric ASPs should likely include appropriate antibiotic initiation, appropriate antibiotic duration, and appropriate antibiotic de-escalation.

ABBREVIATIONS AAP, American Academy of Pediatrics; AIDS, acquired immunodeficiency syndrome; ASHP, American Society of Health-System Pharmacists; ASPs, antimicrobial stewardship programs; CAP, community-acquired pneumonia; CA-UTI, catheter-associated urinary tract infection; CRP, C-reactive protein; ED, emergency department; ESBL, extended-spectrum beta-lactamase; ESR, erythrocyte sedimentation rate; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; IV, intravenous; IVIG, intravenous immunoglobulin; LOS, length of stay; LRTI, lower respiratory tract infection; MDR, multidrug-resistant; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PCR, polymerase chain reaction; PCT, procalcitonin; PICU, pediatric intensive care unit; PRISM-1, Pediatric Risk of Mortality score; SSC, Surviving Sepsis Campaign; UTI, urinary tract infection; VAD, ventricular assist device; VAP, ventilator-associated pneumonia; WBC, white blood cell (count)

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Introduction

Each year in the United States, approximately 2 million pediatric and adult patients develop an infection during a hospital stay.[1] In the pediatric patient population, the etiology of infection depends on many factors including age, recent hospitalization, immunization status, and socioeconomic setting. In 2015, upper respiratory tract infections were the most common respiratory-related ED visit in the United States amongst all pediatric age groups and the fifth most common ED visit by body system, accounting for more than 2 million ED visits.[2,3] It has been shown that greater than 10% of children treated in the PICU for >48 hours will develop a nosocomial infection. Additionally, according to a 2012 consumer report, the rates of bloodstream infections in the PICU were 20% higher than those of adult ICUs (1.5 vs 1.8 per 1000 patient days). This drastically varies in the neonatal patient population depending on the NICU setting, maternal risk factors, and postmenstrual age. Improved prenatal screening measures and infant immunizations have reduced the incidence of serious bacterial infections in full-term infants to 3.75 per 1000 live births.[4]

In pediatric patients, community-acquired viral pathogens such as respiratory syncytial virus, rhinovirus, parainfluenza virus, and adenovirus are a frequent cause of infection. Antibiotics are often prescribed, however, inappropriately owing to physician uncertainty or caregiver demand.[5,6] The role antimicrobial stewardship programs (ASPs) can play in optimizing antimicrobial prescribing habits to improve patient outcomes, reduce the spread of antimicrobial resistance, and reduce hospital costs has been well documented in the adult population.[7] Owing to the growing body of evidence demonstrating

the benefits of ASPs, the Infectious Diseases Society of America (IDSA) in conjunction with the Society for Healthcare Epidemiology of America, American Society of Health-System Pharmacists (ASHP), and The Joint Commission released guidelines on the implementation of an ASP.[5,7-9] Additionally, the Pediatric Infectious Diseases Society released a pediatric ASP toolkit outlining general tools for developing ASP interventions in the inpatient and outpatient settings.

Pediatric critical care areas, such as the PICU and NICU, present a unique problem for traditional ASP strategies. Many of the core ASP approaches described in ASHP guidelines are based on strong data supporting treatment decisions, but for many of the common conditions requiring antibiotics in the PICU and NICU, there is a paucity of clinical data to guide daily ASP practice. These problems include non-specific neonatal sepsis presentation leading to diagnostic difficulties, recommendations to not collect >1 mL of blood from a neonate, limited evidence for definitive treatment durations in many pediatric infections, and fewer pediatric-trained infectious disease physicians.[10-12] Additionally, many ASP implementation studies evaluating the efficacy of ASPs exclude the PICU and NICU.[1] The aims of this review are to explore the challenges of appropriate antibiotic initiation, duration, and de-escalation in the pediatric and neonatal intensive care units and summarize strategies ASPs can use to overcome them.

Importance of Appropriate Empiric Antibiotic Selection and Initiation

Proper risk stratification of patients for multidrug-resistant organisms (MDROs) is a crucial factor in the initial choice of empiric antimicrobial therapy. Critically ill patients are often started on broad-spectrum antibiotics owing to their ill appearance upon admission, hemodynamic instability, or complex medical picture. Despite the critical presentation of many of these patients, they often lack the risk factors for a common MDRO such as extended-spectrum beta-lactamase (ESBL)–positive Enterobacteriaceae, *Pseudomonas* species, or methicillin-resistant *Staphylococcus aureus* (MRSA).[13] While many of these patients do warrant a sufficient bacterial infection rule-out, awareness of risk factors for MDROs can help decrease the unnecessary use of extended-spectrum antibiotics.[13]

Risk factors for an MDRO for presumed community-acquired infections differ from risk factors in nosocomial acquired infections. These risk factors have been well described in the adult population to include recent antibiotic exposure, exposure to other MDRO-colonized patients, transfer from a nursing home, or advanced age.[14] In the pediatric population, however, these risk factors are likely different.[14] Rates of MDROs in pediatrics, specifically ESBL-positive Enterobacteriaceae, increase with ICU admission when compared with acute care patients and outpatients, respectively (2.9% vs 1.1% vs 0.29).[15] Independent risk factors shown to be associated with higher rates of resistant Enterobacteriaceae in pediatric patients are neurologic or gastrointestinal comorbidities, receipt of a third-generation cephalosporin in the previous 30 days, higher Pediatric Risk of Mortality (PRISM)-1 score, presence of a Foley catheter, and mechanical ventilation.[15-17]

Few studies have been performed to evaluate pediatric-specific risk factors for community-acquired MRSA. The most commonly reported risk factors include severe underlying illness, presence of endotracheal tubes, close contact to a health care worker at home, and recent prolonged or recurrent antibiotic exposure.[18] A recent study evaluating 19,113 pediatric sepsis admissions reported that 12,813 (67%) patients had a chronic disease classified by the pediatric complex chronic conditions classification system.[19] The most prominent risk factors for infection caused by MRSA, quantified as >10% incidence amongst the cohort, were devices for patients such as a ventricular assist device (VAD), tracheostomy, neurologic shunt, and pacemaker as well as chronic disease groups including bone marrow transplant, hematologic or solid cancer, congenital heart disease, congenital hematologic or immunologic disease, short-bowel syndrome, and dialysis dependence.[19] Risk factors associated with nosocomial acquired MRSA infections include prolonged ICU stay, indwelling catheters, and recent invasive procedures.[18] Typically, patients without the above risk factors do not warrant empiric coverage for MRSA. The rate of community-acquired MRSA in children without risk factors is still a significant concern that varies across the United States, and thus providers should have a low threshold for addition of MRSA coverage.[20]

In the NICU, risk factors for acquired multidrug-resistant (MDR) infections are drastically different from those of the PICU. Many hospitals use open unit NICUs compared with private room units, which have sparked debate on infection prevention.[21-23] Decreased transmission of pathogens including MRSA in private room NICUs has been theorized, but has not been consistently proven.[21,22] Regardless of room configuration, reported independent risk factors for MRSA infections in the NICU are gestational age <32 weeks, birth weight <1500 g, previous exposure to vancomycin or carbapenems, and being born outside of the NICU.[24-26] Being born outside of the NICU is defined as babies transferred to a tertiary care facility after birth. Risk factors that should be considered for empiric antibiotic coverage in the PICU and NICU populations are summarized in Table 1.

An inclusive approach to antibiotic initiation, including high suspicion of bacterial infection in conjunction with biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), WBC, and erythrocyte sedimentation rate (ESR), may help guide the diagnosis of infection and the optimal use of antibiotic therapy.[27] It has been

Table 1. Risk Factors for Multidrug-Resistant Organisms* in Pediatric Patients[15,16,18-20,24-26]

Community-Acquired MDROs
Known risk factors
Underlying chronic disease†
Endotracheal tube
Mechanical device‡
Close contact to a health care worker at home
Recent prolonged or recurrent antibiotic use
Likely risk factors
MRSA colonization
Hospital-Acquired MDROs
Known risk factors
Underlying chronic disease†
Received third-generation cephalosporin in the previous 30 days
Higher PRISM-1 score
Foley catheter
Mechanical ventilation
Prolonged ICU stay (>48 hr)
Likely risk factors
ICU admission
Indwelling catheters >48 hr
Recent invasive procedure
Specific to the NICU
Known risk factors
Gestational age <32 wk
Birth weight <1500 g
Previous exposure to vancomycin or carbapenems
Being born outside of the NICU§
Likely risk factors
Open NICU configuration (i.e., no private rooms)
Mother colonized with MRSA

MDROs, multidrug-resistant organisms; MRSA, methicillin-resistant Staphylococcus aureus*; PRISM-1, Pediatric Risk of Mortality score*

* Methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase–positive Enterobacteriaceae, and *Pseudomonas* species.

† Bone marrow transplant, hematologic or solid cancer, congenital heart disease, congenital hematologic or immunologic disease, short-bowel syndrome, tracheostomy, or dialysis dependence.

‡ Ventricular assist device, tracheostomy, neurologic shunt, or pacemaker.

§ Born outside of the NICU: transferred to a tertiary care facility after birth.

shown, in the absence of definitive culture data, that using biomarkers indicative of an inflammatory process such as CRP and PCT may positively help guide antibiotic stewardship in critically ill patients.[27] While PCT has been shown in adults to have a high correlation to bacterial infection, specifically infections caused by Gram-negative rods, this correlation has not been reliably proven in children.[28,29] The high prevalence of mixed viral and bacterial infections in the pediatric population makes using a single biomarker difficult.[30] Cies and Chopra[31] evaluated the predictive ability of PCT in 201 patients admitted to the PICU. They found that a PCT level ≥1.45 ng/mL had a positive predictive value of 30% and a negative predictive value of 93% in identifying a serious bacterial infection in these patients. Additionally, clinical care algorithms and score calculators implemented in the NICU, using a multivariable risk prediction model in combination with the infants' clinical appearance, have successfully reduced inappropriate laboratory monitoring and antimicrobial use without apparent adverse effects.[32] Biomarkers should not be expected to solely and objectively distinguish patients who will benefit from starting antibiotics because they can be affected by many non-infectious causes. Nonetheless, biomarkers should be seen as useful tools to help practitioners optimize antibiotic therapy when paired with other clinical indices of infection (Table 2).

Controversies in Management of Hospital-Acquired Lower Respiratory Tract Infections. Nosocomial infections, particularly in the respiratory tract, are a significant problem among critically ill children in ICUs. Suspected pneumonia or lower respiratory tract infections (LRTIs) are one of the most commonly diagnosed nosocomial infections in the PICU, accounting for over half of all antibiotic use.[33,34] Endotracheal aspirates have been thought to be useful in predicting the causative organism of respiratory tract infections in patients with long-term artificial airways because colonization often precedes infection.[35] Endotracheal aspirates have not proved beneficial in predicting the causative organism in bacterial sepsis.[35] Sputum production alone is inadequate in identifying if a patient has an active respiratory infection caused by a bacterial pathogen. Additionally, routine tests such as sputum Gram stains can be difficult to obtain in pediatric patients. Non-quantitative endotracheal aspirates lack a validated threshold for positive predictive value and consequently may not distinguish between bacterial colonization and bacterial infection.[36,37]

Blood cultures are seldom positive in respiratory infections, the utility of chest radiography is limited unless a severe LRTI forms, and invasive procedures such as a bronchioalveolar lavage are reserved for the critically ill.[38] Owing to a lack of guidance on determining colonization and infection, antibiotic therapy is often initiated at the discretion of the prescriber. These insufficiencies may result in the inappropriate management of patients, based on positive tracheal cultures without the presence of an active infection. Proper use of tracheal aspirates to guide antimicrobial therapy should be considered in combination with multiple objective clinical signs or symptoms of systemic infection to increase the probability of actual LRTI. These signs include fever, leukocytosis or leukopenia, clinically significant change in sputum color or consistency, and chest radiographic findings consistent with an acute infectious process (Table 3).[39]

Table 2. Biomarkers of Infection and Common Confounders[85-88]

Biomarker	Time to Detection, hr*	Underlying Disease/Medication	Effect on Serum Concentration of the Biomarker
PCT	2–4	Acute graft disease, burns, trauma, malignancy, ESRD, circulatory support, IL-2 inhibitors, ATG, OKT-3 inhibitors	Elevated (ESRD causes slightly elevated baseline PCT)
		Fungal infections, IVIG	Slight decrease
CRP	12–24	Autoimmune disease (i.e., lupus, T1DM, RA, MS, IBD), malignancy, obesity, organ dysfunction, diabetes, smoking, circulatory support	Elevated (obesity causes slightly elevated baseline CRP)
		NSAIDs, statins, corticosteroids, ASA, magnesium supplementation	Decreased
ESR	24–48	Autoimmune disease (i.e., lupus, T1DM, RA), malignancy, malignancy, obesity, organ dysfunction, diabetes, smoking, circulatory support, anemia	Elevated (obesity causes slightly elevated baseline ESR)
		Leukocytosis, polycythemia, hypofibrinogenemia, red blood cell abnormalities	Decreased
WBC	1–3	Autoimmune disease (i.e., lupus, T1DM, RA, MS, IBD), malignancy, obesity, organ dysfunction, diabetes, corticosteroids, inotropes, smoking, circulatory support	Increased
		Malnutrition, AIDS, underlying immunodeficiency, chemotherapy, viral illness, aplastic anemia, hypersplenism	Decreased

ATG, antithymocyte globulin; CRP, C-reactive protein; ESRD, end-stage renal disease; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disorder; IL, interleukin; MS, multiple sclerosis; PCT, procalcitonin; RA, rheumatoid arthritis; T1DM, type-1 diabetes

* Time in which biomarker level in the blood may be indicative of infection.

Development of a Location-Specific Antibiogram. The development and use of hospital antibiograms as a tool to determine empiric antibiotic therapy is widely outlined in the current literature.[40,41] Hospital antibiograms provide an overall profile on pathogen susceptibility testing to a variety of antimicrobial agents in a specific institution. Pediatric pathogen susceptibility has been shown to drastically differ from that of adults; therefore, institutions who treat both patient populations may improve patient care with a pediatric-specific antibiogram.[42] While the overall incidence of MDROs is low in children, one study showed a significant increase (0.2% to 1.5%) from 2007 to 2015.[43] Pediatric medical residents play a critical role in shaping antimicrobial use patterns because they are the frontline clinicians who often initiate antibiotic therapy and often rotate between adult and pediatric settings. Education during resident training on proper use of clinical antibiograms has been shown to positively impact antimicrobial stewardship in pediatric hospitals.[44]

While most hospitals use an antibiogram as recommended by IDSA/ASHP ASP guidelines, new evidence supports the importance of subanalysis when preparing annual hospital antibiograms.[40] Subanalyses can include inpatient, outpatient, unit, and isolate-specific reports. In the PICU and NICU, sensitivities and pathogen susceptibility can greatly vary when compared with the general hospital owing to a drastically different patient population.[45] Specifically in the NICU, isolates such as *Escherichia coli* have been shown to be less susceptible to ampicillin and *Staphylococcus aureus* has been shown to be more susceptible to nafcillin when compared with hospitalwide susceptibilities.[45]

There are many challenges associated with developing antibiograms specific to the PICU and NICU. Studies have shown that in order to appropriately represent susceptibility patterns across a patient population, a minimum of 30 isolates are required.[46] This may be challenging depending on the size of the institution and unit.[46] Additionally, the PICU in particular has a high rate of patient turnover with a large number of community-acquired infections, rendering a unit-specific antibiogram less representative of the likely pathogens.[47] If feasible, development and extrapolation of an ambulatory-based antibiogram may help guide institutional empiric antibiotic guidelines in patients presenting with community-acquired infections.[46] Ultimately, developing an ICU isolate–specific antibiogram to guide empiric antimicrobial therapy for ICU-acquired infections may be helpful to improve the functionality of hospital antibiograms.

Appropriate Antibiotic Treatment Duration

The 3 most common nosocomial infections in the PICU and NICU are pneumonia, urinary tract infections (UTIs), and bloodstream infections.[48-50] Studies show that following consensus guidelines for antibiotic use in pediatric patients can decrease the use of broad-spectrum antibiotics, increase the use of appropriate first-line antibiotic therapy, and decrease adverse outcomes.[51] Additionally, using guidelines available for the most common infections seen in the PICU and NICU to guide treatment duration may decrease total antibiotic exposure. This is significant because antibiotic exposure early in life has been identified as a risk factor for developing asthma, allergic rhinitis, childhood obesity, eczema, and MDR infections later in life.[51-55]

Pneumonia. The AAP published guidelines in 2012 outlining the appropriate management of community-acquired pneumonia (CAP) in children. The AAP states that 7 to 10 days of appropriate antimicrobial therapy should be sufficient in the treatment of CAP.[56] While some patients seen in the PICU and less so in the NICU may have CAP, many are found to have hospital-acquired pneumonia (HAP), ventilator-acquired pneumonia (VAP), or MDR bacterial pneumonia. Currently, there are no sanctioned guidelines for the management of HAP, VAP, or MDR bacterial pneumonia in children. The IDSA has released guidelines for the management of adults with HAP and VAP, which recommend treating for a shorter course of therapy (7 days) compared with a longer course for most patients.[57] These recommendations stem from literature supporting no difference in mortality, reinfection rates, and a lower incidence of reinfection with MDROs amongst adults treated for VAP with 8 vs 15 days of antibiotics.[58,59] While some patients may have complications such as necrotizing pneumonia, initial treatment failure, or chest tube placement, which would warrant a longer treatment course, many patients can be adequately treated with a short course of appropriate antibiotic therapy. The optimal treatment duration for pneumonia remains uncertain but by extrapolating adult data, we may be able to treat pediatric patients for a shorter duration, sparing unwarranted and unnecessary antibiotic exposure.[58]

Urinary Tract Infections. While the AAP published guidelines in 2011 providing recommendations for the diagnosis and treatment of community-acquired febrile UTIs in children, catheter-associated urinary tract infections (CA-UTIs) are more commonly seen in critically ill children.[60-62] CA-UTIs were not included in these guidelines, leaving debate for optimal antibiotic selection and duration.[61] Development of a CA-UTI in the PICU has been associated with significantly worse outcomes including longer hospital LOS, longer PICU LOS, and mortality.[60] Many factors play a role in the decision behind UTI treatment duration such as isolation to the bladder, kidney involvement, urinary tract abnormalities, and causative organism. Approximately 85% of UTIs in children are caused by *E coli*, and approximately 3% to 15% of children have renal parenchymal defects.[61]

Table 3. Appropriate Clinical Markers With Tracheal Aspirates[39,89]

Criteria for Clinical Infection	Diagnostic Threshold
Serum WBC	Leukopenia or leukocytosis*
Fever	≥38 °C
Chest radiograph	Positive radiographic findings†
Clinical change in sputum	Change in color or increase in purulence‡
Respiratory support	Addition of supplemental oxygen, hypoxemia, increase in respiratory rate, increase in ventilatory support

* ≥15,000 WBCs/mm^3 for ≤12 years of age or >12,000 WBCs/mm^3 for >12 years of age; leukocytosis defined as <4000 WBCs/mm^3.
† Abnormalities consistent with a respiratory infection per radiology read.
‡ Worsening change in color of sputum defined by the change from clear or clear/yellow to yellow or green.

Guidelines were published in 2010 by the IDSA for the diagnosis, prevention, and treatment of CA-UTIs in adults. These guidelines do not explicitly make recommendations for pediatric patients, but the evidence included in the methodology of guideline development did include some pediatric studies, lending them to extrapolation to the PICU.[63] While the guidelines focus largely on diagnosis and preventative methods of CA-UTIs, they do make recommendations on treatment duration. Regardless of catheter removal, a 7-day treatment course is recommended for patients with prompt resolution of symptoms.[63] As the tendency is to treat patients in the PICU with a positive urinalysis or urine culture for 10 to 14 days with antibiotics, patients without sepsis, urinary tract abnormalities, resistant organisms, or pyelonephritis who show prompt symptom resolution may be appropriately treated with a shorter course of antibiotics of 7 days or less. Furthermore, a 14-day treatment course is recommended in those patients with delayed resolution of symptoms.[63]

Treatment of neonatal UTIs is vastly different from that of the PICU population. Signs and symptoms of a UTI in a neonate are non-specific including fever, apnea, bradycardia, poor weight gain, vomiting, jaundice, and loose stools.[64,65] Additionally, there is a strong correlation between UTIs, neonatal sepsis, and meningitis. Some studies emerging have shown adequate treatment may be possible by using early enteral antibiotic switches without increased relapse rates, which may impact future practice.[66] However, with little quality evidence to support shorter durations of therapy in neonates, longer durations are often used. While some may see appropriate responses with 7 days of treat-

Table 4. Recommended Antibiotic Treatment Duration for Common Pediatric Infections[56,57,63,65,68,72,74]

Type of Infection	Length of Therapy*	
	PICU	NICU
Community-acquired pneumonia	5–10 days	—
Hospital-acquired pneumonia	7–10 days	7–10 days
Uncomplicated bloodstream infection†	7–10 days	10–14 days
Complicated bloodstream infection‡	14 days	14–21 days§
Catheter-associated UTI	7 days	7– 14 days
Necrotizing enterocolitis	—	7–14 days
Culture-negative chorioamnionitis	—	48–72 hr

UTI, urinary tract infection

* Length of therapy may vary depending on organism, patient-specific factors, and clinical improvement.
† Bacteremia with prompt symptom resolution and not associated with an indwelling catheter.
‡ Bacteremia associated with indwelling catheter, multiorgan dysfunction, persistent fever >48 hr or persistent positive cultures >48 hr.
§ In complicated bacteremia in a neonate, meningitis must be ruled out.

ment, typically these patients require 10 to 14 days of intravenous antibiotics with sterilization of the urine within 48 hours.[65,67]

Bloodstream Infections. There are no established guidelines specifically for the treatment of bloodstream infections in pediatrics. There are guidelines outlining the management of central line–associated bloodstream infections, which are the most common cause of bloodstream infections in pediatrics.[68] Central venous line infections without accompanying endocarditis or thrombophlebitis may be treated with catheter removal and 7 to 14 days of antibiotic therapy once blood cultures are negative.[68,69] This treatment duration has been shown to be generally safe and effective both in pediatric and adult patients across multiple inpatient settings. Bloodstream infection management can be significantly more complicated in younger pediatric patients, because a central venous line may not be able to be reasonably removed owing to limited IV access. In such complications, as well as endocarditis, thrombophlebitis, and persistent bacteremia (≥72 hours despite appropriate antibiotic therapy), longer durations of therapy are warranted.[68,69]

NICU-Specific Infections. There are several infections that occur more commonly in the NICU population and warrant antibiotic treatment, where duration of therapy should be further evaluated. Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies of a newborn.[70] There are currently no published consensus guidelines for the management of NEC with common antibiotic durations ranging from 7 to 14 days. As some literature supports an increased incidence of fungal infections in neonates medically managed with antibiotics for NEC, limiting duration of antibiotic treatment durations may protect the intestinal microbiome.[71] Additionally, some studies have found similar patient outcomes with shorter regimens of 7 to 10 days than with traditional 14-day regimens, further supporting limiting antibiotic duration.[72] Chorioamnionitis, also known as an intra-amniotic infection resulting in inflammation, is often bacterial in etiology.[73] In asymptomatic newborns born to mothers with chorioamnionitis, the American Committee of Fetus and Newborn recommends discontinuation of antibiotics within 48 to 72 hours if blood cultures remain negative.[10,74]

Ultimately, there is limited evidence and ongoing controversy regarding appropriate treatment duration for many pediatric infections seen in the PICU and NICU. However, using primary literature, societal guidelines, and an institutional guideline–driven approach accompanied with an inclusive clinical picture of the patient, we may be able to shorten antibiotic treatment duration for some of the most common infections seen in the PICU and NICU without increasing patient harm (Table 4).

Appropriate Antibiotic De-escalation

The terms *streamlining* and *de-escalation* describe the practice of using culture results and clinical response as a basis for switching from broad-spectrum antibiotics to narrow or targeted therapy.[27] Reducing patient exposure to broad-spectrum antibiotics, decreasing selective pressures of antimicrobial use, and appropriately following bacterial rule-out durations can result in decreased antimicrobial resistance and cost.[75] While the literature is sparse in pediatrics, a recent publication by Stultz et[76] showed that patients with third-generation cephalosporin exposure for >48 hours in the previous 30 days had 8.6 times higher odds (95% CI, 3.5–21) of third-generation cephalosporin resistance.[76] Additionally, adult studies have found use of empiric antipseudomonal beta-lactams for >48 hours was an independent risk factor for the development of *Clostridioides difficile* infection.[77] Furthermore, in premature infants with sterile cultures in the first week of life, prolonged administration of empiric antibiotics was associated with an increased length of hospitalization, incidence of NEC, and death.[78]

The Surviving Sepsis Campaign (SSC) 2016 International Guidelines promote de-escalation of antibiotics for severe sepsis and septic shock because it has been proven to be a safe and effective strategy associated with lower mortality in adult patients admitted to the ICU.[79,80] However, until recently there were no such

guidelines specific to pediatric patients. In February 2020, the Society of Critical Care Medicine published SSC Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children that recommend a daily clinical and laboratory assessment for de-escalation of antibiotic therapy.[81] The guidelines recommend, once pathogen(s) and sensitivities are available, to narrow original empiric antibiotic coverage.[81] If no pathogen is identified, the guidelines recommend to narrow or stop antibiotic coverage, based on clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement. In children without evidence for immune compromise or MDROs, the guidelines recommend against multiple antibiotics directed at the same pathogen for synergy purposes.[81]

While the concept of step-down or de-escalation of therapy seems intrinsically logical, in clinical practice it faces many barriers. It challenges the natural instinct of the clinician to continue with a treatment that is proving to be effective in managing, in many circumstances, a life-threatening illness or infection in a patient. Additional challenges include time needed for cultures to grow and then identify pathogens and their antibiotic sensitivities, as well as the effect of previous therapy on diagnostic yield.[81] Furthermore, positive cultures in children with suspected bacterial sepsis can be as low as 2.2% to 11.1% depending on etiology of infection and quality of cultures obtained.[82,83] Advances in technology, such as multiplex PCR, are helping to address this challenge by rapidly identifying pathogens.[84] Many of our PICU and NICU patients have complex, long-term medical conditions that inherently will require multiple additional hospitalizations. Sparing unwarranted and unnecessary antimicrobial therapy is essential in retaining the ability to have safe and effective antimicrobial treatment options for future management of their medical conditions.

Conclusion

The importance of implementing ASPs has been outlined by multiple organizations. However, there is little guidance on how to incorporate traditional ASP strategies in pediatric critical care units. This review explores the challenges of appropriate antibiotic use in the pediatric and neonatal intensive care units and summarizes strategies ASPs can use to overcome these challenges. Strategies to overcome common challenges include appropriate initial antibiotic selection, appropriate antibiotic treatment duration, and de-escalation of therapy. Additionally, an institutional guideline–driven approach accompanied with patient-specific factors should be used when societal guidelines are not available. Implementation of the above strategies may be beneficial in reducing the use of broad-spectrum antibiotics, decreasing hospital cost, reducing antibiotic resistance patterns in pediatric critical care units, and improving patient outcomes.

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