



Expanding Existing Antimicrobial Stewardship Programs in Pediatrics: What Comes Next

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The prevalence of pediatric antimicrobial stewardship programs (ASPs) is increasing in acute care facilities across the United States. Over the past several years, the evidence base used to inform effective stewardship practices has expanded, and regulatory interest in stewardship programs has increased. Here, we review approaches for established, hospital-based pediatric ASPs to adapt and report standardized metrics, broaden their reach to specialized populations, expand to undertake novel stewardship initiatives, and implement rapid diagnostics to continue their evolution in improving antimicrobial use and patient outcomes.

Keywords. antimicrobial stewardship; infectious diseases; pediatrics.

The prevalence of antimicrobial stewardship programs (ASPs) that target the pediatric population is increasing across the United States. Although the number of newly developed programs increases annually, many programs have existed for more than 5 years and are prepared to undertake new interventions, track and report novel process measures and clinical outcomes, implement cutting-edge diagnostic assays, and expand their scope to new populations. The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America stewardship guidelines provide a valuable resource for guiding clinicians interested in developing and implementing ASPs [1–3]. Furthermore, regulatory efforts to mandate stewardship activities, such as laws in California and Missouri and the elements of practice required for The Joint Commission accreditation, have increased [4–6]. Although President Obama's executive order in 2014 required the US Department of Health and Human Services to propose new regulations for the implementation of ASPs, work has stalled on making the presence of formal ASPs in acute care hospitals a condition of participation for Medicare and Medicaid Services [7]. The goal of our review was to supplement existing resources by describing the current state of pediatric antimicrobial stewardship in

developed countries and provide suggestions on how ASPs can continue to evolve and extend their efforts in new directions as their programs mature. Expanding stewardship programs into developing countries is critically important but is beyond the scope of this review [8].

ASP COMPOSITION AND PREVALENCE

The presence of ASPs in pediatric facilities is increasing rapidly. As of 2011, a survey of 38 freestanding children's hospitals revealed that 16 (42%) had a formal ASP, whereas an additional 14 (37%) were actively implementing programs [9]. Among the 16 hospitals with an ASP, physician full-time equivalent (FTE) support for their stewardship role was provided in 14 (median, 0.25 FTE [range, 0.1–0.5 FTE]), whereas 13 (81%) hospitals had a dedicated pharmacist FTE (median, 0.5 FTE [range, 0.1–1.5 FTE]). Prospective audit and feedback, formulary restriction, and clinical guidelines were commonly cited (87%) by these programs as strategies used. Although most ASPs follow the model of using dedicated clinical pharmacy and infectious disease (ID) specialists, at least 1 pediatric ASP uses an alternative model to operationalize its program and integrates ASP activities into the daily function of service-based clinical pharmacists and of ID physicians during weekends and holidays [10]. Several reports that described ASPs in adult institutions also described a model of including multiple clinical pharmacists' participation in their ASP activities [11, 12]. Furthermore, a pediatric model of daily face-to-face "handshake stewardship" has been successful in optimizing antimicrobial use and increasing the number of ID consultations [13, 14].

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COMMON AND EMERGING METRICS FOR ONGOING ASP EVALUATION

Although rigorous evaluation of pediatric ASPs has been lacking, studies have found a significant positive effect of both formalized ASPs and other informal antimicrobial stewardship initiatives. In their systematic review, Smith et al [15] evaluated 9 studies that involved formalized pediatric ASPs and 8 studies that included other antimicrobial stewardship activities and found a significant reduction in antibiotic use across centers. Several of the included studies also identified significant cost savings as a result of ASP activities, and others identified improved “appropriateness of use” based on clinical guideline recommendations as the gold standard [15].

Ensuring sustained effectiveness and viability of established ASPs requires formal measurement, which can involve process measures (eg, days of antimicrobial therapy, length of antimicrobial therapy, cost data), clinical outcomes (eg, rates of *Clostridium difficile* infections [CDIs], length of hospital stay, related readmissions), and/or balancing measures (eg, ensuring that use of narrower-spectrum therapies does not result in increased treatment-failure rates). ASPs should measure outcomes across several categories to demonstrate effectiveness and identify areas for improvement.

Process measures generally focus on antibiotic-usage data, calculated at the patient, unit, or hospital level as either the defined daily dose or days of therapy (DOT). DOT is the measure used more commonly in the United States and is recommended by the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America. The DOT metric represents the overall total number of antibiotics administered over a total number of days. For example, a patient who receives 2 antibiotics for 5 days each will have 10 DOT. A limitation of DOT is that it cannot account for spectrum of activity, so the use of a narrow-spectrum multidrug regimen will increase the DOT metric more than the use of a single very-broad-spectrum agent. Similarly, the DOT measure alone cannot capture desired therapy changes, such as deescalation from a single broad-spectrum agent to a more targeted one, but this limitation can be addressed by tracking consumption of specific targeted agents [10]. Complementary metrics, such as the antibiotic spectrum index, have been developed to measure patterns of antibiotic selection and deescalation and address these limitations [16].

A DOT numerator is normalized to the hospital census, generally by using 1000 patient-days as the denominator; patient-days are calculated on the basis of the hospital census at a given time of day (eg, midnight) [17, 18]. Alternatively, the CDC created an electronic tool, called the antibiotic-use option, and encourages acute care facilities to report their antibiotic-usage data to the National Healthcare Safety Network by using the numerator of DOT and the denominator of 1000 days present to encourage risk-adjusted interfacility and intrafacility benchmarking of antibiotic use [19]. The days-present metric is calculated as the number of patients who were present for any

portion of a day during a calendar month at a specific location. For example, if a patient were to be admitted to the pediatric intensive care unit (PICU) on Monday afternoon, remain there Tuesday and Wednesday, and be transferred to the general pediatric ward Wednesday and discharged home later that day, he or she would contribute 3 days toward the PICU days-present denominator and 1 day toward the pediatric-ward denominator. Note the subtle difference between patient days and days present; patient days are often 1 less than the hospital length of stay (2 days in the example above, because the patient was present only at midnight on 2 days), whereas the days-present denominator enables capture of the entire time in the hospital and time in different locations (3 days present in the PICU plus 1 day present in the medical ward in the example above). In this regard, the days-present measure enables a more nuanced assessment and benchmarking of where antibiotic use occurs within a hospital.

Length of therapy (LOT), defined as the total number of calendar days on which a patient received antibiotics, can be useful also. For example, the DOT/LOT ratio provides a measure of the mean number of antibiotics received by each patient per day. Evaluating these metrics for a hospital overall, and according to clinical unit (eg, medical or PICU), service line (eg, pulmonary or hematology/oncology), antibiotic class (eg, macrolides or carbapenems), or route (eg, oral or intravenous), are all informative for a program that seeks to identify areas for further work. Last, hospitals can compare themselves to one another; ASPs from hospitals that participate in the Pediatric Health Information Systems database have collaborated to share antibiotic-use data and benchmark against one another [20].

Beyond these utilization metrics, ASPs can consider monitoring other process measures, such as time to optimal therapy for patients with an invasive infection, percent agreement with ASP recommendations, percent of peripherally inserted central catheters potentially avoided, and time to conversion from intravenous to oral administration of highly bioavailable antibiotics. These data, when stratified according to clinical unit or service line, can suggest areas for ongoing improvement. ASPs should monitor proactively for compensatory changes in antibiotic-prescribing behavior on the basis of their activities (ie, balancing measures such as an increase in piperacillin-tazobactam use after carbapenem access restriction), and periodically reevaluate whether program strategies should be updated (such as adding new formulary restrictions).

Although process measures are important for ASPs to monitor, they might not be compelling to prescribing clinicians; therefore, some resources should be applied to evaluating clinical outcomes that can be reported to clinicians. Programs can track clinical data, including mortality rate, hospital length of stay, and readmissions, especially when focused on patients confirmed to have an infection (eg, bloodstream infection) [21–23]. Programs should especially consider tracking the CDI

rate because it is a concretely measurable outcome and is associated with increased LOS and cost and death among children, and ASP efforts have been found to reduce the incidence of CDIs [24, 25]. Tracking CDI rates among children is not without some difficulty, however, given the various diagnostic tests available and the prevalence of *C difficile* colonization among young children [26]. Other potentially relevant clinical outcomes include antibiotic appropriateness and incidence of antibiotic-resistant pathogens. ASPs might need to communicate that, even if an improvement in clinical outcome is not observed, a lack of worsening clinical outcomes (eg, finding that reducing the duration of therapy for patients with community-acquired pneumonia from 10 to 5 days does not increase hospital readmissions) might be just as meaningful. Also, it must be acknowledged that assigning causality to changes in clinical outcomes can be challenging, because certain events, such as death, are relatively rare in children.

EXTENDING ASP STRATEGIES TO NEW TARGET AREAS AND POPULATIONS

Many ASPs have focused on the use of specific targeted antibiotics through either preprescription authorization or post-prescription audit and feedback. Focusing instead on specific infectious syndromes might be more meaningful to clinicians, because they are invested directly in their patients' outcomes but might be less concerned with specific antibiotic-use metrics. For example, the message "we want to improve the diagnosis and treatment of children with hospital-acquired pneumonia" might foster more clinician engagement than "we want to reduce unnecessary vancomycin use." A number of clinically relevant syndromes should be considered for targeting, including community-acquired pneumonia [27, 28], skin and soft-tissue infections [29], appendicitis [30, 31], bone and joint infections [32], and prevention of surgical-site infection [33].

Established programs should consider expanding their efforts to include subpopulations that account for a small percentage of the overall population but receive a disproportionately high percentage of antibiotics. Stewardship activities have been successful and are warranted in these subpopulations, including children with a malignancy, solid organ or hematopoietic stem cell transplantation recipients [34, 35], neonates [36], children in the emergency department [37, 38], and children with a medically complex condition, such as those with cystic fibrosis [39] or who are undergoing a surgical procedure [40]. A reasonable starting point for any new effort is to develop evidence-based local guidelines that include input from a multidisciplinary team, which is best achieved through in-person meetings. ASP members might find that integrating their efforts into existing clinical specialty workgroups and meetings is a good entry point. Process and outcome measures should be relevant to the specific service(s) targeted; thus, inclusion of

a physician or pharmacist champion from an individual service who will assist in developing relevant stewardship metrics is critical [3, 41]. As an example, when developing guidelines with a PICU that involve reducing the duration of therapy for children with ventilator-associated pneumonia, the ASP might believe that the emergence of resistant pathogens is an important outcome, whereas the PICU faculty might think that reintubation rates are more meaningful.

Other novel populations for ASPs to target are defined not by their underlying disease process but by other facets of their care. For example, ASPs can focus on children being discharged to undergo outpatient parenteral antimicrobial therapy (OPAT). Overuse of OPAT exposes patients to complications such as catheter-associated infections and thrombosis, and OPAT can be avoided in some children in favor of oral therapy for infections such as osteomyelitis [32, 42, 43]. Similarly, investigating and removing unnecessary β -lactam allergy labels represents an opportunity for ASPs to direct patients toward first-line, generally more narrow-spectrum, agents [44, 45]. ASPs can contribute to our understanding of optimal antibiotic dosing and pharmacokinetics by periodically updating local standards around antibiotic use (eg, considering use of the vancomycin area under the curve/minimum inhibitory concentration ratio or use of extended-infusion β -lactams) [46, 47]. Electronic health record order sets have been modified to decrease the duration of antibiotics for those with some common infections, and use of automatic antibiotic order discontinuation after a brief period of empiric use seems safe and effective at reducing broad-spectrum antibiotic use [23, 48]. Hospitals with a large referral base can even consider using their local ASP resources to provide stewardship remotely to other community hospitals [49]. Last, because more than 80% of all pediatric antibiotic use occurs in an ambulatory setting, some ASPs are expanding to provide resources and guidance for patients in these settings [50–52].

IMPLEMENTATION OF ASP INTERVENTIONS WITH RAPID DIAGNOSTICS

The clinical microbiology laboratory's role in stewardship activities has been limited to developing guidelines for appropriate specimen testing, antibiogram creation, and selective reporting ("blinding") of antibiotic-susceptibility test results. However, the recent explosion of new technologies that enable both earlier identification of pathogens and detection of select antibiotic-resistance genes brings the clinical microbiology laboratory to the forefront of ASP activities. ASP leaders can work with microbiologists to provide clinician education about specific diagnostics before implementation. Table 1 summarizes the targets, turnaround times, and clinical outcomes associated with commonly used rapid diagnostic tests in the clinical microbiology laboratory.

Table 1. Select US Food and Drug Administration–Approved Rapid Diagnostic Assays Used in Clinical Practice

Technology	Manufacturer(s)	Specimen Origin	Organisms Detected	Resistance Target(s)	Approximate Time Required (hours)	Notes*
MALDI-TOF MS [58, 59, 90–93]	Bruker Daltonics, Inc.; bioMérieux, Inc.	All body sites	Large numbers of bacteria and yeast	None	0.2	Reduces costs, high sensitivity and specificity except for polymicrobial cultures; decreases LOS and costs
PNA FISH [94–99]	AdvandX, Inc.	Blood	<i>Staphylococcus aureus</i> /coagulase-negative staphylococci, <i>Enterococcus faecalis</i> /other <i>Enterococcus</i> spp., <i>Escherichia coli</i> / <i>Klebsiella pneumoniae</i> / <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i> / <i>C parapsilosis</i> / <i>C tropicalis</i> / <i>C glabrata</i> / <i>C krusei</i>	<i>mecA</i>	<2	Reduces LOS, costs, time to effective therapy, and mortality rate
Nucleic acid microarray BC-GP [53–55]	Nanosphere, Inc.	Blood	<i>Staphylococcus</i> spp (<i>S aureus</i> , <i>S epidermidis</i> , <i>S lugdunensis</i>), <i>Streptococcus</i> spp (<i>S pneumoniae</i> , <i>S pyogenes</i> , <i>S agalactiae</i> , <i>S anginosus</i> group), <i>E faecalis</i> , <i>Enterococcus faecium</i> , <i>Listeria</i> spp	<i>mecA</i> , <i>vanA</i> , <i>vanB</i>	<3	Reduces time to effective therapy, LOS, and costs
Nucleic acid microarray BC-GN [100, 101]	Nanosphere, Inc.	Blood	<i>E coli</i> / <i>Shigella</i> spp, <i>K pneumoniae</i> , <i>K oxytoca</i> , <i>P aeruginosa</i> , <i>S marcescens</i> , <i>Acinetobacter</i> spp, <i>Proteus</i> spp, <i>Citrobacter</i> spp, <i>Enterobacter</i> spp	<i>bla_{TEM}</i> , <i>bla_{SHV}</i> , <i>bla_{CTX-M}</i> , <i>bla_{IMP}</i> , <i>bla_{OXA}</i>	<3	Reduces time to effective therapy, costs, and mortality rate
FilmArray [60, 102, 103]	BioFire, Inc.	Blood, cerebrospinal fluid, stool	<i>E coli</i> , <i>K oxytoca</i> , <i>K pneumoniae</i> , <i>Enterobacter cloacae</i> , <i>Serratia</i> spp, <i>Proteus</i> spp, <i>Acinetobacter baumannii</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>P aeruginosa</i> , <i>Staphylococcus</i> spp (<i>S aureus</i>), <i>Streptococcus</i> spp (<i>S agalactiae</i> , <i>S pyogenes</i> , <i>S pneumoniae</i>), <i>Enterococcus</i> spp, <i>Listeria monocytogenes</i> , <i>Clostridium difficile</i> , <i>C albicans</i> , <i>C glabrata</i> , <i>C parapsilosis</i> , <i>C krusei</i> , <i>C tropicalis</i> , <i>Cryptococcus neoformans</i> ; CMV, HSV, HHV6, enterovirus, parechovirus, norovirus, adenovirus	<i>mecA</i> , <i>vanA</i> , <i>vanB</i> , <i>bla_{TEM}</i> , <i>bla_{SHV}</i>	<2	Reduces treatment of contaminated blood cultures, broad-spectrum antibiotic use, and time to appropriate antibiotic escalation and deescalation ^b
qPCR [56, 57, 61]	BD GeneOhm, Inc., Cepheid	Blood, wounds	<i>S aureus</i> , coagulase-negative <i>Staphylococcus</i> spp	<i>mecA</i> , <i>SCCmec</i>	<2	Reduces time to appropriate therapy, LOS, and costs
FilmArray [104]	BioFire, Inc.	Respiratory secretions	Adenovirus, coronavirus, human metapneumovirus, influenza A, influenza B, parainfluenza, rhinovirus/enterovirus, RSV, <i>Bordetella pertussis</i> , <i>Chlamydia pneumoniae</i> , <i>Mycoplasma pneumoniae</i>	None	<2	Reduces antibiotic use among patients with influenza

Abbreviations: BC-GN, Gram-negative blood culture test; BC-GP, Gram-positive blood culture test; CMV, cytomegalovirus; HHV6, human herpesvirus 6; HSV, herpes simplex virus; LOS, length of stay; MALDI-TOF, matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry; PNA FISH, fluorescence in situ hybridization using peptide nucleic acid probes; qPCR, quantitative polymerase chain reaction; RSV, respiratory syncytial virus.

*Successful outcomes described in this column often involved active assistance from an antimicrobial stewardship program.

^bRandomized controlled trial—level data.

The use of many of these diagnostic tests has been associated with decreased time to effective therapy [53–57], shorter hospital lengths of stay [53, 56–59], reduced hospital costs [53, 54, 56, 57], and reduced mortality rates [53, 59]. However, to optimize clinical outcomes, these novel diagnostics should ideally be implemented with clinical decision support that guides result interpretation and appropriate antibiotic prescribing [58–62]. Such decision support comes in many forms, from electronic comments within the microbiology result report to real-time auditing and feedback by an ASP.

An important caveat is that rapid molecular diagnostics used to detect resistance determinants among Gram-positive organisms can predict methicillin or vancomycin resistance reliably and lead to antibiotic escalation and deescalation. In contrast, Gram-negative bacteria contain a plethora of resistance mechanisms, including β -lactamases, porin mutations, and efflux pumps, so currently available molecular platforms that identify specific β -lactamases are useful to rule in drug resistance and escalate therapy but cannot rule out resistance and are unlikely to affect decisions about deescalating antibiotics for these infections [63]. Last, some diagnostic tests can be overused or used incorrectly (such as ordering *C difficile* testing for an infant), so programs should steward microbiologic diagnostic testing, because doing so has the potential to decrease unnecessary antibiotic use and improve patient outcomes [64].

Because much of the antibiotic use in hospitalized children is empiric, use of rapid diagnostics to identify specific viral infections (such as RSV or HSV) can help reduce unnecessary antibiotic use [65]. Procalcitonin (PCT) is a diagnostic test that is used increasingly as a biomarker to distinguish bacterial infections from other infectious and inflammatory conditions. Although most studies to date have been in adults, the literature on the utility of PCT in the evaluation of infants with fever, pneumonia, and severe bacterial infections is growing [66–68]. Several studies in adults have found that when PCT testing is combined with treatment algorithms developed by ASPs, patients are exposed to significantly shorter antibiotic courses with no increase in adverse clinical outcomes [69, 70]. PCT testing may similarly enhance judicious antibiotic prescribing for children and deserves further study.

TRAINING OTHER STAFF IN STEWARDSHIP EFFORTS

The sustainability of stewardship requires its adoption across providers and disciplines, beyond ID physicians and clinical pharmacists, and requires ongoing education. For 2017, The Joint Commission developed a new antimicrobial stewardship standard that requires hospitals to educate antibiotic prescribers about appropriate antibiotic use, such as through use of existing CDC tools or other locally developed materials [6]. Engaging other hospital pharmacists who are not members of the ASP is a way to extend ASP activities across the hospital. Furthermore,

nurses are increasingly identified as critical partners in stewardship activities [71, 72]. According to the CDC core elements for antibiotic stewardship, nurses are encouraged to review medications as part of their routine duties and can prompt discussions of antibiotic treatment, indication, duration, and patient readiness to transition to oral therapy [73, 74]. Hospitalists can likewise be vital partners in stewardship efforts, because their discipline is expanding rapidly, and they often are involved with quality improvement efforts and the efficient use of healthcare resources. A previous multisite hospitalist collaborative successfully enhanced antimicrobial documentation, accessibility to local guidelines, and implementation of a 72-hour antibiotic timeout [75]. The Vermont Oxford Network's Newborn Improvement Collaborative for Quality is an interdisciplinary association that has focused on antimicrobial stewardship for its 2016 and 2017 organization goals [76]. Integration of formal stewardship training activities into medical education, such as online curricula and lectures for medical students or rotations in stewardship for residents and fellows, is also essential for ensuring adequate preparation for the future generation of antibiotic prescribers [77, 78].

FUTURE RESEARCH TARGETS

Over the past several years, an increasing number of acute care facilities have implemented pediatric ASPs [79]. With this growth comes the opportunity to engage in research that examines understudied aspects of stewardship, such as the role of behavior change in intervention implementation, stewardship in novel patient care settings, and using targeted assessments of stewardship outcomes to optimize stewardship interventions.

Although the aim of stewardship interventions is to prompt behavior changes in antibiotic prescribers [80], most stewardship interventions lack an assessment of the behavioral determinants of prescribing practices to produce sustainable change [81]. Studies that have examined behavioral determinants have identified a "prescribing etiquette" that includes adherence to social norms [82] and the influence of the medical hierarchy [81] as factors that underlie certain prescribing behaviors. Additional studies that identify the beliefs that drive antibiotic-prescribing practices and the barriers to practicing stewardship are needed to direct the development of sustainable stewardship interventions.

In addition, given the variety of patient care settings and the disparities between resources available to clinicians across these settings, it is clear that a one-size-fits-all approach cannot address the stewardship needs of the larger medical community effectively [83]. Much of the pediatric research performed to date has assessed stewardship programs in the acute care setting, primarily within freestanding children's hospitals [84]. The need to expand antimicrobial stewardship across the healthcare spectrum and the need for further research in pediatric long-term care facilities has become evident.

Likewise, community hospitals might not have regular access to those specialists who traditionally comprise an ASP, such as ID physicians or clinical pharmacists [85]. Although strategies about how to tailor the composition of an ASP to community hospital settings have been suggested [79, 83], studies that validate the efficacy of these approaches, including the role of telemedicine, have been lacking.

In the tertiary care pediatric inpatient setting, more work is also needed to understand patterns of antiviral and antifungal use and to curb their overuse, given their potential for toxicity and high cost [86]. As electronic medical record systems continue to evolve, the ability to use advanced decision support to optimize antibiotic prescribing in real time for individual patients will also become increasingly widespread.

If the aim of stewardship is to optimize clinical outcomes and minimize unintended consequences of antibiotic use by improving antibiotic prescribing, it follows that studies are needed to evaluate the effect of stewardship interventions on clinical outcomes. However, studies that evaluate ASPs have focused mostly on process outcomes, such as decreased antibiotic use and decreased cost [87]; data on the effect of stewardship interventions on clinical outcomes have been generally limited to specific disease syndromes [88]. Although economic metrics have been helpful in obtaining support from hospital administrators [89], these metrics fail to provide an adequate assessment of a given intervention's ability to accomplish the aims of stewardship, and formal economic evaluation of costs avoided is difficult. Studies that evaluate clinical outcomes (eg, clinical cure or failure, resistance rates, rates of CDI, adverse drug reactions or interactions, and length of stay) are needed to aid in further determining optimal interventions and to highlight the importance of stewardship programs for clinicians.

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