



Antibiotic Stewardship in Pediatrics

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Antibiotic overuse contributes to antibiotic resistance, which is a threat to public health. Antibiotic stewardship is a practice dedicated to prescribing antibiotics only when necessary and, when antibiotics are considered necessary, promoting use of the appropriate agent(s), dose, duration, and route of therapy to optimize clinical outcomes while minimizing the unintended consequences of antibiotic use. Because there are differences in common infectious conditions, drug-specific considerations, and the evidence surrounding treatment recommendations (eg, first-line therapy, duration of therapy) between children and adults, this statement provides specific guidance for the pediatric population. This policy statement discusses the rationale for inpatient and outpatient antibiotic stewardship programs; essential personnel, infrastructure, and activities required; approaches to evaluating their effectiveness; and gaps in knowledge that require further investigation. Key guidance for both inpatient and outpatient antibiotic stewardship programs are provided.

REVIEW OF EVIDENCE

Overview

Antibiotics are the most common class of medications prescribed to children.¹ Although antibiotic therapy has saved countless lives, their overuse can cause harm. Antibiotic exposure can lead to antibiotic resistance, *Clostridioides difficile* infections (CDIs), and other drug-related adverse events, such as end-organ toxicities, diarrhea, rashes, cytopenia, and anaphylaxis. The Centers for Disease Control and Prevention (CDC) estimates that antibiotic-resistant microbes cause nearly 3 million infections and 35 000 deaths each year in the United States.² Antibiotics are frequently used in both pediatric inpatient and outpatient settings, with a significant proportion of antibiotic use considered unnecessary.³ Antibiotic stewardship is a practice dedicated to using antibiotics only when necessary and, when antibiotics are deemed necessary, to targeting the spectrum of activity and using the appropriate dose, route, and duration of therapy to optimize clinical outcomes while minimizing the

abstract

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undesirable consequences of antibiotic use.⁴ A growing body of evidence demonstrates that antibiotic stewardship programs (ASPs) reduce antibiotic overuse while improving patient outcomes. Consistent with the CDC, the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society, the American Academy of Pediatrics endorse the development and implementation of ASPs across pediatric health care settings.

This policy statement discusses the rationale for inpatient and outpatient ASPs; essential personnel, infrastructure, and activities required; approaches to evaluating their effectiveness; and gaps in knowledge that require further investigation.

The Role of ASPs

Strategies to address antimicrobial use and the emergence of antimicrobial-resistant pathogens, including formulary management and restriction, have been used for more than 4 decades, but results of such interventions were variable. Briceland et al⁵ published the first evidence showing the positive effects from the use of a formal program with an infectious disease physician and pharmacist audit and feedback in 1988, and thereafter, there have been increasing efforts to customize and apply such stewardship strategies at hospitals throughout the United States. In a consensus statement by the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society, antibiotic stewardship has been defined as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration.”⁶ Although most of the evidence base

for antibiotic stewardship has focused on the acute care setting, the CDC has published core elements of antibiotic stewardship for acute care (including small and critical access hospitals), long-term care, and ambulatory care settings.⁷

Unintended Consequences of Antibiotic Use in Children

Although numerous antibiotics have been developed since the discovery of penicillin, they have been closely followed by the development of increasingly complex mechanisms of antibiotic resistance by bacterial pathogens as these agents have been introduced into clinical practice.⁸ The increase in multidrug-resistant infections has outpaced the development of novel antibiotics capable of treating them.⁹ Although not addressed in this document, the use of antibiotics in animal agriculture also contributes to antibiotic resistance.¹⁰

Adverse consequences associated with antibiotic use extend beyond the development of resistance in targeted organisms. As seen from evaluation of pediatric data from the National Electronic Injury Surveillance System in the United States between 2011 and 2015, antibiotic-associated adverse drug events accounted for almost 50% of emergency department visits for adverse events from systemic medications.¹¹ CDI is another potential consequence of antibiotic use. In a large surveillance study, 71% of CDI cases in children were community associated and generally developed after exposure to antibiotics prescribed during ambulatory encounters for otitis media, sinus infections, or acute respiratory tract infections (ARTIs).¹² Researchers in more recent investigations have explored the effect of antibiotic exposure on the intestinal microbiome. Data suggest the potential for antibiotic exposures, especially when frequent and occurring early in life, to promote

intestinal dysbiosis and possible effects on the development of conditions such as juvenile idiopathic arthritis, inflammatory bowel disease, asthma, and diabetes.^{13–15}

Inpatient ASPs

Stewardship programs dedicated to a variety of pediatric patient populations are becoming increasingly prevalent in the United States. A 2011 survey of 38 freestanding children’s hospitals reported that 42% had established ASPs and an additional 37% were in the process of implementing programs.¹⁶ In 2014, the CDC compiled a checklist of “Core Elements of Hospital Antibiotic Stewardship Programs” that included the following: support from leadership for the ASP, including appropriate financial support; an identified physician leader for the ASP; a pharmacist coleader; support from other relevant stakeholders (ie, microbiology laboratory personnel, infection prevention team members, information technology staff, and nursing and other allied health professionals, among others); specific interventions to improve antibiotic use (eg, prior approval, postprescription review with feedback, etc); pharmacy-driven interventions (eg, dose optimization, therapeutic drug monitoring, automatic conversion of intravenous to oral antibiotic therapy, etc); recommendations for the diagnosis and treatment of specific syndromes (eg, community-acquired pneumonia, urinary tract infections, etc); monitoring antibiotic prescribing and resistance patterns and regularly reporting findings to health care workers; and educating health care workers about resistance and optimal prescribing.¹⁶ In January 2017, The Joint Commission (TJC) Antimicrobial Stewardship Standard went into effect, further emphasizing the need for all acute care facilities to have ASPs.¹⁷ The Pediatric Antibiotic Stewardship Program Toolkit

developed by the American Academy of Pediatrics and the Pediatric Infectious Diseases Society offers guidance more specific to the pediatric population.¹⁸ For hospitals with both adult and pediatric patients, inclusion of a pediatric infectious diseases physician and/or pharmacist as members of the ASP is recommended.

The core team members of ASPs include physician and pharmacist leaders, according to both the CDC Core Elements¹⁶ and TJC Antimicrobial Stewardship Standard.¹⁷ Dedicated financial support to these leaders is critical to enable the success of stewardship programs.¹⁹ Ideally, both physicians and pharmacists will have an infectious diseases fellowship or postgraduate year 2 infectious diseases residency training, respectively, to ensure comprehensive knowledge of the diagnosis and management of infectious diseases.²⁰ In resource-limited settings, ASPs may be led by physicians and/or pharmacists without formal infectious diseases training; however, an ASP team member with pediatric expertise is required. Although team members are encouraged to develop program goals together, unique roles for the physician leader include underscoring to other clinicians how the overarching goals of the ASP are to optimize patient outcomes and prevent unnecessary harm to patients and to function as a bridge to hospital executive leadership. Pharmacists typically conduct the majority of routine interventions and often lead efforts to compile and validate antibiotic use data. The pharmacist also functions as a liaison between providers and both the department of pharmacy and the therapeutic standards committee to encourage agreement between stewardship and pharmacy goals.

Close relationships between stewardship leaders and hospital

leaders can further the goals of the stewardship program.^{16,17} Along with financial resources, executives can facilitate the involvement of stewardship leaders in strategic high-level meetings and connect the stewardship team to institution-wide stakeholders who can help further disseminate concepts of stewardship.

Both the CDC Core Elements and TJC Antimicrobial Stewardship Standard highlight the importance of monitoring antibiotic use and antibiotic resistance.^{16,17} A data analyst can support the stewardship program by compiling relevant antibiotic use and microbiological data that can periodically be fed back to hospital administration and clinicians and identify necessary interventions led by the ASP. Moreover, the data analyst can lead efforts to report institutional data to the CDC National Healthcare Safety Network Antimicrobial Use and Resistance Module.¹⁶

Nurses are valuable partners in antibiotic stewardship efforts and can be actively integrated into stewardship interventions.²¹ Bedside nurses provide continuity of care to patients and can be vital in ensuring that goals of care are carried over and readdressed on a daily basis.²² Furthermore, nurses can assist with alleviating patient and guardian concerns about antibiotic use (or a perceived but appropriate “lack” of antibiotic use). Additional guidance on specific examples of how valuable nurses can be to stewardship efforts are available.^{21,23} Additionally, the stewardship team may consider working closely with the clinical microbiology laboratory to assist with antibiogram development (ie, a periodic report summarizing the susceptibility activity of a bacteria to a variety of antibiotics), help inform selective reporting of antibiotic susceptibility results, and improve the selection and implementation of rapid diagnostic tests. The stewardship team can also function as

a conduit between the microbiology laboratory and clinician by educating providers about appropriate culture specimen collection and testing criteria as well as interpretation of the antibiogram and rapid diagnostic test results.²⁴ Finally, stewardship teams can work with the infection prevention team as the infection prevention team compiles data on hospital-wide resistant organism trends and *C difficile* laboratory-infectious disease events (a metric standardly collected by many US hospitals on a quarterly basis and reported to the CDC) that can be informative in guiding stewardship interventions.

Stewardship Strategies in the Inpatient Setting

Local Guidelines

The development and dissemination of institutional guidelines for diagnosing and treating common infectious syndromes is a key function of stewardship programs. Guidelines provide evidence-based and standardized diagnostic and treatment recommendations based on local data and promote adherence to the use of formulary drugs. Inpatient antibiotic guidelines can be developed to target common indications for antibiotic use, such as community-acquired pneumonia, urinary tract infections, hospital- and ventilator-associated pneumonia, skin and soft tissue infections, intraabdominal infections, and neonatal and pediatric sepsis. These indications represent the majority of antibiotic use in most institutions.²⁵ Inpatient guidelines can discuss appropriate clinical criteria suggestive of bacterial infections, diagnostic testing (including imaging studies when needed), specific empirical and targeted therapy (including dosing and options for severe drug allergies), and appropriate durations of therapy. Each guideline can be developed with input from each of the relevant

specialties and include medical, pharmacy, and nursing representatives. Ensuring guidelines are available at the point of care (eg, intranet, patient unit handbooks, pocket cards, apps, etc) increases the likelihood that clinicians will easily access them when necessary. Finally, periodic reviews and updates of local guidelines by the stewardship team will maintain their relevance as new evidence emerges.

Prior Approval Versus Postprescription Review With Feedback

Stewardship programs should determine their approach to interventions on the basis of available resources.²⁶ Direct, face-to-face interactions such as “handshake stewardship” is always favored when possible, because they foster a collaborative relationship between the stewardship team and clinicians, but they can be labor intensive.²⁷ Although telephone calls or notes in the medical record will never be substitutes for human interactions, they can play an important role in promoting evidence-based antibiotic use and may be more feasible for many programs. Stewardship programs may want to consider prior approval, postprescription review with feedback, or a combination of the 2 approaches to encourage judicious antibiotic use.²⁶ Prior approval generally consists of a phone call to the stewardship team for select anti-infectives justifying the use of the agent before it is dispensed by pharmacy. This approach can reduce unnecessary antibiotic initiation, optimize the selection of empirical antibiotics, provide information on optimal culture techniques, and encourage infectious diseases consultations when necessary. Drawbacks of this approach include its focus on specific restricted agents, potential to disrupt front-line clinician workflow, potential delays in antibiotic administration for sepsis, and an inability to address downstream

antibiotic use, such as intravenous to oral conversion or duration of therapy.

Postprescription review with feedback generally occurs 48 to 72 hours after antibiotics are initiated, when more clinical data are available to make recommendations. Advantages to this approach include greater flexibility in the timing of interventions and the ability to address targeted therapy decisions. An important limitation with this approach is that recommendations are generally optional because most stewardship programs are not able to enforce mandatory discontinuation of antibiotics. Additionally, postprescription review generally does not affect the first 2 to 3 days of antibiotic therapy, which often constitute a large portion of inpatient antibiotic use. A hybrid approach including a component of prior approval and postprescription review is often the most effective.²⁸

Syndrome-Specific Stewardship

Syndrome-specific interventions target specific disease processes such as community-acquired pneumonia²⁹ or skin and soft tissue infections.³⁰ It also includes perioperative prophylaxis recommendations or surgical conditions such as the management of appendicitis.^{31–33} Perioperative prophylaxis remains an important target because approximately 40% of all antibiotics in the inpatient setting are administered to surgical patients.³⁴ Syndrome-specific stewardship is generally operationalized through the development of local guidelines and targeted educational interventions around the syndrome.²⁹ Benefits include engagement of front-line clinicians and facilitation of sustained practices. Additionally, syndrome-specific stewardship can address both empirical and targeted prescribing and is generally viewed as a measure toward optimizing “patient safety” or “quality improvement,” rather than as

an approach involving less-attractive restrictive interventions.

Disadvantages include incomplete capture of all cases of a specific condition, particularly if a culture result is not the usual trigger (eg, community-acquired pneumonia); challenges obtaining consensus approaches among various stakeholders; and the inability to target antibiotic use that occurs without clear indications. When developing specific treatment recommendations in local guidelines for specific syndromes, clear criteria for determination of penicillin allergies and when penicillin allergy testing might be necessary can be helpful.

Rapid Diagnostic Tests

Diagnostic test implementation provides a unique opportunity for stewardship teams to educate providers in real time and to inform prescribing practices.²⁴ Rapid diagnostics can facilitate antibiotic de-escalation (eg, switching from vancomycin to oxacillin for methicillin-susceptible *Staphylococcus aureus* bacteremia), broadening therapy when necessary (eg, switching from vancomycin to daptomycin for vancomycin-resistant *Enterococcus faecium* bacteremia), stopping therapy (eg, discontinuing vancomycin for a single positive culture for coagulase-negative *Staphylococcus* bacteremia), or in some cases, identifying a viral etiology that may reduce the likelihood of a bacterial pathogen. Before implementing a new test, the stewardship team may want to develop and disseminate a guidance document for prescribers on how to interpret results of the new test. Moreover, the team can develop language to include in the electronic health record that is concise, relevant, and understandable to clinicians. The main disadvantage of interventions around implementation of rapid diagnostic tests is that the impact is generally limited to a small number of

patients (eg, patients with bloodstream or respiratory tract infections). Furthermore, these tests can be costly and sometimes resource intensive. Stewardship programs may also struggle with ensuring prescriber “buy-in” if the test does not have negative or positive predictive values approaching 100%.

Outpatient ASPs

The vast majority of antibiotic prescribing occurs in the outpatient setting.³⁵ One in 5 pediatric ambulatory visits result in an antibiotic prescription, accounting for nearly 50 million antibiotic prescriptions annually in the United States, at least half of which are considered inappropriate.³⁶ ARTIs account for more than two-thirds of antibiotic prescriptions for children, at least one-third of which are unnecessary.³⁷ Although most outpatient pediatric antibiotic prescriptions come from primary care encounters, subspecialty practices, emergency departments, urgent care clinics, retail clinics, and dentists’ offices are also important settings for outpatient antibiotic stewardship.

As with inpatient stewardship, effective outpatient stewardship requires strong leadership. Ideally, a single clinician leader with expertise in antibiotic use in the outpatient setting is identified. If the practice is part of a larger organization (eg, health care network), commitment from administrators, such as salary support and providing the authority to implement change, is important. Last, the ability to track and report antibiotic prescribing and, ideally, clinical outcomes data is critical for measuring the impact of interventions (and potentially as a tool for influencing appropriate antibiotic use). The Antimicrobial Stewardship Standard of TJC for the outpatient setting went into effect in January 2020.³⁸

Stewardship Strategies in the Outpatient Setting

Standard antibiotic stewardship approaches recommended for the hospital setting, such as prior approval and real time, postprescription review with feedback, are not practical in the ambulatory setting. However, a variety of stewardship strategies have been successfully implemented in outpatient practices, and their effects on antibiotic prescribing and clinical outcomes have been reviewed.^{39,40} These include, but are not limited to, clinical decision support, clinician and/or patient education (eg, watchful waiting for acute otitis media, when appropriate), and audit with feedback of antibiotic prescribing. Implementation of a systematic approach to follow up negative culture results and discontinue antibiotics that were initiated on the basis of initial signs and symptoms can also reduce exposure to antibiotics. It is common for there to be a system to notify the patient and families of positive results in cases in which an antibiotic was not prescribed; however, it is important to also have a comparable process for discontinuing antibiotics when final results are negative. Because communication between the clinician and patient and/or caregiver can influence the decision to prescribe an antibiotic, communication training is another potential strategy.⁴¹ Consideration of the sociobehavioral aspects and context of the encounter during which antibiotic prescribing might occur have also been shown to be important levers for improving practice.^{42,43} Furthermore, educating parents about the natural course of viral and bacterial infections can foster an understanding of expectations (eg, prolonged cough for viral pharyngitis). The emergency department remains a hybrid in which elements of both inpatient and outpatient stewardship generally

need to be merged to optimize antibiotic prescribing for both patients discharged from the hospital and for those who will ultimately be hospitalized.

Unnecessary Prescribing

Clinical encounters in which antibiotics could be avoided altogether can be a primary target for outpatient stewardship. Examples include antibiotic prescribing for nonspecific upper respiratory infection, bronchiolitis, acute bronchitis, asthma exacerbation, or conjunctivitis. When considering the epidemiology of bacterial infections presenting in the ambulatory setting requiring antibiotics, it has been conservatively estimated that antibiotic prescribing could be safely reduced by 30%.³⁷

Diagnosis Stewardship

Just as antibiotic prescribing rates vary across providers and practices, rates of diagnosis of the most common childhood infections have been shown to vary substantially.⁴⁴ Thus, “diagnostic stewardship” can be considered as a means to reduce prescribing. Examples include reserving antibiotic treatment of pharyngitis for children with a positive group A streptococcal test result and only testing children with a suggestive clinical syndrome, requiring characteristic findings identified by pneumatic otoscopy and clinical signs of middle ear infection to confirm and treat acute otitis media, demonstrating pyuria in conjunction with signs and symptoms suggestive of a urinary tract infection and to distinguish asymptomatic bacteriuria from true infection, and confirming severe, progressive, or prolonged and unrelenting symptoms for the diagnosis and treatment of acute bacterial sinusitis.

Antibiotic Choice

Even when antibiotics are indicated, outpatient stewardship interventions can improve patient care. Broad-spectrum second-line antibiotics are prescribed as often as first-line

recommended narrow-spectrum agents for ARTIs.³⁶ This practice can lead to avoidable adverse drug events and antibiotic resistance and can increase overall health care costs without clinical benefit over narrow-spectrum agents.⁴⁵ In some cases, these nonrecommended antibiotics are less likely to cover the most likely offending pathogen, such as oral cephalosporins or azithromycin for pneumococcus, the prime target for acute otitis media, sinusitis, and pneumonia.

Duration and Route of Therapy

Even when the right drug and dose are prescribed, the duration of therapy is an important stewardship target. Many infections treated for 10 or 14 days will respond to shorter antibiotic courses, including most uncomplicated skin and soft tissue infections, pneumonia, and urinary tract infections.⁴⁶ The use of outpatient parenteral antibiotic therapy can be limited to conditions for which oral therapy is known to be less effective.^{47,48} A large proportion of outpatient parenteral antibiotic therapy for children is unnecessary, and use of peripherally inserted central catheters is associated with a high rate of adverse events in children.⁴⁹⁻⁵¹

Challenges to implementing antibiotic stewardship in the outpatient setting include finding resources to support a program, identifying a clinician leader who has the time and interest to commit to engaging outpatient clinicians in a quality improvement initiative, obtaining data to identify high-impact targets and track process improvement and clinical outcomes, and sustaining improvement over time.

Measuring the Success of ASPs

Process Measures

When evaluating ASPs, outcomes are frequently categorized into those that are related to process outcomes (eg, antibiotic use) or to clinical outcomes (eg, length of hospital stay). This distinction is debatable, because

process outcomes, with all of their downstream effects, are themselves arguably a clinically relevant outcome. Antibiotic usage outcomes generally examine changes in antibiotic use practices after the implementation of stewardship interventions. It is always preferred to use data reporting antibiotics dispensed from the pharmacy or administered to patients rather than purchasing data when measuring antibiotic use because the former more accurately assesses antibiotic exposure. Published data from pediatric ASPs have consistently demonstrated that these programs can effectively decrease antibiotic use.⁵²⁻⁵⁷ These findings were summarized in a systematic review including 9 studies reporting outcomes from US pediatric ASPs.⁵⁸

In the past, defined daily doses per 1000 patient-days was widely accepted as an antibiotic stewardship process outcome in the inpatient setting but has largely been replaced in the United States by days of therapy (DOTs) per 1000 patient-days. As opposed to defined daily doses, DOTs have the advantage of not being affected by variations in dosing and, therefore, are more representative of pediatric prescribing practices in which dosing can vary greatly between age groups. DOTs account for the number of different antibiotics (but not doses) administered each day. For example, if a child receives cefepime, gentamicin, and vancomycin on a hospital day, this would contribute 3 DOTs. Limitations of this metric include the lack of accounting for antibiotics prescribed at the time of hospital discharge, which make it sensitive to changes in the mean hospital length of stay,^{59,60} and its inability to discriminate between antibiotic spectrum of activity (eg, a day of ceftriaxone and metronidazole would count as 2 DOTs, whereas a day of meropenem would count as 1 DOT).

Metrics that can be considered in outpatient settings include the

number of antibiotic prescriptions per monthly patient-visits, proportions of all visits or sick visits leading to antibiotics, and proportions of visits for particular diagnoses leading to antibiotics. However, because of inherent differences in the acuity of patients visiting urgent care centers versus primary care clinics and challenges with providing close follow-up of patients in urgent care settings, comparisons between antibiotic use across these practices can be problematic.

In the current medical landscape, in which payment requirements are becoming increasingly stringent, cost-saving strategies are of particular interest to health care administrators. Several investigators have found implementation of pediatric ASPs to be associated with reduced antibiotic-related expenditures.^{52,61} This is particularly true in the initial years after implementation but has also been shown to be sustainable.⁵³ Although cost savings are appealing to administrators and regulatory bodies and therefore improve resource allocation and “buy-in,” focusing on clinical outcomes is more likely to influence clinician antibiotic prescribing behavior.

Clinical Outcomes Measures

Clinical outcomes are more challenging to measure than antibiotic use, because they are more resource intensive to collect; may be rare (eg, death), so may not provide sufficient statistical power when evaluated in the context of ASP interventions; and are potentially attributable to multiple other non-stewardship-related interventions. Although improvement in clinical outcomes after optimization of antibiotic therapy is ideal, a reduction in antibiotic use without worsening clinical outcomes is also acceptable. Examples of clinical outcomes to consider include CDI, antibiotic resistance, antibiotic-

associated adverse drug events, length of stay, hospital readmission, and mortality.

CDI is a common adverse event associated with antibiotic use that has been well-studied in the adult population but less so in children. The most common standardized CDI metric is CDI cases per 10 000 hospitalizations. Reductions in rates of CDI with stewardship programs have been identified in adult populations^{38,62-64} but have not been observed in children, in part because the incidence of CDI is lower in children compared with adults, and *C difficile* has a high likelihood of being a colonizer (rather than a pathogen) in young children, making it challenging to adequately power a study to demonstrate a difference in CDI rates.

Decreasing rates of antibiotic resistance is an important goal of a stewardship program; however, similar to CDI rates, they are difficult to demonstrate, mostly because there are numerous alternate pathways by which the development and spread of antibiotic resistance occur, including lapses in infection prevention practices, outpatient antibiotic use, and mixing of patient populations from outside institutions. In addition, resistance is a dynamic process and may take months to years to emerge. A reduction in antibiotic resistance attributable to pediatric stewardship programs has not been the subject of extensive evaluation, and when it has been assessed, results have been conflicting.^{57,65-67} These findings are similar to what has been observed with adult ASPs.⁶⁸⁻⁷⁰

Hospital length of stay is frequently studied as a metric in health care interventions, although less often for ASPs. In one children's hospital in which postprescription review and feedback was used, hospital length of stay was reduced by approximately 1 day, and 30-day readmission was reduced by 3%.⁷¹ Although

decreasing length of stay is an important goal of health care institutions, it is inherently multifactorial and, thus, not ideal as a primary outcome of ASPs.

Decreased mortality is difficult to associate with ASP interventions, because it is a relatively rare outcome in children in general and because excessive antibiotic use is unlikely to meaningfully affect survival. Mortality has not been shown to be a feasible outcome of stewardship programs in either children or adults, and its use as a primary outcome is discouraged.

Gaps in Knowledge

Although the field of antibiotic stewardship has made considerable advancements over the past decade, notable knowledge gaps remain.²¹ Some gaps in knowledge for antibiotic stewardship to highlight include (1) effective adaptation of the organizational structure and interventions established for the acute care setting to ambulatory and long-term care settings, (2) understanding the cultural and adaptive influences of antibiotic prescribing, (3) understanding how best to incorporate nursing into stewardship efforts and fostering an environment in which nursing contribution is actively encouraged, (4) defining the optimal treatment of common bacterial infections specific to the pediatric population (eg, comparisons of different drug regimens, durations of therapy, parenteral versus oral therapy, and optimal dosing strategies) to improve the evidence base for stewardship recommendations, (5) developing and validating metrics that consider the potential harm of antibiotics and weigh the risks versus the benefits (ie, an antibiotic-associated harm score), (6) establishment of risk-adjusted antibiotic use benchmarking approaches, (7) approaches to effectively teaching clinicians to become "self-stewards," and (8) incorporating the patient and family

perspective and shared decision-making into stewardship.

RECOMMENDATIONS

1. The American Academy of Pediatrics and the Pediatric Infectious Diseases Society recommend establishing ASPs to improve antibiotic prescribing.
2. ASPs governing antibiotic use for children should include specialists with pediatric expertise.
3. Inpatient ASPs are ideally composed of a medical director and a clinical pharmacist(s), both with expertise in pediatric infectious diseases and/or antibiotic stewardship.
4. Inpatient ASPs can use clinical guidelines, prior approval, and postprescription review and feedback as core interventions.
5. Inpatient ASPs can include pharmacy-driven interventions such as dose optimization, therapeutic drug monitoring, automatic conversion of intravenous to oral antibiotic therapy, or dose adjustments in cases of organ dysfunction.
6. Inpatient ASPs can consider auditing, analyzing, and reporting local unit-specific antibiotic prescribing data periodically to relevant stakeholders.
7. Outpatient primary care practices, urgent care clinics, and emergency departments could consider establishing standardized approaches for antibiotic prescribing including clinical guidelines and/or decision support.
8. Outpatient stewardship can focus on judicious use of antibiotics for ARTIs, including avoidance of antibiotic prescribing for undifferentiated upper respiratory tract infection, bronchiolitis, acute bronchitis, and nonstreptococcal pharyngitis; refraining from prescribing antibiotics for urinary

tract infections in the absence of a urinalysis and urine culture; and judicious diagnosis of acute otitis media, acute sinusitis, and group A streptococcal pharyngitis.

9. Outpatient stewardship efforts can emphasize use of the narrowest-spectrum antibiotics for the shortest duration of therapy that will adequately treat bacterial infections.

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ABBREVIATIONS

ARTI: acute respiratory tract infection
ASP: antibiotic stewardship program
CDC: Centers for Disease Control and Prevention
CDI: *Clostridioides difficile* infection
DOT: day of therapy
TJC: The Joint Commission

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REFERENCES

1. Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D. Trends of outpatient prescription drug use in US children, 2002-2010. *Pediatrics*. 2012; 130(1):23–31
2. The Centers for Disease Control and Prevention. Antibiotic / antimicrobial resistance (AR / AMR): biggest threats and data. Available at: www.cdc.gov/DrugResistance/Biggest-Threats.html. Accessed December 7, 2019
3. Soyka LF, Robinson DS, Lachant N, Monaco J. The misuse of antibiotics for treatment of upper respiratory tract infections in children. *Pediatrics*. 1975; 55(4):552–556
4. American Academy of Pediatrics. Antimicrobial Resistance and Antimicrobial Stewardship: Appropriate and Judicious Use of Antimicrobial Agents. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2018: 906–910
5. Briceland LL, Nightingale CH, Quintiliani R, Cooper BW, Smith KS. Antibiotic streamlining from combination therapy to monotherapy utilizing an interdisciplinary approach. *Arch Intern Med*. 1988;148(9):2019–2022
6. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol*. 2012;33(4):322–327
7. Mansour ME, Rose B, Toole K, Luzader CP, Atherton HD. Pursuing perfection: an asthma quality improvement initiative in school-based health centers with community partners. *Public Health Rep*. 2008;123(6):717–730
8. Medernach RL, Logan LK. The growing threat of antibiotic resistance in children. *Infect Dis Clin North Am*. 2018; 32(1):1–17
9. Tamma PD, Hsu AJ. Defining the role of novel β -lactam agents that target carbapenem-resistant gram-negative organisms. *J Pediatric Infect Dis Soc*. 2019;8(3):251–260
10. Paulson JA, Zaoutis TE; Council on Environmental Health; Committee on Infectious Diseases. Nontherapeutic use of antimicrobial agents in animal agriculture: implications for pediatrics. *Pediatrics*. 2015;136(6). Available at: www.pediatrics.org/cgi/content/full/136/6/e1670
11. Lovegrove MC, Geller AI, Fleming-Dutra KE, Shehab N, Sapiano MRP, Budnitz DS. US emergency department visits for adverse drug events from antibiotics in children, 2011-2015. *J Pediatric Infect Dis Soc*. 2019;8(5):384–391
12. Wendt JM, Cohen JA, Mu Y, et al. *Clostridium difficile* infection among children across diverse US geographic locations. *Pediatrics*. 2014;133(4): 651–658
13. Horton DB, Scott FI, Haynes K, et al. Antibiotic exposure, infection, and the development of pediatric psoriasis: a nested case-control study. *JAMA Dermatol*. 2016;152(2):191–199
14. Vangay P, Ward T, Gerber JS, Knights D. Antibiotics, pediatric dysbiosis, and disease. *Cell Host Microbe*. 2015;17(5): 553–564
15. Hildebrand H, Malmborg P, Askling J, Ekbohm A, Montgomery SM. Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. *Scand J Gastroenterol*. 2008; 43(8):961–966
16. Newland JG, Gerber JS, Weissman SJ, et al. Prevalence and characteristics of antimicrobial stewardship programs at freestanding children's hospitals in the United States. *Infect Control Hosp Epidemiol*. 2014;35(3):265–271
17. The Joint Commission Antimicrobial Stewardship Standard. Approved: new antimicrobial stewardship standard. Available at: https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf. Accessed December 5, 2019
18. Pediatric Infectious Diseases Society. Pediatric antibiotic stewardship program toolkit. Available at: www.pids.org/asp-toolkit.html. Accessed June 22, 2020
19. Doernberg SB, Abbo LM, Burdette SD, et al. Essential resources and strategies for antibiotic stewardship programs in the acute care setting. *Clin Infect Dis*. 2018;67(8):1168–1174
20. Nichols K, Stoffella S, Meyers R, Giroto J; Advocacy Committee for the Pediatric Pharmacy Advocacy Group. Pediatric antimicrobial stewardship programs. *J Pediatr Pharmacol Ther*. 2017;22(1): 77–80
21. Olans RN, Olans RD, DeMaria A Jr. The critical role of the staff nurse in antimicrobial stewardship—unrecognized, but already there. *Clin Infect Dis*. 2016;62(1):84–89
22. Monsees E, Popejoy L, Jackson MA, Lee B, Goldman J. Integrating staff nurses in antibiotic stewardship: opportunities and barriers. *Am J Infect Control*. 2018; 46(7):737–742
23. Monsees EA, Tamma PD, Cosgrove SE, Miller MA, Fabre V. Integrating bedside nurses into antibiotic stewardship: a practical approach. *Infect Control Hosp Epidemiol*. 2019;40(5):579–584
24. Avdic E, Carroll KC. The role of the microbiology laboratory in antimicrobial stewardship programs. *Infect Dis Clin North Am*. 2014;28(2): 215–235
25. Magill SS, Edwards JR, Beldavs ZG, et al.; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Prevalence of antimicrobial use in US acute care hospitals, May–September 2011. *JAMA*. 2014;312(14): 1438–1446
26. Barlam TF, Cosgrove SE, Abbo LM, et al. Executive summary: implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):1197–1202
27. Messacar K, Campbell K, Pearce K, et al. A handshake from antimicrobial stewardship opens doors for infectious disease consultations. *Clin Infect Dis*. 2017;64(10):1449–1452
28. Tamma PD, Avdic E, Keenan JF, et al. What is the more effective antibiotic stewardship intervention: preprescription authorization or

- postprescription review with feedback? *Clin Infect Dis*. 2017;64(5):537–543
29. Avdic E, Cushinotto LA, Hughes AH, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. *Clin Infect Dis*. 2012;54(11):1581–1587
 30. Pasquale TR, Trienski TL, Olexia DE, et al. Impact of an antimicrobial stewardship program on patients with acute bacterial skin and skin structure infections. [published correction appears in *Am J Health Syst Pharm*. 2014;71(15):1243]. *Am J Health Syst Pharm*. 2014;71(13):1136–1139
 31. Kronman MP, Hersh AL, Gerber JS, et al. Identifying antimicrobial stewardship targets for pediatric surgical patients. *J Pediatric Infect Dis Soc*. 2015;4(4):e100–e108
 32. Sandora TJ, Fung M, Melvin P, Graham DA, Rangel SJ. National variability and appropriateness of surgical antibiotic prophylaxis in US children's hospitals. *JAMA Pediatr*. 2016;170(6):570–576
 33. Bratzler DW, Ma A, Nsa W. Surgical care improvement project adherence and postoperative infections. *JAMA*. 2010;304(15):1670; author reply 1671–1672
 34. Gerber JS, Kronman MP, Ross RK, et al. Identifying targets for antimicrobial stewardship in children's hospitals. *Infect Control Hosp Epidemiol*. 2013;34(12):1252–1258
 35. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Danziger LH. A national evaluation of antibiotic expenditures by healthcare setting in the United States, 2009. *J Antimicrob Chemother*. 2013;68(3):715–718
 36. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics*. 2011;128(6):1053–1061
 37. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *JAMA*. 2016;315(17):1864–1873
 38. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69(7):1748–1754
 39. McDonagh M, Peterson K, Winthrop K, Cantor A, Holzhammer B, Buckley DI. *Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2016
 40. Drekonja DM, Filice GA, Greer N, et al. Antimicrobial stewardship in outpatient settings: a systematic review. *Infect Control Hosp Epidemiol*. 2015;36(2):142–152
 41. Mangione-Smith R, Zhou C, Robinson JD, Taylor JA, Elliott MN, Heritage J. Communication practices and antibiotic use for acute respiratory tract infections in children. *Ann Fam Med*. 2015;13(3):221–227
 42. Meeker D, Knight TK, Friedberg MW, et al. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. *JAMA Intern Med*. 2014;174(3):425–431
 43. Meeker D, Linder JA, Fox CR, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: a randomized clinical trial. *JAMA*. 2016;315(6):562–570
 44. Gerber JS, Prasad PA, Russell Localio A, et al. Variation in antibiotic prescribing across a pediatric primary care network. *J Pediatric Infect Dis Soc*. 2015;4(4):297–304
 45. Gerber JS, Ross RK, Bryan M, et al. Association of broad- vs narrow-spectrum antibiotics with treatment failure, adverse events, and quality of life in children with acute respiratory tract infections. *JAMA*. 2017;318(23):2325–2336
 46. Spellberg B, Rice LB. Duration of antibiotic therapy: shorter is better. *Ann Intern Med*. 2019;171(3):210–211
 47. Hersh AL, Olson J, Stockmann C, et al. Impact of antimicrobial stewardship for pediatric outpatient parenteral antibiotic therapy. *J Pediatric Infect Dis Soc*. 2018;7(2):e34–e36
 48. Olson J, Thorell EA, Hersh AL. Evaluation of discharge antibiotic prescribing at a freestanding children's hospital: opportunities for stewardship. *J Pediatric Infect Dis Soc*. 2019;8(6):563–566
 49. Ruebner R, Keren R, Coffin S, Chu J, Horn D, Zaoutis TE. Complications of central venous catheters used for the treatment of acute hematogenous osteomyelitis. *Pediatrics*. 2006;117(4):1210–1215
 50. Kovachich A, Tamma PD, Advani S, et al. Peripherally inserted central venous catheter complications in children receiving outpatient parenteral antibiotic therapy (OPAT). *Infect Control Hosp Epidemiol*. 2016;37(4):420–424
 51. Norris AH, Shrestha NK, Allison GM, et al. 2018 Infectious Diseases Society of America clinical practice guideline for the management of outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. 2019;68(1):e1–e35
 52. Agwu AL, Lee CK, Jain SK, et al. A World Wide Web-based antimicrobial stewardship program improves efficiency, communication, and user satisfaction and reduces cost in a tertiary care pediatric medical center. *Clin Infect Dis*. 2008;47(6):747–753
 53. Sick AC, Lehmann CU, Tamma PD, Lee CK, Agwu AL. Sustained savings from a longitudinal cost analysis of an internet-based preapproval antimicrobial stewardship program. *Infect Control Hosp Epidemiol*. 2013;34(6):573–580
 54. Newland JG, Stach LM, De Lurgio SA, et al. Impact of a prospective-audit-with-feedback antimicrobial stewardship program at a children's hospital. *J Pediatric Infect Dis Soc*. 2012;1(3):179–186
 55. Chan S, Hossain J, Di Pentima MC. Implications and impact of prior authorization policy on vancomycin use at a tertiary pediatric teaching hospital. *Pediatr Infect Dis J*. 2015;34(5):506–508
 56. Hersh AL, De Lurgio SA, Thurm C, et al. Antimicrobial stewardship programs in freestanding children's hospitals. *Pediatrics*. 2015;135(1):33–39
 57. Di Pentima MC, Chan S, Hossain J. Benefits of a pediatric antimicrobial stewardship program at a children's hospital. *Pediatrics*. 2011;128(6):1062–1070

58. Smith MJ, Gerber JS, Hersh AL. Inpatient Antimicrobial stewardship in pediatrics: a systematic review. *J Pediatric Infect Dis Soc.* 2015;4(4): e127–e135
59. Ibrahim OM, Polk RE. Antimicrobial use metrics and benchmarking to improve stewardship outcomes: methodology, opportunities, and challenges. *Infect Dis Clin North Am.* 2014;28(2):195–214
60. Moehring RW, Dodds Ashley ES, Ren X, et al.; Centers for Disease Control and Prevention Epicenters Program. Denominator matters in estimating antimicrobial use: a comparison of days present and patient days. *Infect Control Hosp Epidemiol.* 2018;39(5): 612–615
61. Metjian TA, Prasad PA, Kogon A, Coffin SE, Zaoutis TE. Evaluation of an antimicrobial stewardship program at a pediatric teaching hospital. *Pediatr Infect Dis J.* 2008;27(2):106–111
62. Aldeyab MA, Kearney MP, Scott MG, et al. An evaluation of the impact of antibiotic stewardship on reducing the use of high-risk antibiotics and its effect on the incidence of *Clostridium difficile* infection in hospital settings. *J Antimicrob Chemother.* 2012;67(12): 2988–2996
63. Valiquette L, Cossette B, Garant MP, Diab H, Pépin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis.* 2007;45(suppl 2):S112–S121
64. Wensch JM, Equiluz-Bruck S, Fudel M, et al. Decreasing *Clostridium difficile* infections by an antimicrobial stewardship program that reduces moxifloxacin use. *Antimicrob Agents Chemother.* 2014;58(9):5079–5083
65. Di Pentima MC, Chan S. Impact of antimicrobial stewardship program on vancomycin use in a pediatric teaching hospital. *Pediatr Infect Dis J.* 2010;29(8): 707–711
66. Toltzis P, Yamashita T, Vilt L, et al. Antibiotic restriction does not alter endemic colonization with resistant gram-negative rods in a pediatric intensive care unit. *Crit Care Med.* 1998; 26(11):1893–1899
67. Toltzis P, Dul MJ, Hoyen C, et al. The effect of antibiotic rotation on colonization with antibiotic-resistant bacilli in a neonatal intensive care unit. *Pediatrics.* 2002;110(4):707–711
68. Cook PP, Gooch M. Long-term effects of an antimicrobial stewardship programme at a tertiary-care teaching hospital. *Int J Antimicrob Agents.* 2015; 45(3):262–267
69. Dancer SJ, Kirkpatrick P, Corcoran DS, Christison F, Farmer D, Robertson C. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile*, extended-spectrum β -lactamase-producing coliforms and methicillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents.* 2013;41(2): 137–142
70. Taggart LR, Leung E, Muller MP, Matukas LM, Daneman N. Differential outcome of an antimicrobial stewardship audit and feedback program in two intensive care units: a controlled interrupted time series study. *BMC Infect Dis.* 2015;15:480
71. Lee BR, Goldman JL, Yu D, et al. Clinical impact of an antibiotic stewardship program at a children's hospital. *Infect Dis Ther.* 2017;6(1):103–113