REVIEW

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Antimicrobial stewardship program in pediatric medicine

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ABSTRACT

The rising threats from antimicrobial resistance due to inappropriate utilization of antimicrobial agents in health care including the pediatric population has been a topic of concern at the global level for the last several decades. The antimicrobial stewardship program (ASP) is a multidisciplinary institutional initiative focusing primarily on the improvement of antimicrobial prescribing practices and limiting inappropriate use. ASPs play an important role in the implementation of healthcare strategies in pediatrics worldwide to reduce antimicrobial resistance. Many published reports demonstrate how adapted ASPs in pediatrics result in improvement of unnecessary antimicrobial utilization, decreasing drug resistance and treatment failure, minimization of adverse clinical outcomes, decreasing healthcare costs and hospital length of stay, and optimization of diagnostic strategies. However, some barriers in pediatric ASP still exist. This narrative review describes core elements of ASP, the impact of implemented ASPs on pediatric healthcare, and challenges of pediatric ASP as seen by the authors.

KEYWORDS
Antimicrobial stewardship, Pediatrics, Antimicrobial resistance, Infection control

Introduction

The discovery of natural penicillin in 1928, followed by its ultimate purification and use as an antimicrobial agent against streptococci in 1940, ushered in the era of antimicrobial agents which include antibacterial, antiviral, antifungal, and antiparasitic drugs. Antimicrobial drugs are among the most frequently used mediations worldwide and the most commonly prescribed medications in children in the United States (U.S.).[1] Antimicrobial drugs are categorized based on mechanism of action (inhibition of cell wall synthesis, depolarization of the cell membrane, inhibition of protein synthesis, inhibition of nucleic acid synthesis, and inhibition of metabolic pathways in bacteria), method of administration (oral and intravenous use), purpose (empiric, prophylactic and definitive treatment), elimination (by kidney or liver), and the spectrum of effect (narrow and broad-spectrum) etc.[2] All these and many other characteristics serve as a decision-making platform for appropriate use of antimicrobials, to avoid side effects and long-term impact on microorganisms, such as developing antimicrobial resistance.

With the increasing use of antimicrobial agents and the emergence of resistant strains, awareness about antimicrobial misuse started to grow worldwide.[3-7] The terminology of "stewardship" was first introduced by John McGowan and Dale Gerding in the U.S. in 1996.[8] Interestingly, this term was coined after listening to a church sermon of "being a good steward" which, in this context, meant contributing to support of the church.[9] In 1997, Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) joint committees officially presented antimicrobial stewardship

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principles through "guidelines for the prevention of antimicrobial resistance in hospitals".[10] Since that time the concept of antimicrobial stewardship spread around the world and subsequently was adopted by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

The concept of antimicrobial stewardship and the development of antimicrobial stewardship programs (ASPs) has grown significantly over the past few decades. This narrative review describes core elements of ASP, the impact of implemented ASPs on pediatric healthcare, and challenges of pediatric ASP as seen by the authors.

Antimicrobial resistance

Antimicrobial resistance is defined by the World Health Organization (WHO) as "one of the biggest threats to global health, food security, and development today".[11] In the setting of insufficient innovations and resources related to the development of new antimicrobials in recent decades, antimicrobial resistance continues to emerge. Although antimicrobial resistance can impact anyone regardless of age, gender, socio-economic, or health status, some vulnerable populations, such as young children, older adults, those with complex health conditions, malnutrition or immunocompromised state can be disproportionally affected. Antimicrobial resistance is precipitated either by appropriate or inappropriate use of antimicrobials, with inappropriate use considered as a modifiable factor.

Microorganisms may have an intrinsic resistance to antimicrobials or the ability to develop extrinsic resistance through acquired mechanisms. Intrinsically resistant microorganisms are insensitive to certain groups of antimicrobials due to specific genomic traits, and independent from selection due to multiple drug exposure.[12] Extrinsic antimicrobial resistance is an adaptive trait facilitated by the stress response to multiple antimicrobial exposure and occurs through mutation in the genome with the development of resistance genes, selection in a heterogenous population, or horizontal gene transfer of resistance elements.[13] In 2008, through collaborative efforts by the U.S. Centers for Disease Control and Prevention, and the European Center for Disease Prevention and Control, definitions for antimicrobial resistance were created to ensure consistency with reporting and reliability of epidemiologic surveillance data collection. These definitions included those for multi-drug resistant (MDR), extensively drug-resistant, and pan-drug-resistant bacterial strains.[14] These strains play a major role in severe lower respiratory and other infections worldwide, and do not have effective standard treatment. This further contributes to increased incidence of hospital-acquired infections (HAI), and morbidity and mortality (M&M) from infection caused by MDR organisms, especially, among vulnerable populations such as neonates, immunocompromised or those with complex medical conditions requiring multiple hospitalizations. Further, antimicrobial resistance leads to major public health concerns due to the economic burden on healthcare systems, and increased cost of health care for patients and families.

The rising threats from antimicrobial resistance due to inappropriate antibiotic utilization in pediatrics is a concerning topic globally since half of those seeking health care are receiving antibiotics for viral infections, or have been prescribed broader spectrum antibiotics, or unnecessarily longer courses of antibiotics.[15] The Global Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey conducted in 2012 showed concerning data about a broad-spectrum antibiotic prescription for HAIs amongst hospitalized children in Latin America (49.9%), Asia (34.9%), and North America (33.7%).[16] Another point prevalence survey conducted using two independent global networks among pediatric hospitals in 56 countries (the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children, and the Global Point Prevalence Survey on Antimicrobial Consumption and Resistance), showed that broad-spectrum antibiotic prescriptions varied between countries.[17] Furthermore, broad-spectrum antibiotic prophylaxis was reported in a high proportion of hospitalized children in 41 countries, with Southern Europe and Asia having significantly more frequent prescriptions.[18] Thus, effort should be directed towards the elimination of inappropriate antibiotic use that can be beneficial in reducing antimicrobial resistance in outpatient and inpatient settings. Therefore, antimicrobial stewardship initiatives play an essential role in the implementation of health care strategies in pediatrics worldwide. The Pediatric Infectious Diseases Society recently published a policy statement on ASPs in pediatrics outlining many of the principles discussed below.[19]

Antimicrobial stewardship core elements

ASPs in the U.S. were formally started as multidisciplinary institutional programs in 2007, with the collaborative recommendations of the American Academy of Pediatrics (AAP), American Society of Health-System Pharmacists, Infectious Diseases Society for Obstetrics and Gynecology, Pediatric Infectious Diseases Society, Society for Hospital Medicine, and Society of Infectious Diseases Pharmacists.[20] The focus was on patient care improvement through minimizing antimicrobial misuse, harm from drug toxicity, selection of pathogenic organisms such as *Clostridium difficile*, and preventing the emergence of antimicrobial resistance.[20] The Core Elements of ASP included: prospective audit with intervention and feedback, formulary restriction and preauthorization requirements for specific agents, education, guidelines and clinical pathways, antimicrobial cycling and scheduled antimicrobial switch, antimicrobial order forms, combination therapy, streamlining or de-escalation of

therapy, dose optimization, and conversion from parenteral to oral therapy.[20]

In 2019, the core elements were updated and included: hospital leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, education.[21] Finally, while ASP is mostly focusing on the improvement of antibiotic use and antibiotic resistance, the platform was designed to account for all antimicrobials such as antiviral, antifungal, and antiparasitic agents use, as well as the utilization of an advanced diagnostic approach for overall better quality of health care.

Hospital leadership commitment

The mainstay of success for an ASP is access to hospital resources through senior leadership support. This includes the designation of a team that has dedicated time to operate daily activities of the ASP, monitor ongoing progress, and anticipate future plans and needed resources. The hospital leadership team can foster successful collaboration of the ASP team with other major stakeholders such as the hospitalist, infectious disease (ID), pharmacy, infection control (IC), microbiology, and information technology (IT) departments. This multidisciplinary inclusion is important for patient safety efforts, facilitation of appropriate antimicrobial use, oversight of antimicrobials prescription and toxicity, improvement of the diagnostic process, creation of antibiograms, improvement of HAI rate, and reporting of antimicrobial resistance. Each department is essential in the creation of an ASP and in sustaining the program. Therefore, hospital leadership and administration play a vital role in the inclusion of these groups and the identification of personnel in each department to lead these initiatives. IT plays an important role in ASP initiatives by facilitating the use of elaborated order sets, easy access to pathways, and guidelines in electronic medical records (EMR). Clinical decision support systems (CDSS) that include incorporating pathways in EMR, computerized decision-taking tools, or order sets can dramatically improve the decision-making performance of clinicians. CDSS can be syndromic-specific and linked to patient data with the output of treatment or diagnostic algorithms after execution. The major benefit of CDSS is the feasibility of implementation not only in inpatient but also in outpatient settings, with no need for direct ASP involvement.[22] IT services also play a vital role in outside hospital activities such as online training courses for providers/staff and participation in national and/or international meetings that help providers to develop and maintain the necessary skills needed for successful ASP processes. Furthermore, IT is vital in the ability to collect data related to antimicrobial prescriptions needed for further analysis.

Accountability

An ASP must have an appointed and dedicated leader (either clinician or pharmacist) who will be responsible for successful program management, outcomes, and further development. The expectation from each member of the ASP is to participate in "diagnostic stewardship" that includes measures for improving diagnostic decisions for appropriate antimicrobial prescription[23] and "handshake stewardship" where there is personal interaction with prescribers to improve antimicrobial use.[24] Each member in the program should have clear responsibilities and expertise in their area, as designation of specific personnel for specific tasks promotes accountability. Furthermore, it is beneficial for ASP if ID-trained physicians are included in the core team, or those without ID expertise to have training in ASP principles and practices, especially in small hospitals.[25]

Pharmacy expertise

The ASP team needs to include ID-trained pharmacists given their unique expertise in the pharmacokinetics/pharmacodynamics of prescribed antimicrobials.[20,26] In small hospitals this can be challenging. Therefore, hospital leadership can provide support with stewardship training through available resources.[27] The inclusion of pharmacists in the core ASP team promotes substantial improvement in antimicrobial misuse in hospitals.[28,29] Examples of pharmacy initiated interventions in antimicrobial stewardship include dose adjustment based on the drug level (gentamicin, vancomycin) or creatinine clearance in patients with renal insufficiency, prevention of drug-drug interaction, drug or dose optimization, monitoring unnecessary double anaerobic coverage to minimize risk for *Clostridium difficile* infection (CDI), assist with formulary, and appropriate antimicrobial route of administration.

Action

Different strategies can be used to successfully implement ASP in both inpatient and outpatient settings. Some are suitable to specific environments or circumstances and depend on the healthcare system and program resources: *Prospective audit and feedback* defined as an independent review of existent antimicrobial prescription 1–2 days after treatment initiation and analysis for appropriateness of prescribing (type of antimicrobials, dose, route of administration, and duration).[30] Next, "*handshake stewardship*" as post-audit personal feedback can be performed.[24] This provides educational opportunity and collaborative relationship between stewards and clinicians while maintaining autonomy and clinical judgment.[31] Real-time, individualized, nonpunitive, and customized feedback can provide effective results in the improvement of the antimicrobial prescription pattern.[32] *Preauthorization* is the stewardship intervention that implies the approval by the stewardship team of certain restricted formulary before administration.[33] Antimicrobials that should be under restriction would

be defined by local antibiograms. Preauthorization can decrease unnecessary antimicrobial use, optimize empiric choice, and reduce cost.[34,35] However, it potentially can impact patient care due to delays in the process of dispensing antimicrobial agents, especially during overnight hours. The ASP team can choose the specific time frame and/or days for preauthorization calls with no preauthorization outside of the designated schedule to prevent delays in treatment. *Behavioral intervention* includes the incorporation of order sets in the EMR with suggested alternative non-antimicrobial options, required free-text justifications for the chosen antibiotic, or peer comparison data demonstrating the lowest rate of inappropriate antimicrobial prescriptions.[36] Another, less common sophisticated behavior intervention tool called *user-centered design* was recently studied.[37] This instrument allows a systematic approach to detect prescription patterns for each provider using an interface with automated antimicrobial stewardship feedback.[37] *Diagnostic and treatment guidelines* are also an important part of ASP and can be designed to fit internal policies and practices. Guidelines can vary based on nosology or preferred goal for improvement (for example, optimization of empirical antimicrobial choice with subsequent narrowing of treatment, duration of introvenous treatment, total duration of treatment, etc.). Adherence to guidelines can be significantly improved if used with other ASP interventions.[38] *Diagnostic stewardship* plays an important role in facilitating timely and appropriate treatment initiation, escalation, de-escalation, or discontinuation, and minimizing diagnostic uncertainty. Rapid identification of microorganisms by molecular detection of resistance genes can shorten time to appropriate targeted treatment and have a positive impact on favorable clinical outcomes after initiation of optimal antimicrobial treatment.

Tracking

A vital part of an ASP is the ability to examine the impact of the conducted intervention and to determine the next targets for initiatives. *Process measurement* can be carried out by acceptance of recommendations from prospective audit, feedback, or preauthorization; provider adherence to clinical guidelines or clinical pathways; delay of appropriate therapy due to preauthorization; late transition to oral antibiotics; and unnecessary double coverage. *Outcome measurement* categories include changes in antimicrobial prescribing in response to stewardship interventions, outpatient sick visits with an antibiotic prescription, outpatient prescription per month or year, antibiotic prescription by provider type, antimicrobial resistance, adverse drug events, cost, hospital length of stay (LOS), readmissions within 30 days, HAI, clinical failure, source control for specific infections, utilization of carbapenem or broad-spectrum antifungal agents, outpatient parenteral antibiotic therapy, diagnostic test utilization, infection-related mortality, CDI rate, and other metrics discussed in the 2016 IDSA antimicrobial stewardship guidelines.[33,39-41] Furthermore, in 2019 the Canada Alliance for Stewardship of Antimicrobials in Pediatrics proposed 4 metrics such as days of therapy (DOTs) per 1000 patient-days, total antimicrobial days, 30-day readmission rate, and adherence to the ASP recommendations, that can be successfully adapted for use in pediatrics.[41] DOTs per 1000 patient-days is broadly used in pediatric stewardship since it is not affected by dosing.

Reporting

Relevant results from process and outcome measures should be translated to all stakeholders of the ASP team including leadership (trends or flags), clinicians (feedback, antimicrobial use, concerns), nurses, and as applicable to the health department in a regular manner. Reporting also includes an antibiogram that can be prepared systematically by a pharmacist, microbiologist, IC expert, or epidemiologist. Collaboration between local ASP and health department's ASP or IC is mutually beneficial. Reporting of antimicrobial prescribing patterns can significantly motivate prescribers to change their decision-making process in favor of improvements in antimicrobial prescription.[36]

Education

Education is a critical component of an ASP and embraces many disciplines that are involved in the process. Educational initiatives are tightly interconnected with other ASP core elements and are necessary for everyone involved in patient care including physicians, nurse practitioners, physician assistants, pharmacists, patients, and caregivers. The format of educational interventions can include didactics, posters, flyers, individual education during "handshake rounds", online resources,[42] clinical decision tools, review of cases, and discussion during M&M conferences. The role of ongoing education as an ASP intervention in outpatient settings can be significant. Here interventions can include CDSS and direct education through didactics and interviews. In addition, education of patients/families through direct communication, posters, or public resources can also improve their antimicrobial stewardship knowledge, adherence to infection prevention and control, as well as antimicrobial overprescribing by providers.[43,44] In academic settings, regular education of trainees through stewardship-focused curricula combined with feedback can promote adherence to institutional guidelines with subsequent improvement of antimicrobial use.[45]

Areas of pediatric antimicrobial stewardship

There has been rapid growth in pediatric ASPs over the past decade with collaboration between all stakeholders being key to the success of these programs. For inpatient settings, ASP should be incorporated within

different departments (general inpatient, intensive care unit (ICU), outpatient, and specialty care clinics). The setting is important given the differences in dynamics and challenges in each area. Therefore, one method of antimicrobial stewardship may not be conducive in every environment.[46,47]

Methods identified as effective in general inpatient pediatric wards include antimicrobial agent restriction and preauthorization, establishing guidelines for switching from broad-spectrum to narrow spectrum, or deescalation intravenous to oral antibiotics, prospective audit and feedback, and training and education of healthcare professionals.[48,49] However, there is a paucity of literature on ASPs in ICU settings. The ICU is a unique environment where broad-spectrum antimicrobials are used to empirically cover MDR infections due to the critical status of their patients. While restriction and preauthorization may not be the best method here, rapid identification of bacterial infection and education would be appropriate.[50]

High-risk children such as neonates, immunocompromised, those with underlying complex conditions, or critical care patients often have the most antimicrobial prescriptions and associated MDR infections. Given multiple risk factors, medical providers are often hesitant to follow ASP recommendations for de-escalation or discontinuation of antimicrobial therapy. Although there is a lack of sufficient data about the efficacy of implementation of ASP initiatives in special populations (neonates, immunocompromised), some reports show that following ASP recommendations at least did not result in poor clinical outcomes.[51]

Benefits of antimicrobial stewardship in pediatrics

Antibiotics are the most common, and often unnecessarily prescribed medication in pediatric outpatient settings (e.g. for viral respiratory infections).[52] Antimicrobial usage, either appropriate or inappropriate, can lead to the development of drug resistance, increased risk for antibiotic-related adverse effects such as CDI, drug reaction, or anaphylaxis that can substantially increase costs of healthcare. Children with prolonged outpatient antimicrobial treatment can develop serious adverse effects that include diarrhea, catheter-related complications, myelosuppression, renal impairment, and hepatotoxicity.[53] The emergence of new broad-spectrum oral antibiotics in pediatrics can also lead to their overuse over narrower spectrum agents for the management of pneumonia and acute otitis.[54]

Implementation of ASP interventions, which include the components described above, frequently results in the improvement of antimicrobial use in pediatric inpatient settings. Horikoshi et al[55] demonstrated a stable reduction of carbapenem utilization in pediatric patients associated with a decrease of *Pseudomonas aeruginosa* resistance to meropenem by 72% in a pre- and post-intervention study conducted by the ASP team. Jones et al[56] reported decreased rate of antibiotic prescribing by 7% and utilization of broad-spectrum antimicrobials (meropenem) by 18% in ICUs after prospective audit with positive feedback was implemented as part of ASP. Another study showed a 15% absolute reduction of antimicrobial prescription in hospitalized children 2 years of age with respiratory syncytial virus infection after 2 years of prospective audit and feedback.[57] Further, ASP strategies are reported to be associated with reduction of LOS without negatively affecting clinical outcomes.[55,58]

Pentima et al[59] examined the impact of ASP on prescribing errors and reported that the most common prescribing errors in pediatrics were dose-related (underdosing) and usage of inappropriate antimicrobial agents. Later, the same authors reported a significant reduction of antimicrobial prescription after ASP intervention, although usage of different antimicrobials varied.[60]

Infections with antimicrobial resistant microorganisms dramatically increase healthcare costs due to association with a higher rate of morbidity, multiple procedures, prolonged hospital stay, discharge with outpatient parenteral antibiotic therapy, multidisciplinary team involvement, and treatment with expensive antimicrobials. Therefore, ASP can help to reduce healthcare costs by improving unnecessary use of broad-spectrum antimicrobials and decreasing the risk of antimicrobial resistance. Sick et al[54] reported that after implementation of preauthorization for 5 antibiotics, the program saved $103 787 (95% *CI*, $98 583–$109 172) per year due to the reduction of dispensed doses of those antibiotics. Another study demonstrated that once-daily ceftriaxone and metronidazole is a cost-effective regimen (cost savings were $111 247 for a 32-month study period) with shorter time to afebrile state for nonperforated, perforated, and abscessed appendicitis, compared to cefoxitin or ertapenem, though with similar clinical efficacy.[61] Even addressing the appropriateness of a single class of broad-spectrum antimicrobial such as carbapenems, as was demonstrated by Seah et al, can remarkably reduce the financial burden.[62]

Based on the National Ambulatory and National Hospital Ambulatory Medical Care surveys from 2006 to 2008, 21% of outpatient visits result in an antibiotic prescription, with 23% of those prescriptions found to be not clearly indicated.[52] Antimicrobial stewardship interventions used in inpatient settings such as CDSS can be adapted in ambulatory settings with a significant impact on prescribing behavior. Recently, Zahlanie et al[63] showed that implementation of computerized treatment pathways in addition to personalized education sessions for

primary care providers resulted in a substantial increase in the proportion of first-line antibiotic prescriptions and reduction of antibiotic duration for children with a bacterial acute respiratory infection (ARI), and seeking medical attention in outpatient settings compared to the control group. A recently published report by Diaz et al[64] showed successful utilization of personalized scheduled audit and feedback to outpatient providers with the improvement of antibiotic prescriptions for community-acquired pneumonia. Another research team was able to successfully reduce inappropriate use of oral third-generation cephalosporins in children seen in ambulatory settings after implementation of intermittent education and audit with feedback from the antimicrobial stewardship team.[65] Furthermore, the implementation of clinical guidelines can be successful in improving not only the rate of inappropriate antimicrobial prescription but also antimicrobial resistance in outpatient settings. For example, Gagliotti et al[66] reported the reduction of macrolide prescription for pharyngitis by 28%, and the decline of *Streptococcus pyogenes* erythromycin resistance by 14% after new guidelines for the management of acute pharyngitis and otitis were released.

Stewardship intervention is not only beneficial for the improvement of antibacterial medication use but also for other anti-infectives. MacBrayne et al[67] showed a decrease in antifungal use by 43% over a 5 year post-implementation period of handshake stewardship. Furthermore, Hsu et al[68] showed that antimicrobial stewardship measures such as antiretroviral regimen optimization in children with resistant mutations, switching to other antiretroviral medications with better side effect profiles, and preventing drug to drug interactions, lead to a reduction in viral load and significant improvement of clinical outcome in children with HIV. Another research group examined risk factors for severe respiratory syncytial virus infection to determine indications for inhaled ribavirin use in pediatrics as part of antiviral stewardship.[69] The authors were unable to establish if patients would benefit from inhaled ribavirin treatment and suggested limiting the use of this antiviral medication due to adverse effects, teratogenicity, and difficulty with drug administration that also can be cost-effective.[69]

Diagnostic strategies focusing on rapid identification of organisms or genes responsible for resistance can be invaluable for patient care in combination with other ASP interventions due to reduction of time for de-escalation or even discontinuation of antimicrobial therapy if appropriate, decreased rate of adverse events, minimization of unnecessary broad-spectrum anti-infective prescription, reduction of LOS, and improving M&M rates. Tribble et al[70] examined the impact of a rapid diagnostic platform for gram-positive blood cultures combined with results notification to providers on antimicrobial treatment in the pediatric population and observed a substantial decline of vancomycin use with a shorter period to targeted antimicrobial treatment. Utilization of rapid blood diagnostic tests alone, however, without ASP interventions is not effective for optimization of antimicrobial prescription.[71] Moreover, using a rapid respiratory multiplex molecular assay for most common respiratory pathogens in hospitalized children with ARI was reported to be associated with decreased utilization of radiologic tests, less antibiotic exposure, reduction of antimicrobial treatment duration, decreased hospital LOS, and appropriate antiviral management.[72] In addition, using a rapid multiplex meningitis/encephalitis PCR panel in children shortens the period for unnecessary exposure to empiric antibacterial treatment.[73]

Challenges in pediatric antimicrobial stewardship

Pediatric antimicrobial stewardship has a number of challenges to overcome in the near future. The emergence and spread of MDR in gram-negative organisms, retroviruses, and mycobacteria, necessitate attention from all levels of healthcare, from patients' families and providers to public health authorities. These challenges include the complexity of research with respect to specific pediatric bioethical principles and boundaries for conducting clinical trials compared to the adult population. Novel antimicrobials that are available in adults are not easily accessible or sometimes restricted in pediatrics due to multiple reasons. Certain antimicrobials lose practicality in pediatrics due to a lack of specific formulations or are not authorized due to lack of clinical effectiveness in pediatric studies.

ASP is a complex intervention where success depends on many factors. Some stewardship strategies easily conducted in academic settings or freestanding children's hospitals would not be practical in non-freestanding children's hospitals due to lack of trained providers (ID- and ASP-trained pharmacist or pediatrician) dedicated to pediatric antimicrobial stewardship.[46] Further, the shortage of funding, workforce, and IT resources are major barriers for ASP in community children's hospitals and underserved areas in middle-low and low-income countries. While the vast majority of ASP guidelines and policies originated in the U.S., in 2019, WHO issued a practical toolkit to support ASP implementation in healthcare facilities in low-income and middle-income countries.[74] However, ASP implementation in pediatric settings might require significant adjustment in many countries with different healthcare systems and/or cultural and legislative practices.

Outpatient antimicrobial stewardship also has limitations. Antimicrobials are mostly prescribed in outpatient pediatric offices, emergency departments, urgent care clinics, walk-in clinics, long-term facilities, and subspecialty clinics by different types of providers (pediatrician, family medicine

practitioner, nurse practitioner, physician assistant). Given such diversity of healthcare providers in the outpatient realm, it is difficult to keep optimal stewardship strategies. For example, the audit and feedback process can be time-consuming and requires more effort for implementation compared to inpatient settings. Therefore, more effort is required to establish effective stewardship interventions in ambulatory settings.[75]

Antimicrobial resistance is a major problem worldwide, especially in low and middle-income countries. Antimicrobial resistance is growing alongside antimicrobial inappropriate prescription and overuse due to limited diagnostic capability and lack of resources in many developing countries. The rate of HAI in those countries is high due to catheter-related bloodstream infections and ventilator-associated pneumonia that arise from "inadequate environmental hygienic conditions; poor infrastructure; insufficient equipment; understaffing; overcrowding; the paucity of knowledge and application of basic infection-control measures; prolonged and inappropriate use of invasive devices and antimicrobials; and scarcity of local and national guidelines and policies".[76] Pediatric antimicrobial stewardship initiatives are limited in those settings due to insufficient diagnostic and administrative resources. Therefore, more antimicrobial stewardship attention and involvement are needed to battle antimicrobial resistance in low resource settings.[77]

In addition, limited access to appropriate antibiotics is a barrier to successful and meaningful antimicrobial stewardship in low and middle income countries.[78,79]

Furthermore, a recently published report of Dantuluri et al, that shows a higher rate of inappropriate ARI-related antibiotic use in children residing in rural compared to urban counties, highlights the importance of reproducible antimicrobial stewardship interventions in pediatrics in rural areas, as well as, low-resourced settings to account for cultural and regional differences.[80]

Conclusion

Convincing data are demonstrating the need for ASPs for reducing antimicrobial overuse and improving patient outcomes. While the general principles of ASPs are universal, different environments: i.e. inpatient units *vs* outpatient settings, academic *vs* community hospitals, or high-income *vs* low-income and middle-income countries, all present their own unique opportunities and challenges in terms of implementation and sustainability of such programs. Given the continuous emergence of MDR, extensively drug-resistant and pan-drug-resistant bacterial strains globally, it is necessary to continue implementing ASPs worldwide and conduct ASP research in the pediatric population to assess clinical outcomes and antimicrobial resistance.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest concerning this manuscript.

REFERENCES

1. Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D. Trends of outpatient prescription drug utilization in US children, 2002-2010. Pediatrics. 2012;130:23-31.
2. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc. 2011;86:156-167.
3. Schollenberg E, Albritton WL. Antibiotic misuse in a pediatric teaching hospital. Can Med Assoc J. 1980;122:49-52.
4. Perry TL, Guyatt GH. Antimicrobial drug use in three Canadian general hospitals. Can Med Assoc J. 1977;116:253-256.
5. Price DJ, Sleigh JD. Control of infection due to Klebsiella aerogenes in a neurosurgical unit by withdrawal of all antibiotics. Lancet. 1970;2:1213-1215.
6. Castle M, Wilfert CM, Cate TR, Osterhout S. Antibiotic use at Duke University Medical Center. JAMA. 1977;237:2819-2822.
7. Roberts AW, Visconti JA. The rational and irrational use of systemic antimicrobial drugs. Am J Hosp Pharm. 1972;29:828-834.
8. McGowan JE, Jr., Gerding DN. Does antibiotic restriction prevent resistance? New Horiz. 1996;4:370-376.
9. Dyar OJ, Huttner B, Schouten J, Pulcini C. What is antimicrobial stewardship? Clin Microbiol Infect. 2017;23:793-798.
10. Shlaes DM, Gerding DN, John JF Jr, Craig WA, Bornstein DL, Duncan RA, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis. 1997;25:584-599.
11. World Health Organization. Antibiotic resistance. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Accessed May 1, 2021.
12. Cox G, Wright GD. Intrinsic antibiotic resistance: mechanisms, origins, challenges and solutions. Int J Med Microbiol. 2013;303:287-292.
13. Martinez JL. General principles of antibiotic resistance in bacteria. Drug Discov Today Technol. 2014;11:33-39.
14. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268-281.
15. Esposito S, Blasi F, Allegra L, Principi N. Use of antimicrobial agents for community-acquired lower respiratory tract infections in hospitalised children. Eur J Clin Microbiol Infect Dis. 2001;20:647-650.
16. Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H, ARPEC project group. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. J Antimicrob Chemother. 2016;71:1106-1117.
17. Hsia Y, Lee BR, Versporten A, Yang Y, Bielicki J, Jackson C, et al. Use of the WHO Access, Watch, and Reserve

classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. Lancet Glob Health. 2019;7:e861-e871.
18. Hufnagel M, Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H. High rates of prescribing antimicrobials for prophylaxis in children and neonates: Results from the antibiotic resistance and prescribing in European children point prevalence survey. J Pediatric Infect Dis Soc. 2019;8:143-151.
19. Gerber JS, Jackson MA, Tamma PD, Zaoutis TE. Policy statement: Antibiotic stewardship in pediatrics. J Pediatric Infect Dis Soc. 2021;10:641-649.
20. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159-177.
21. Centers for Disease Control and Prevention. The Core Elements of Hospital Antibiotic Stewardship Programs: 2019. https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf. Accessed May 1, 2021.
22. Holstiege J, Mathes T, Pieper D. Effects of computer-aided clinical decision support systems in improving antibiotic prescribing by primary care providers: a systematic review. J Am Med Inform Assoc. 2015;22:236-242.
23. Dik JH, Poelman R, Friedrich AW, Niesters H, Rossen J, Sinha B. Integrated stewardship model comprising antimicrobial, infection prevention, and diagnostic stewardship (AID stewardship). J Clin Microbiol. 2017;55:3306-3307.
24. Searns JB, Williams MC, MacBrayne CE, Wirtz AL, Leonard JE, Boguniewicz J, et al. Handshake antimicrobial stewardship as a model to recognize and prevent diagnostic errors. Diagnosis (Berl). 2020;dx-2020-0032. (Online ahead of print)
25. Stenehjem E, Hyun DY, Septimus E, Yu KC, Meyer M, Raj D, et al. Antibiotic stewardship in small hospitals: Barriers and potential solutions. Clin Infect Dis. 2017;65:691-696.
26. Heil EL, Kuti JL, Bearden DT, Gallagher JC. The essential role of pharmacists in antimicrobial stewardship. Infect Control Hosp Epidemiol. 2016;37:753-754.
27. Centers for Disease Control and Prevention. Patient and Healthcare Provider Information. https://www.cdc.gov/antibiotic-use/community/materials-references/print-materials/index.html. Accessed May 1, 2021.
28. Magedanz L, Silliprandi EM, dos Santos RP. Impact of the pharmacist on a multidisciplinary team in an antimicrobial stewardship program: a quasi-experimental study. Int J Clin Pharm. 2012;34:290-294.
29. Centers for Disease Control and Prevention. Five Ways Pharmacists Can Be Antibiotics Aware. https://www.cdc.gov/antibiotic-use/community/pdfs/Hospital-Pharmacist-Poster-508.pdf. Accessed May 1, 2021.
30. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:CD003543.
31. Szymczak JE, Kitt E, Hayes M, Chiotos K, Coffin SE, Schriver ER, et al. Threatened efficiency not autonomy: Prescriber perceptions of an established pediatric antimicrobial stewardship program. Infect Control Hosp Epidemiol. 2019;40:522-527.
32. Patel SJ, Saiman L, Duchon JM, Evans D, Ferng YH, Larson E. Development of an antimicrobial stewardship intervention using a model of actionable feedback. Interdiscip Perspect Infect Dis. 2012;2012:150367.
33. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. 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:e51-77.
34. Lai CC, Shi ZY, Chen YH, Wang FD. Effects of various antimicrobial stewardship programs on antimicrobial usage and resistance among common gram-negative bacilli causing health care-associated infections: A multicenter comparison. J Microbiol Immunol Infect. 2016;49:74-82.
35. Lee KR, Bagga B, Arnold SR. Reduction of Broad-Spectrum Antimicrobial Use in a Tertiary Children's Hospital Post Antimicrobial Stewardship Program Guideline Implementation. Pediatr Crit Care Med. 2016;17:187-193.
36. Meeker D, Linder JA, Fox CR, Friedberg MW, Persell SD, Goldstein NJ, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: A randomized clinical trial. JAMA. 2016;315:562-570.
37. Ward MJ, Chavis B, Banerjee R, Katz S, Anders S. User-Centered Design in Pediatric Acute Care Settings Antimicrobial Stewardship. Appl Clin Inform. 2021;12:34-40.
38. Metz J, Oehler P, Burggraf M, Burdach S, Behrends U, Rieber N. Improvement of Guideline Adherence After the Implementation of an Antibiotic Stewardship Program in a Secondary Care Pediatric Hospital. Front Pediatr. 2019;7:478.
39. Rungsitsathian K, Wacharachaisurapol N, Nakaranurack C, Usayaporn S, Sakares W, Kawichai S, et al. Acceptance and Outcome of Interventions in Meropenem De-escalation ASP in Pediatrics. Pediatr Int. 2021. DOI: 10.1111/ped.14703. (Online ahead of print)
40. Niwa T, Shinoda Y, Suzuki A, Ohmori T, Yasuda M, Ohta H, et al. Outcome measurement of extensive implementation of antimicrobial stewardship in patients receiving intravenous antibiotics in a Japanese university hospital. Int J Clin Pract. 2012;66:999-1008.
41. Science M, Timberlake K, Morris A, Read S, Le Saux N, Groupe Antibiothérapie en Pédiatrie Canada Alliance for Stewardship of Antimicrobials in Pediatrics (GAP Can ASAP). Quality Metrics for Antimicrobial Stewardship Programs. Pediatrics. 2019;143:e20182372.
42. Agency for Healthcare Research and Quality. Quality AfHRa. AHRQ Safety Program for Improving Antibiotic Use. https://www.ahrq.gov/hai/tools/antibiotic-stewardship/index.html. Accessed May 1, 2021.
43. Meeker D, Knight TK, Friedberg MW, Linder JA, Goldstein NJ, Fox CR, et al. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. JAMA Intern Med. 2014;174:425-431.
44. Kilpatrick M, Hutchinson A, Manias E, Bouchoucha SL. Paediatric nurses', children's and parents' adherence to infection prevention and control and knowledge of antimicrobial stewardship: A systematic review. Am J Infect Control. 2021;49:622-639.
45. VanLangen KM, Dumkow LE, Axford KL, Havlichek DH, Baker JJ, Drobish IC, et al. Evaluation of a multifaceted approach to antimicrobial stewardship education methods

for medical residents. Infect Control Hosp Epidemiol. 2019;40:1236-1241.
46. Kronman MP, Banerjee R, Duchon J, Gerber JS, Green MD, Hersh AL, et al. Expanding existing antimicrobial stewardship programs in pediatrics: What comes next. J Pediatric Infect Dis Soc. 2018;7:241-248.
47. Bielicki J, Lundin R, Patel S, Paulus S. Antimicrobial stewardship for neonates and children: a global approach. Pediatr Infect Dis J. 2015;34:311-313.
48. Klatte JM. Pediatric antimicrobial stewardship programs: Current perspectives. Pediatric Health Med Ther. 2020;11:245-255.
49. Grammatico-Guillon L, Abdurrahim L, Shea K, Astagneau P, Pelton S. Scope of Antibiotic Stewardship Programs in Pediatrics. Clin Pediatr (Phila). 2019;58:1291-1301.
50. Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, Biscaia di Biase C, Murni IK, Dramowski A, et al. Role of antimicrobial stewardship programmes in children: a systematic review. J Hosp Infect. 2018;99:117-123.
51. Goldman JL, Newland JG, Price M, Yu D, Lee BR. Clinical impact of an antimicrobial stewardship program on high-risk pediatric patients. Infect Control Hosp Epidemiol. 2019;40:968-973.
52. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. Pediatrics. 2011;128:1053-1061.
53. Olson SC, Smith S, Weissman SJ, Kronman MP. Adverse Events in Pediatric Patients Receiving Long-Term Outpatient Antimicrobials. J Pediatric Infect Dis Soc. 2015;4:119-125.
54. 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;34:573-580.
55. Horikoshi Y, Suwa J, Higuchi H, Kaneko T, Furuichi M, Aizawa Y, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. Int J Infect Dis. 2017;64:69-73.
56. Jones AS, Isaac RE, Price KL, Plunkett AC. Impact of Positive Feedback on Antimicrobial Stewardship in a Pediatric Intensive Care Unit: A Quality Improvement Project. Pediatr Qual Saf. 2019;4:e206.
57. Kalil J, Bowes J, Reddy D, Barrowman N, Le Saux N. Pediatric Inpatient Antimicrobial Stewardship Program Safely Reduces Antibiotic Use in Patients with Bronchiolitis Caused by Respiratory Syncytial Virus: A Retrospective Chart Review. Pediatr Qual Saf. 2019;4:e211.
58. Wattier RL, Levy ER, Sabnis AJ, Dvorak CC, Auerbach AD. Reducing Second Gram-Negative Antibiotic Therapy on Pediatric Oncology and Hematopoietic Stem Cell Transplantation Services. Infect Control Hosp Epidemiol. 2017;38:1039-1047.
59. Di Pentima MC, Chan S, Eppes SC, Klein JD. Antimicrobial prescription errors in hospitalized children: role of antimicrobial stewardship program in detection and intervention. Clin Pediatr (Phila). 2009;48:505-512.
60. Di Pentima MC, Chan S, Hossain J. Benefits of a pediatric antimicrobial stewardship program at a children's hospital. Pediatrics. 2011;128:1062-1070.
61. Hurst AL, Olson D, Somme S, Child J, Pyle L, Ranade D, et al. Once-daily ceftriaxone plus metronidazole versus ertapenem and/or cefoxitin for pediatric appendicitis. J Pediatric Infect Dis Soc. 2017;6:57-64.
62. Seah XF, Ong YL, Tan SW, Krishnaswamy G, Chong CY, Tan NW, et al. Impact of an antimicrobial stewardship program on the use of carbapenems in a tertiary women's and children's hospital, Singapore. Pharmacotherapy. 2014;34:1141-1150.
63. Zahlanie Y, Mang NS, Lin K, Hynan LS, Prokesch BC. Improved antibiotic prescribing practices for respiratory infections through use of computerized order sets and educational sessions in pediatric clinics. Open Forum Infect Dis. 2021;8:ofaa601.
64. Diaz M, Handy LK, Crutchfield JH Jr, Cadilla A, Hossain J, Werk LN. Impact of a personalized audit and feedback intervention on antibiotic prescribing practices for outpatient pediatric community-acquired pneumonia. Clin Pediatr (Phila). 2020;59:988-994.
65. Taylor M, Liechti S, Palazzi D. Intermittent Education and audit and feedback reduce inappropriate prescribing of oral third-generation cephalosporins for pediatric upper respiratory tract infections. Jt Comm J Qual Patient Saf. 2021;47:250-257.
66. Gagliotti C, Buttazzi R, Di Mario S, Morsillo F, Moro ML. A regionwide intervention to promote appropriate antibiotic use in children reversed trends in erythromycin resistance to Streptococcus pyogenes. Acta Paediatr. 2015;104:e422-424.
67. MacBrayne CE, Williams MC, Levek C, Child J, Pearce K, Birkholz M, et al. Sustainability of handshake stewardship: Extending a hand is effective years later. Clin Infect Dis. 2020;70:2325-2332.
68. Hsu AJ, Neptune A, Adams C, Hutton N, Agwu AL. Antiretroviral stewardship in a pediatric HIV clinic: Development, implementation and improved clinical outcomes. Pediatr Infect Dis J. 2016;35:642-648.
69. Hoover J, Eades S, Lam WM. Pediatric antiviral stewardship: Defining the potential role of ribavirin in respiratory syncytial virus-associated lower respiratory illness. J Pediatr Pharmacol Ther. 2018;23:372-378.
70. Tribble AC, Gerber JS, Bilker WB, Lautenbach E. Impact of rapid diagnostics with antimicrobial stewardship support for children with positive blood cultures: A quasi-experimental study with time trend analysis. Infect Control Hosp Epidemiol. 2020;41:883-890.
71. Faugno AK, Laidman AY, Perez Martinez JD, Campbell AJ, Blyth CC. Do rapid diagnostic methods improve antibiotic prescribing in paediatric bacteraemia? J Paediatr Child Health. 2021;57:574-580.
72. Lee BR, Hassan F, Jackson MA, Selvarangan R. Impact of multiplex molecular assay turn-around-time on antibiotic utilization and clinical management of hospitalized children with acute respiratory tract infections. J Clin Virol. 2019;110:11-16.
73. Malcolmson C, Ng K, Hughes S, Kissoon N, Schina J, Tilley PA, et al. Impact of matrix-assisted laser desorption and ionization time-of-flight and antimicrobial stewardship intervention on treatment of bloodstream infections in hospitalized children. J Pediatric Infect Dis Soc. 2017;6:178-186.
74. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A WHO practical toolkit. https://apps.who.int/iris/bitstream/handle/10665/329404/9789241515481-

eng.pdf. Accessed May 1, 2021.
75. Kilgore JT, Smith MJ. Outpatient pediatric antibiotic use: a systematic review. Curr Infect Dis Rep. 2019;21:14.
76. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011;377:228-241.
77. Iroh Tam PY. The challenge and opportunity of pediatric antimicrobial stewardship in low resource settings. J Trop Pediatr. 2020;66:1-3.
78. Knowles R, Sharland M, Hsia Y, Magrini N, Moja L, Siyam A, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. Bull World Health Organ. 2020;98:177-187C.
79. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. Lancet. 2016;387:168-175.
80. Dantuluri KL, Bruce J, Edwards KM, Banerjee R, Griffith H, Howard LM, et al. Rurality of residence and inappropriate antibiotic use for acute respiratory infections among young Tennessee children. Open Forum Infect Dis. 2021;8:ofaa587.

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