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## New Horizons for Pediatric Antibiotic Stewardship

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### Synopsis

Antibiotic resistance remains a major health threat and the overuse of antimicrobials contributes to this serious problem. Antimicrobial stewardship programs (ASPs) are effective in decreasing the inappropriate use of antimicrobials. The development of pediatric ASPs is on the rise and these programs have proven effective in optimizing antimicrobial use in children. The value of ASPs is gaining recognition, and the expansion of stewardship into additional health care settings is expected. Collaborative efforts are underway among pediatric ASPs to enhance best practices and develop efficient and effective strategies to minimize unnecessary antimicrobial use in children.

### Keywords

pediatrics; antimicrobial stewardship; antimicrobial resistance

### Introduction

Antimicrobial resistance is a major health threat resulting in at least 2 million illnesses and 23,000 deaths in the U.S. annually. The cause of antimicrobial resistance is multi-factorial with the overuse and inappropriate use of antimicrobials contributing to the development of resistance. Unfortunately, the threat of bacterial resistance is widespread as these pathogens can be acquired in hospitals, nursing homes and in the community. The dearth of new antimicrobial development over recent decades to treat highly resistant pathogens has forced clinicians to rely on older antimicrobials that can be associated with more severe adverse effects. Preservation of available antimicrobials to assure appropriate and optimal use has become a necessity.

Incorporation of antimicrobial stewardship programs (ASPs) into medical care has become a popular strategy to optimize antimicrobial use with the ultimate goal of reducing antimicrobial resistance. As a high rate of antimicrobial prescribing occurs in children,

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pediatric ASPs have continued to develop and increase in number. Although many of the overarching principles of stewardship apply to children and adults alike, many factors related to pediatric stewardship are unique to children.

In this chapter, new developments in pediatric antimicrobial stewardship will be reviewed. Current practices and approaches to expand pediatric stewardship will be described. Finally, policies and collaborative efforts directed to further augment stewardship strategies on a national scale will be outlined.

## Antimicrobial Stewardship Guidelines and Strategies

For over 25 years, the need to improve the use of antimicrobials has been well-recognized. Guidelines addressing antimicrobial resistance in the hospital setting were originally published in 1988, followed by a joint statement in 1997 from the Society for Healthcare Epidemiology of America and Infectious Diseases Society of America recognizing the importance of integrating antimicrobial stewardship programs (ASPs) in health care settings.<sup>1,2</sup> Revised guidelines published in 2007 specifically outlined strategic approaches for implementing stewardship programs.<sup>3</sup> Although, the recommendations are not specific to the pediatric population, the current guidelines provide valuable information concerning ASP implementation in any hospital setting, including pediatric institutions.

The overarching goal of an ASP is to optimize and control the use of antimicrobials to prevent and decrease the emerging resistance of bacterial pathogens. Cost savings and a decrease in the undesired side effects associated with antimicrobials (e.g. *Clostridium difficile*, gastrointestinal distress, adverse drug reactions) are additional benefits of stewardship. (Table 1)

In the hospital setting, implementation of antimicrobial monitoring and optimization is frequently performed by implementing one or both of the core stewardship strategies: 1) formulary restriction and preauthorization and 2) prospective audit with feedback intervention and feedback (Table 2). As outlined in Table 2, both strategies have strengths and limitations and both approaches can be used and are not mutually exclusive. Additional supplemental strategies of ASPs that have been shown to improve antimicrobial use are: clinical pathways/clinical practice guidelines,<sup>4,5</sup> conversion from parenteral to oral therapy,<sup>6,7</sup> and integration of computer surveillance and decision support to facilitate stewardship.

The core ASP team should consist of a clinical pharmacist and/or an infectious diseases physician. Additionally, microbiologists, infection preventionists, epidemiologists and data analysts are essential in improving the use of antimicrobials and monitoring antimicrobial resistance trends (Figure 1). Finally, hospital administration is critical in providing the financial and political support for the implementation and ongoing efforts of an ASP.

## Trends in Emergence of Pediatric Antimicrobial Stewardship Programs

The American Academy of Pediatrics and the Pediatric Infectious Diseases Society endorse the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of

America guidelines for developing an institutional program to enhance antimicrobial stewardship as it is well-recognized that the pediatric population must be included in stewardship efforts. Several pediatric hospitals have successfully implemented ASPs with the prevalence of pediatric ASPs increasing over the past decade.<sup>8-11</sup> In 2008, just one year following publication of the IDSA stewardship guidelines, a national survey was conducted to inquire about pediatric ASP development.<sup>12</sup> Approximately 50% of those surveyed (70/138; 51%) reported either having or planning implementation of an ASP. However, a dedicated full-time equivalent (FTE) to support the programs was limited, with 40% of institutions polled reporting no FTE for the program. Lack of funding and time represented the most commonly perceived challenges for those programs without an active ASP.

A follow up survey of free standing children's hospitals was conducted in 2011.<sup>13</sup> Of the 38 hospitals included in the study, 16 (42%) reported having a formal ASP which meant dedicated FTE(s) were committed to the program. The median number of total FTEs was 0.63 with pharmacists having 0.1 – 1.5 FTEs and physicians having 0.1 – 0.5 FTEs. Among these 16 hospitals, 13 (81%) implemented an ASP after the 2007 stewardship guidelines. Furthermore another 14 hospitals reported to be developing an ASP. These data demonstrate an emerging trend toward uptake of formal ASPs in children's hospitals across the U.S.

These hospitals with dedicated FTEs for stewardship or formal ASPs have been shown to perform better than hospitals with stewardship activity but without FTEs dedicated to supporting the program. Hersh and colleagues demonstrated that for a select group of broad-spectrum antibiotics a greater decline in use was present in hospitals with a formal ASP.<sup>14</sup> Furthermore, a study showed that when support is withdrawn and an ASP is discontinued, the gains made in improving antimicrobial use vanish rapidly.<sup>15</sup>

## Targets for Pediatric Stewardship

Special considerations specific to children must be recognized when considering implementation of a pediatric ASP. Children are not little adults and therefore the disease processes, antimicrobial resistance patterns, dosing strategies, and commonly prescribed antimicrobials differ in children when compared to adults. Identifying specific targets for stewardship is critical; and priority areas vary by hospitals, communities and country regions.

Common diagnoses such as pneumonia, appendicitis, infections in patients with cystic fibrosis, and skin and soft tissue infections are frequently associated with immense variability in antimicrobial prescribing in children.<sup>16,17</sup> These diagnoses are therefore frequent targets for stewardship and interventions as antimicrobial recommendations can be centered on available national guidelines in addition to local resistance patterns.<sup>4,18,19</sup>

In addition to specific diagnoses, ASPs often direct efforts towards broad spectrum antimicrobial agents in efforts to minimize unnecessary use. Linezolid, carapenems, vancomycin and fluoroquinolones are commonly targeted antimicrobials among pediatric stewardship programs, similar to many adult stewardship programs.<sup>12</sup> However, prescribing in children is quite different than adults and the frequency of encountering these broad agents is less frequent in the pediatric population. Targeting antimicrobials that are

commonly used and potentially fraught with either selection or dosing errors such as 3<sup>rd</sup> generation cephalosporins should be considered targets in pediatric ASPs.

The types of recommendations frequently provided by ASPs vary (Table 3) and are dependent upon the encountered clinical scenarios. The recommendation to stop antimicrobial therapy due to no indication is not uncommon; however stewardship programs also provide guidance to optimizing therapy and provide recommendations on when an infectious diseases consultation should be considered.<sup>11</sup> The implementation of local clinical practice guidelines for prescribing clinicians can also be an effective method to enhance best prescribing practices.<sup>5</sup>

## Expansion of Pediatric ASPs Outside of the Hospital Setting

Antimicrobial stewardship needs to extend beyond the hospital setting as the majority of inappropriate prescribing occurs in the ambulatory setting. Antibiotics are prescribed in nearly one in five pediatric outpatient visits. Nearly 25% of those antimicrobials are unnecessary; being prescribed for diagnoses such as asthma and viral pneumonia and resulting in millions of unnecessary antimicrobials prescribed each year.<sup>20</sup> Rapid patient turnover, and the filling of prescriptions in the outpatient pharmacy setting, makes the traditional prospective-audit with feedback or restriction stewardship strategies utilized in the hospital setting less pragmatic in the outpatient or emergency department setting.

Nevertheless, antimicrobial stewardship has been effective in the pediatric clinic setting. Clinician education coupled with personalized provider audit and feedback has resulted in a decrease of unnecessary broad spectrum antimicrobial use for pneumonia, and sinusitis in outpatient pediatric practices.<sup>21</sup> However when these stewardship interventions were removed, previous rates of broad spectrum antimicrobial prescribing resumed.<sup>22</sup> Therefore, expansion of ASPs into the outpatient setting requires innovative approaches that are sustainable and adaptable and likely will depend on the type of outpatient setting (e.g. urgent care versus pediatrician office).

The transition period during which a hospitalized patient is preparing for discharge is yet another area for which stewardship is needed. Outpatient parental antimicrobial therapy (OPAT) is commonly prescribed at the point of hospital discharge for the continued treatment of infections in the outpatient setting. Although OPAT has proven cost effective when compared to hospitalization, outpatient administration of intravenous antimicrobials is associated with complications including central line-associated bloodstream infections, thrombosis, and mechanical difficulties resulting in unintended medical care visits.<sup>23,24</sup> OPAT is often either not indicated when prescribed to children, or requires modification in dose or duration.<sup>25</sup> The transition to oral antibiotics after an initial course of intravenous antibiotics instead of prolonged parenteral antibiotic administration has proven effective when treating pediatric conditions such as acute osteomyelitis and intra-abdominal infections, reducing the need for OPAT in some clinical scenarios.<sup>26,27</sup>

As OPAT is associated with a relatively high risk of complications, standardized approaches involving infectious diseases specialists and a checklist of processes to minimize risk has been recommended.<sup>28</sup> Stewardship programs have the potential to improve the safety and

efficacy by assuring the appropriate use of OPAT, optimizing drug selection and dosing, and reducing unnecessary OPAT when oral conversion is a therapeutic option. However, involvement of ASPs with OPAT prescribing is rare in children highlighting the importance of expanding pediatric stewardship beyond the hospital setting.

## The Future of Pediatric ASPs

In September 2014, the President of the United States released an executive order on combating antibiotic-resistant bacteria.<sup>29</sup> Additionally, the White House released a National Strategy on combating antibiotic-resistant bacteria and the President's Council of Advisors on Science and Technology published their report on antibiotic resistance.<sup>30</sup> In total, the executive order and these documents recognized both the health and economic threat of antimicrobial resistance. Several key efforts were highlighted as critical in the fight against antimicrobial resistance including: the development of new, effective antibacterials; the expansion of rapid diagnostic technologies to detect resistance; the preservation of efficacious antimicrobial use; and the enhancement antimicrobial stewardship. The executive order proposed that by the end of the year in 2016, the Department of Health and Human Services will require the implementation of ASPs in hospitals and inpatient health care systems and recommend stewardship programs in outpatient settings.

These national efforts emphasize the critical importance of ASPs and strongly suggest that stewardship will be an expected part of health care in the near future. Therefore, the opportunities to enhance pediatric stewardship are anticipated as more programs develop, mature and succeed. The ability for pediatric stewardships across the country to gain knowledge about effective stewardship strategies and develop sustainable collaborative efforts to determine best practices is critical to move the field of pediatric stewardship forward. Despite the uniqueness of individual hospitals, many if not all centers that provide medical care to children have some overlapping commonality for joined stewardship approaches.

Recently, a pediatric ASP collaborative was initiated in the fall of 2013. The SHARPS (Sharing Antimicrobial Reports for Pediatric Stewardship) collaborative is comprised of 32 pediatric ASPs across the U.S. working together to improve antimicrobial use. The collaborative uses benchmarked antimicrobial data to drive stewardship interventions. Individual stewardship programs develop effective interventions based on the needs and data of the respective hospital. However, the information is then disseminated to all ASPs. This approach is widely beneficial as programs with similar challenges or needs can apply already proven techniques or avoid those that failed. Collaborative efforts such as SHARPS will play a critical role as ASPs strive to develop the best practices to optimize antimicrobial use in children.<sup>31</sup>

## Conclusion

ASPs have proven successful in decreasing inappropriate antimicrobial prescribing. As pediatric ASPs continue to advance and become an expected part of medical care, standardization of best practices directly linked with outcome measures is critical.

Collaboration among government, hospital and outpatient health care facilities, and communities is needed to advance stewardship and fully augment effective strategies to battle the threat of bacterial resistance.

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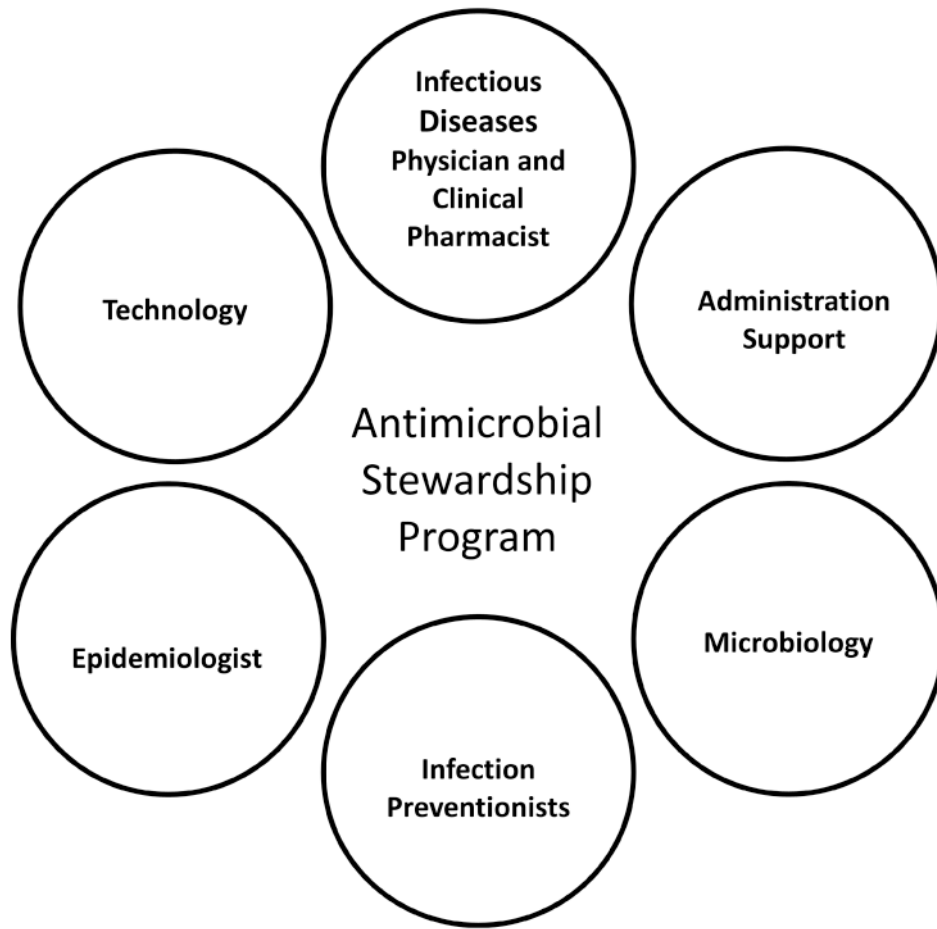
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### Key Points

1. Inappropriate antimicrobial prescribing in pediatrics is common and the number of pediatric antimicrobial stewardship programs (ASPs) continues to grow
2. Many targets for pediatric ASP interventions differ when compared to adults due to differences in common diseases and prescribed antibiotics unique to children
3. Combating antimicrobial resistance is gaining recognition by government and policy makers reinforcing the importance of stewardship
4. Collaborative efforts among ASPs nationally will continue to strengthen the approach to pediatric stewardship initiatives



**Figure 1. Key Elements of an Antimicrobial Stewardship Program**

**Table 1**  
**Goals of an Antimicrobial Stewardship Program**

<ul style="list-style-type: none"><li>• Decrease unnecessary use of antimicrobials</li><li>• Decrease antimicrobial resistance</li><li>• Optimize antimicrobial selection</li><li>• Decrease cost</li></ul>	<ul style="list-style-type: none"><li>• Avoid unnecessary use of prolonged intravenous antimicrobials if transition to peroral medication can be tolerated</li><li>• Decrease side effects of antimicrobials (<i>C. difficile</i>, allergic reactions) by eliminating unnecessary antimicrobial use</li><li>• Improve patient outcomes and safety</li></ul>
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**Table 2**  
**Antimicrobial Stewardship Program Strategies**

Strategy Type	Strengths	Limitations
<p><i>Formulary restriction and preauthorization</i></p> <ul style="list-style-type: none"> <li>• Prescribing physician must receiving approval prior to or immediately following antimicrobial initiation</li> <li>• Recommendation is provided at the time of antimicrobial initiation</li> </ul>	<ul style="list-style-type: none"> <li>• Influence empirical antimicrobials at the point of initial prescribing</li> </ul>	<ul style="list-style-type: none"> <li>• Potential barrier or delay in initial antimicrobial initiation</li> </ul>
<p><i>Prospective Audit with Feedback</i></p> <ul style="list-style-type: none"> <li>• Antimicrobial indication is evaluated following the initial prescribing</li> <li>• Recommendation is provided after antimicrobial initiation</li> </ul>	<ul style="list-style-type: none"> <li>• Greater clinical information available to guide recommendations</li> <li>• Does not interfere with initial prescribing</li> </ul>	<ul style="list-style-type: none"> <li>• More labor intensive and time consuming</li> </ul>

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**Table 3**  
**Types of Recommendations Provided by an Antimicrobial Stewardship Program**

<b>Stop Therapy</b> <ul style="list-style-type: none"><li>• No indication</li><li>• Redundant coverage unnecessary</li></ul>
<b>Modify Therapy</b> <ul style="list-style-type: none"><li>• Shorten duration</li><li>• Extend duration</li><li>• Broaden or narrow empirically</li></ul>
<b>Optimize Therapy</b> <ul style="list-style-type: none"><li>• Intravenous to peroral conversion</li><li>• Adjust dose or frequency</li><li>• Modify based on culture results</li></ul>
<b>Consult Infectious Diseases</b>

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