Antimicrobial Stewardship in Pediatric Intensive Care
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Objectives
- Describe the recommended composition of an antibiotic stewardship program
- Identify evidence-based practices for reducing cost and antibiotic resistance
- Describe evidence supporting antibiotic stewardship programs in pediatric critical care

Key words: value, quality, antibiotic stewardship, resistance

In 2006, the Infectious Diseases Society of America (IDSA) in conjunction with the Society for Healthcare Epidemiology of America published guidelines to assist institutions in the development of an antibiotic stewardship program (ASP). The goal of these guidelines is to provide evidence-based recommendations that improve clinical outcomes by reducing iatrogenic harm from antimicrobials through the creation of antimicrobial stewardship programs. ASPs promote appropriate use of antimicrobial agents, including their selection, dose, route, and duration. While the majority of the data used in the development of these recommendations were derived from studies of hospitalized adults, the benefits clearly apply to pediatric populations, particularly those in critical care settings. These recommendations have been endorsed by both the American Academy of Pediatrics and the Pediatric Infectious Diseases Society. The guidelines were released in the context of increasing rates of multidrug-resistant organisms (MDROs), such as methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*, and knowledge that antimicrobial resistance among various pathogens increases morbidity and mortality and contributes to increasing healthcare costs.

**ELEMENTS OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM**

**Team Composition**
IDSA recommends that ASPs be multidisciplinary, including a pediatric infectious disease physician leader, a clinical pharmacist (preferably with infectious disease training), a clinical microbiologist, an information system specialist, an infection prevention specialist, and a hospital epidemiologist. Nguyen-Ha et al described a more limited ASP team with decreased drug starts, decreased drug use, and decreased costs. These teams work in concert with primary teams, even when not technically consulted, often constantly surveying positive cultures and reviewing use of broad-spectrum antibiotics.

A single-center study looking at patients within the pediatric ICU (PICU) and pediatric cardiac ICU (PCICU) who had positive blood cultures showed a large delay in physician response to these cultures. In the patients in whom antibiotics were changed within 24 hours of positive cultures, investigators reported an average delay of 6 hours and 35 minutes from the time of clinician notification of positive culture to the time of antimicrobial change. While no differences were noted in clinician response between the PICU and PCICU, 65% of the positive cultures originated from the PICU, indicating a substantial number of patients with delayed clinician response. Thus, additional team members are needed on the ASP, including pharmacists, microbiologists, and infection prevention specialists.

**Formulary Restriction**
Formulary restriction can lead to reductions in overall antimicrobial use without an increase in treatment failure. The use of order sets,
Guidelines, and clinical decision support that direct clinicians toward appropriate antimicrobial selection can ameliorate microbial resistance patterns by preventing the use of overly broad-spectrum antibiotics. Clinical decision support should be based on evidence-based practice guidelines, hospital-specific antibiograms, sensitivities, and formulary and cost data (Table 1). Some institutions have chosen to “hide” certain restricted broad-spectrum or expensive antimicrobials in their ordering libraries, restricting their use to ASP order sets that require indication and/or approval for use. By also incorporating costs based on hospital formulary preferences, this method can assist in overall reduction of medication costs.

### Table 1. Clinical Decision Support Example: Staphylococcus aureus

<table>
<thead>
<tr>
<th>Sensitivities</th>
<th>Cost</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline resistant</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>Oxacillin resistant</td>
<td>$</td>
<td></td>
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<tr>
<td>Erythromycin resistant</td>
<td>$$</td>
<td></td>
</tr>
<tr>
<td>Clindamycin sensitive</td>
<td>$$</td>
<td>Click here to order</td>
</tr>
<tr>
<td>Linezolid sensitive</td>
<td>$$$$</td>
<td></td>
</tr>
</tbody>
</table>

**Prospective Audits With Feedback**

Prospective audits with practitioners, including immediate feedback and direct communication, can reduce inappropriate prescribing as well as inform future prescribing patterns. With the aid of clinical pharmacists and information systems specialists, clinicians can review their own ordering patterns as well as those of their peers. Solomon et al demonstrated that one-on-one education and instruction from a clinical pharmacist to resident physicians resulted in a 37% reduction in the number of unnecessary days of use of levofloxacin and ceftazidime by decreasing the duration of therapy and also decreased the initiation of inappropriate and unnecessary antibiotic regimens.

### Guideline Development and Education

While education is an important component of any intervention, feedback on the use of learned behaviors is necessary as well. IDSA guidelines recommend a stepwise approach, which starts with passive interventions such as direct education and promotion of proper use of antimicrobials through clinical order sets, followed by active interventions such as prospective audits.

Although nationally recognized clinical guidelines are available for management of some infectious diseases, these guidelines do not incorporate local pathogen prevalence or antibiograms and do not instruct providers on implementation of recommended practices on the institutional level. A multidisciplinary ASP can assist in developing and implementing evidence-based practice guidelines using these factors on a local level. Guidelines may involve drug selection, dosing, and route; in addition, cost savings may be appreciated through decreased ordering of drug levels and de-escalation. Vancomycin guidelines created by one ASP resulted in a 32.5% reduction in vancomycin use in a children’s hospital. In an Australian study, providing pediatric junior and senior level physicians with a simple laminated card that displayed recommended antimicrobial therapies for 20 common pediatric infectious illnesses resulted in increases in appropriate selection and dosage of antibiotics with a secondary benefit of a 53% reduction in annual cost of broad-spectrum antibiotics (specifically third-generation cephalosporins).

### Antimicrobial Cycling and De-escalation

Cycling of antimicrobials, which entails scheduled removal or substitution of a certain antimicrobial or class with another antimicrobial or class with similar spectrum of activity, is another area where an ASP can assist. The more often a certain antimicrobial is prescribed, the increased likelihood that resistance will develop. Cycling theoretically allows resistance rates to decrease or stabilize for that particular drug.
However, data are mixed on whether cycling actually results in long-term reduction of antimicrobial resistance.

De-escalation of antimicrobials is an important component of antimicrobial stewardship. Protracted use of broad-spectrum and combination therapies unnecessarily increases the risk of morbidity secondary to promoting resistance and risk of adverse reactions while also placing an increased financial burden on both patient and hospital. One study looking at the inappropriate use of vancomycin and cefepime in a children’s hospital showed that the most common reason for inappropriate use was failure to discontinue or de-escalate therapy, and the rate of inappropriateness was greater in the PICU than on the general pediatric ward. Once laboratory results such as cultures are available, clinical pharmacists and infectious disease specialists as part of an ASP can provide invaluable assistance in promoting the timely de-escalation of empirical antimicrobial therapies and the elimination of superfluous combination therapies to more effectively target causative pathogens.

**Dose, Route, and Duration Optimization**

Patients in a PICU vary in age and weight to a greater degree than do patients in neonatal or adult ICUs. Clinical pharmacists should be consulted to optimize antimicrobial dosing. Dosing based on individual patient characteristics, as well as factors including renal function, causative organism, infectious source, and pharmacological properties of the requested drug, is an important part of an ASP. Introduction of vancomycin use guidelines by one ASP reduced vancomycin dosing errors. Additionally, the introduction of automatic stop reports, which consisted of a list of all patients due to stop vancomycin on a given day, resulted in a decrease in inappropriate cessation of that antibiotic.

Timing of switching parenteral medications to enteral routes can vary widely between physicians. An ASP can be used to develop clinical criteria for conversion to oral agents in order to decrease length of stay, central line entries, and overall healthcare costs.

Institutional agreements on length of therapy for common pediatric infectious diseases can promote appropriate duration of antimicrobial therapy. One retrospective cohort study looked at the duration of antimicrobial use for patients with bacteremia in adult ICUs and found a variability ranging from 9 to 17.5 days of therapy despite similarity in underlying infectious syndromes. In this study, infectious disease consultation was less common in patients receiving shorter lengths of therapy and crude hospital survival was lower among those patients with shorter lengths of therapy.

**BENEFITS WITHIN PEDIATRIC INTENSIVE CARE UNITS**

Newland et al recently evaluated the benefits of implementing an ASP in a tertiary children’s hospital; multiple system-wide benefits were noted, including in the PICU. However, in 2013 only 16 of the 38 freestanding hospitals surveyed in the United States had an ASP.

**Reduction of Prescribing Errors**

Newland et al showed that the greater the number of full-time employees on an ASP team, the larger the number of monitored antibiotics. This is significant in that multiple studies have shown worsened mortality and morbidity among patients started on inappropriate empirical antimicrobials. The data clearly show that inappropriate antimicrobial selection is common and that inappropriate selection increases mortality independent of other risk factors.

In one academic hospital, the rate of inappropriate use of vancomycin and cefepime was highest in the PICU compared with general pediatric wards and higher among surgical services compared with medical services, indicating the need for system-wide ASPs.
Decrease in Multidrug-Resistant Organisms

One study showed that in an Australian PICU, more than 13% of cases of bacteremia and nearly 8% of cases of pneumonia were caused by MDROs, equating to 1.2% of the total PICU population. In addition, the annual rate of MDRO infections increased significantly over several years. However, correlating with the introduction of an ASP, the rates of MDRO infections decreased yearly over a 3-year period.

Cost Benefits

Lee et al showed that for targeted broad-spectrum antibiotics (meropenem, piperacillin-tazobactam, and cefepime), hospital-wide days of therapy per 1,000 patient-days decreased by 33% after implementation, resulting in a 70% cost reduction in total antibiotic purchasing. In their PICU, the days of therapy per 1,000 patient-days for these targeted antibiotics were reduced from 227 to 57 (75% reduction) only 6 months after guideline implementation, which was associated with significant cost savings as well. However, the study showed that the development of the ASP in itself did not result in an improvement in those areas. It was only after the implementation of antimicrobial use guidelines with retrospective review and direct feedback that an improvement in critical area antimicrobial use was seen. In addition, investigators did not find a statistically significant difference in the number of deaths in the critical care units after implementation of the guidelines.

In another study, investigators surveyed 22 freestanding children’s hospitals to determine why no ASP programs had been implemented; 8 of the hospitals were not attempting to implement a program, listing lack of funding and lack of personnel as the largest barriers to initiating a program. Given the significant cost-saving benefits of ASP initiation, proposals will benefit from a projected return on investment analysis.

Multiple studies have demonstrated cost savings without increased harm due to ASP implementation and guideline utilization. Healthcare cost reduction is obligatory, and this is one area for improvement likely to also reduce other hospital-acquired harms.

REFERENCES