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Pediatric research priorities in healthcare-associated infections and antimicrobial stewardship

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Original Article

Abstract

Objective: To develop a pediatric research agenda focused on pediatric healthcare-associated infections and antimicrobial stewardship topics that will yield the highest impact on child health.

Participants: The study included 26 geographically diverse adult and pediatric infectious diseases clinicians with expertise in healthcare-associated infection prevention and/or antimicrobial stewardship (topic identification and ranking of priorities), as well as members of the Division of Healthcare Quality and Promotion at the Centers for Disease Control and Prevention (topic identification).

Methods: Using a modified Delphi approach, expert recommendations were generated through an iterative process for identifying pediatric research priorities in healthcare associated infection prevention and antimicrobial stewardship. The multistep, 7-month process included a literature review, interactive teleconferences, web-based surveys, and 2 in-person meetings.

Results: A final list of 12 high-priority research topics were generated in the 2 domains. High-priority healthcare-associated infection topics included judicious testing for Clostridioides difficile infection, chlorhexidine (CHG) bathing, measuring and preventing hospital-onset bloodstream infection rates, surgical site infection prevention, surveillance and prevention of multidrug resistant gram-negative rod infections. Antimicrobial stewardship topics included β-lactam allergy de-labeling, judicious use of perioperative antibiotics, intravenous to oral conversion of antimicrobial therapy, developing a patient-level “harm index” for antibiotic exposure, and benchmarking and or peer comparison of antibiotic use for common inpatient conditions.

Conclusions: We identified 6 healthcare-associated infection topics and 6 antimicrobial stewardship topics as potentially high-impact targets for pediatric research.

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The burden of healthcare-associated infections (HAIs) among hospitalized infants and children is substantial and approximates rates reported in adults. A point-prevalence survey conducted in
199 hospitals in 2015 demonstrated that the rate of HAI in children aged 1–17 years was similar to that observed in patients aged ≥18 years (2.5% vs 3.5%).3 Although the risks of an HAI are similar among children and adults, few pediatric studies support evidence-based prevention strategies. Importantly, several observations demonstrate why evidence derived from adult studies cannot always be applied to children.6 First, the spectrum of HAIs experienced by pediatric patients differs significantly from that experienced by adult patients. For example, respiratory viral infections are one of the leading causes of pediatric HAIs and cause significant morbidity and mortality in vulnerable pediatric populations, but this HAI is rarely identified in hospitalized adults.7 Second, many HAI prevention strategies that have been developed and tested in adult populations cannot be easily implemented in the pediatric healthcare setting. Developmentally appropriate behaviors make interventions, such as a daily sedation vacation, impracticable and potentially unsafe in young children who require invasive mechanical ventilation. Third, the types of HAI, risk factors for HAI, and HAI prevention strategies may even differ over the age-spectrum pediatric patients, which ranges from very-low-birth-weight, preterm infants to adolescents.

Despite growing recognition that overuse is the primary driver of antimicrobial resistance, an estimated 60% of hospitalized children receive antimicrobial agents, including >90% of children who undergo surgery or require critical care.3 Numerous studies have suggested that as much as half of antibiotic use in both inpatient and outpatient settings is not indicated.4,5 To address this, national guidelines recommend that both adult and pediatric hospitals conduct antimicrobial stewardship (AS). Although the general principles of stewardship are shared across patient populations and settings, application of these principles to pediatrics requires consideration of important differences between adult and pediatric patients. For example, appendicitis, cystic fibrosis, and neonatal fever are some of the most common indications for antibiotic use in children’s hospitals. For infections that are commonly identified in both children and adults, such as pneumonia, urinary tract infections, and cellulitis, the selection and pharmacokinetics of antibiotics often differ.8

A pediatric research agenda is needed to focus on pediatric HAIs and AS questions that will yield the highest possible impact on child health. The Centers for Disease Control and Prevention (CDC)–sponsored Prevention Epicenters Program is a collaborative network of academic investigators conducting innovative infection prevention and control as well as AS research. The University of Pennsylvania/Children’s Hospital of Philadelphia Prevention Epicenter convened a network of investigators composed of pediatric HAI and AS expert clinicians, researchers, and stakeholders in the spring of 2018 to discuss gaps in evidence and identify priorities to inform the field of pediatric HAI and AS research.

Methods and Results

Overview

A working group of experts in pediatric HAI prevention and AS research and operations convened in the spring of 2018 to discuss potential priority topics for pediatric research in these fields. We surveyed attendees using a modified Delphi approach to generate expert opinions regarding the highest priority research topics in these 2 domains. The iterative process included a literature review, 3 teleconferences, 3 web-based surveys, and 2 in-person meetings. Throughout the process, attendees were encouraged to provide feedback and suggest additional approaches to ranking pediatric priorities for HAI and AS research in inpatient and outpatient settings.

Reviewing recent literature

Using Medline, the group leaders (S.E.C. and J.S.G.) conducted a comprehensive literature review of peer-reviewed, English-language articles published from January 2010 to June 2018 related to pediatric HAI and AS. The following search terms were used: healthcare-associated infections, drug-resistant organisms, antimicrobial resistance, and antimicrobial stewardship. Topics were limited by using the filter “child: age <18 years.” Experts also submitted additional publications considered relevant for inclusion. Title and abstract reviews were undertaken to ensure relevance to human health and to exclude case reports. A bibliography including titles and abstracts of identified articles was constructed by sorting articles into the following domains: infection prevention/HAI, device-related infections, multidrug-resistant organisms, neonatal HAI/AS, viral HAI, and AS. Our search identified 295 English-language publications related to pediatric HAI and AS. The structured bibliography was shared with expert panelists to ensure a shared understanding of the current body of relevant literature.

Expert participants

Authors S.E.C. and J.S.G. invited 26 experts to participate from geographically diverse institutions with research and clinical operations expertise in HAI or AS to participate in the process (Appendix 1 online). As sponsors of the Epicenters Program with expertise in HAIs and AS issues from a public health perspective, members of the Division of Healthcare Quality and Promotion at CDC also participated in the topic identification but not in the ranking of priorities.

Soliciting topic ideas

Each expert completed an open-ended REDCap survey asking about potential priority topics for pediatric HAI and AS research. For each topic, the expert was asked to provide a brief rationale, approach to study design, feasibility, and potential overall cost. In total, 15 topic ideas were submitted, many of which overlapped.

Ranking: Round 1

The group leaders created a risk assessment table by compiling topics identified by the literature review and by the experts. An initial 55 topic submissions were aggregated into 28 topics. Prior to expert ranking, 16 HAI topics were grouped into 4 categories (antibiotic resistant organisms, HAIs, metrics, and other topics), and 12 AS topics were presented without grouping. Major HAI topics included resistant gram-negative organisms, surgical site infections, and *Clostridiodes difficile* infections. AS topics included overuse of broad-spectrum therapy in inpatient settings, short course therapy in inpatient and outpatient settings, and rapid diagnostics (Appendix 2 online). A second REDCap survey was then distributed, asking experts to rank each topic on 3 attributes: magnitude, impact, and research opportunity: 1 (low) to 3 (high). For each topic, the mean score was calculated for each attribute, then the 3 mean values were multiplied to obtain a final score. Experts were also asked to identify a specific target population for each topic.


**Ranking: Round 2**

Experts attended a 1-day, in-person meeting to refine the prioritization of pediatric HAI and AS research topics. After presenting the results of the first round of ranking, several experts presented key published articles that focused on gaps in pediatric HAI and AS research. Experts were then grouped by their major domain of research (HAI or AS) to discuss the results of voting in round 1. Each group was asked to identify the top 10 priority topics in their domain. Thereafter, all participants convened to share perspectives. An additional round of ranking was then conducted using Poll Everywhere (San Francisco, CA), a web-based participant-response system. Each expert voted privately on their ranking of the 13 HAI topics, and 15 AS topics advanced after group discussions. Experts were asked to rank HAI and AS topics from highest priority lowest priority; HAI and AS lists were ranked independently.

**Payoff matrix**

After the in-person meeting, we recognized the need for further refinement of prioritization schemes because many topics in both domains were tightly clustered with similar composite ranking scores. We used a “payoff matrix” that assessed the magnitude of impact and ease of conducting research for each topic. Participants assigned each topic into 1 of 4 categories: group 1 (feasible and high-impact), group 2 (low feasibility but high-impact), group 3 (feasible but low-impact) and group 4 (low feasibility and low-impact). Experts were sent a remote link to complete this payoff matrix for each of the 13 HAI topics, and 15 AS topics established at the June 2018 in-person meeting.

Using the “payoff matrix” led to a substantial reordering of priorities among HAI topics based on the assessment of “feasible and high-impact” compared with “low-feasibility, but high-impact” (Table 1). Two HAI topics that had received relatively lower overall rankings (ie, chlorhexidine bathing to reduce colonization with drug-resistant organisms and developing a hospital-onset bloodstream infection metric) were included in the 3 topics categorized as “feasible and high impact.” Three HAI projects were considered “feasible and high impact.” These included the evaluation of a diagnostic stewardship bundle to reduce the inappropriate diagnosis of C. difficile infection, the development of a new metric for healthcare-onset bloodstream infections, and the assessment of antiseptic bathing to prevent colonization and infection with MDROs in various pediatric populations. In contrast, the relative priority rankings of antimicrobial resistance and AS topics were not substantially changed by the application of the payoff matrix. The 4 AS projects were considered “feasible and high impact.” These included β-lactam allergy de-labeling in low-risk outpatients, judicious use of perioperative antibiotics, shortening the duration of antibiotic therapy for common bacterial infections, and increased use of oral (instead of intravenous) antimicrobial therapy.

**Final selection of topics**

After the results of the payoff matrix voting were available, 2 teleconferences for attendees were convened. The HAI expert group developed consensus that the top 6 research topics should be considered high priority. The AS expert group identified 9 research topics from the payoff matrix and chose to re-rank them using additional participant voting; the group developed consensus that the top 6 should be considered high priority.

**Table 1. Final Pediatric Research Priorities Ranked by Final Payoff Matrix Score**

<table>
<thead>
<tr>
<th>Payoff Matrixa</th>
<th>Healthcare-Associated Infection Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasible and high impact</td>
<td>Diagnostic stewardship interventions for Clostridiodes difficile</td>
</tr>
<tr>
<td>Low feasibility but high impact</td>
<td>Surgical site infection prevention for specific high-risk pediatric procedures: ventriculo-peritoneal shunts; spinal fusion with instrumentation; cardiothoracic surgery</td>
</tr>
<tr>
<td>Low feasibility but high impact</td>
<td>Molecular epidemiology and transmission dynamics of multidrug-resistant gram-negative rods in critically ill children</td>
</tr>
<tr>
<td>Low feasibility but high impact</td>
<td>Novel central-line-associated bloodstream infection prevention bundles for high-risk pediatric populations</td>
</tr>
<tr>
<td>Feasible and high impact</td>
<td>β-lactam allergy de-labeling in low-risk outpatients</td>
</tr>
<tr>
<td>Feasible and high impact</td>
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<td>Low feasibility but high impact</td>
<td>Increased use of oral (instead of intravenous) therapy</td>
</tr>
<tr>
<td>Low feasibility but high impact</td>
<td>Develop patient-level “harm index” of antibiotics</td>
</tr>
<tr>
<td>Low feasibility but high impact</td>
<td>Benchmarking and/or peer comparisons of antibiotic use for common inpatient conditions</td>
</tr>
</tbody>
</table>

*Topics categorized as “feasible, but low impact” or “low feasibility and low impact” in the payoff matrix removed.

**Discussion**

To identify gaps in evidence and opportunities for impactful research, we leveraged available data, individual expertise, and structured discussion to identify and prioritize topics for pediatric HAI and AS research. Serial voting, using the Delphi process, was employed to focus and categorize identified topics by relative priority and level of difficulty performing the evaluation. This process generated 6 HAI and 6 AS topics as high priority targets for future research.

Ultimately, 3 HAI and 4 AS projects were considered high impact and feasible to initiate. The perceived ease of executing the HAI projects was likely related to the fact that most of the key data elements were routinely captured as part of clinical care. In contrast, the need to secure substantial funding and solidify a multicenter research network, led 2 high-priority HAI topics, both related to identifying the reservoirs and transmission patterns of multidrug-resistant gram-negative organisms, to be categorized as projects with “low feasibility but high impact.” The perceived ease of executing the 4 identified AS projects was likely related to the large numbers of relevant patient encounters and readily available clinical data required to study these topics. Alternatively, developing a patient-level “harm index” of antibiotics and benchmarking and/or peer comparisons for treating common inpatient conditions were identified as “low feasibility but high impact” due to the more challenging nature of establishing definitions, data collection, and analytic approaches.
Several barriers limited our efforts to identify pediatric priorities for HAI and AS research. Most participants were affiliated with an academic children’s facility. Although most complex inpatient pediatric care is delivered at tertiary-care and academically affiliated centers, our experience with pediatric care delivered in community hospitals was limited. Similarly, we had fewer participants with research and practice experience in outpatient pediatrics, although much of pediatric care is delivered in ambulatory settings.

In summary, we reviewed the published literature and leveraged the knowledge of content experts with contributions by and guidance from CDC colleagues. This systematic approach to building expert opinion identified specific HAI and AS research topics that are most likely to have a substantial positive impact on the health outcomes of children.

**Supplementary material.** To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2020.1267

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