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Healthcare-associated infections in the pediatric intensive care unit

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Abstract. Healthcare-associated infections cause significant morbidity and mortality in pediatric intensive care unit (PICU) patients. Critically ill children frequently require the placement of invasive devices, such as central venous catheters, urinary catheters, and endotracheal tubes. Each device increases a patient's risk of acquiring infection. In this review, the diagnosis and management of common healthcare-associated infections in the PICU is discussed. This review also examines several infection prevention strategies used in the PICU.

Keywords: Healthcare-associated infection, central line-associated bloodstream infection, ventilator-associated pneumonia, catheter-associated urinary tract infection, hospital-onset respiratory virus infection

1. Introduction

Healthcare-associated infections (HAI) cause significant morbidity and mortality in acute care hospitals. A point prevalence survey conducted by the Center for Disease Control and Prevention (CDC) concluded that on any given day, 4% of all hospitalized patients have at least one HAI [1]. Of the 452 patients identified with an HAI in this survey, 55 (12%) were younger than 18 yr of age [1].

Pediatric critical care frequently requires invasive devices for both monitoring and therapeutic purposes. Each device increases the child's risk of HAI, such as central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), or a ventilator-associated event (VAE). Elimination of these HAIs has become a healthcare priority, as these infections have become the subject of great scrutiny from healthcare authorities and the general public alike [1, 2]. Evidence-based preventive measures and "bundles" have dramatically decreased the rates of several pediatric HAIs in the past decade; one CLABSI prevention collaborative of 29 pediatric intensive care units (PICUs) reported a 56% CLABSI rate reduction from 2006 to 2009, from 5.2 CLABSIs per 1000 line-days to 2.3 CLABSIs per 1000 line-days [3]. Similarly, one large children's hospital reduced their CAUTI rate by 50% after implementing a CAUTI prevention bundle [4].

In this review, the diagnosis and management of common HAIs in the PICU setting are discussed. In addition, several strategies to prevent HAIs in the PICU setting are reviewed. Evidence-based recommendations are made when supportive scientific evidence is available for this specific patient population.

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2. CLABSI

It is estimated that 41,000 CLABSIs occur in hospitals in the United States annually [5]. CLABSIs are one of the most common HAIs that occur in the PICU population. A recent study found that one pediatric CLABSI was associated with a mean attributable cost of $55.64 [6]. Risk factors for CLABSI specific to PICU patients include duration of central access, receipt of parenteral nutrition, receipt of blood transfusion, presence of gastrostomy tube, non-operative cardiovascular disease, and ICU placement of central venous catheter [7]. The anatomic site of line insertion has not been identified as a risk factor for CLABSI in children. In contrast, central line placement into the femoral vein is a CLABSI risk factor in adults [8]. Not specific to the PICU, Lundgren et al. [9] found that repair of a broken CVC was associated with a 2- to 4-fold higher risk of developing CLABSI within thirty days of repair in pediatric patients.

The most common pathogens associated with CLABSI are Gram-positive organisms, including coagulase-negative Staphylococci (e.g. *Staphylococcus epidermidis*) and *Staphylococcus aureus*. Critically ill children in the ICU setting are also at risk of Gram- negative bacilli and candidal CLABSI, including multi-drug-resistant Gram-negative bacilli in some geographical areas. Knowledge about community and institutional antimicrobial resistance is critical when managing children with possible CLABSI.

2.1. Clinical manifestation and laboratory diagnosis

The earliest clinical sign of CLABSI is often age-dependent change in body temperature. Neonates may develop hypothermia or fever, and older children usually present with fever. CLABSI can quickly progress to sepsis; thus, CLABSI should always be considered in a febrile child with an indwelling intravascular catheter. If skin or soft tissue involvement is noted, such as erythema or tenderness at the catheter site, the patient should also be evaluated for other catheter-related infections. These include exit site infections, tunnel infections, and pocket infections (for totally implanted devices). Exit site infection is defined as erythema, induration, and/or tenderness within 2 cm of a catheter exit site [10]. The child may have other signs and symptoms of infection, such as fever or purulence from the exit site. A tunnel infection is defined as tenderness, erythema, and/or induration >2 cm from the catheter exit site, along the subcutaneous tract of a tunneled catheter [10]. A pocket infection occurs when infected fluid or tissue is found in the subcutaneous pocket of a completely implanted intravascular device (e.g. port), usually associated with tenderness, erythema, and/or induration of the skin and soft tissues overlying the device [10]. In all three scenarios, blood cultures may be positive, but are not required to diagnose the infection.

The clinical diagnosis of CLABSI is usually based on the presence of a bloodstream infection (BSI) in a child with an indwelling intravascular catheter, and the catheter is the presumed source of infection. It is frequently a challenge to definitively attribute the BSI to the catheter alone. Secondary BSI from an identifiable source (such as pneumonia, acute hematogenous osteomyelitis, and urinary tract infection) should be ruled out.

National Infectious Disease Society of America guidelines exist for the diagnosis and management of CLABSI [10]. However, a number of the recommendations do not easily apply to pediatric patients. The guideline recommends that when CLABSI is suspected, paired blood samples (catheter and peripheral vein) should be cultured before initiation of antimicrobial therapy. Further, the guideline recommends that if a blood sample cannot be collected from a peripheral vein, then two or more blood samples should be drawn through different catheter lumens [10]. The volume of blood required for multiple cultures, the difficulty in obtaining peripheral venous samples, and the small size of catheter lumens (especially in premature infants) pose a challenge for pediatric diagnosis of suspected CLABSI. However, whenever feasible, it is ideal to collect at least two age-appropriate volume blood cultures prior to the first dose of antimicrobial therapy. Determining if an organism is a true pathogen versus a "contaminant" can be challenging, especially when a commensal organism is recovered in the blood culture (e.g. *S. epidermidis*, viridans group streptococcus). Obtaining more than one blood culture during the initial assessment can assist in the determination; if more than one culture is positive, then the likelihood of CLABSI is higher.

2.2. Management

Initial empiric antimicrobial therapy for suspected CLABSI should include an antibiotic with reliable

Gram-positive coverage such as oxacillin, nafcillin, or vancomycin in areas with an increased prevalence of methicillin-resistant staphylococci. Empiric coverage for Gram-negative bacilli should also be included; selection of the specific agent should be based on local antimicrobial susceptibility trends, severity of disease, and specific host factors. For example, in areas where multi-drug resistant Gram-negative organisms are common, a fourth-generation cephalosporin, B-lactam/B-lactamase combination, or carbapenem may be indicated. If the child has underlying oncologic disease or neutropenia, then anti-pseudomonal coverage (e.g. cefepime, ceftazidime, piperacillin, or carbapenem) should be included in the initial empiric therapy.

Antifungal therapy is generally not recommended for all patients with suspected CLABSI, unless risk factors are present. A tertiary care children's hospital recently identified several risk factors for pediatric candidal CLABSI including intestinal failure, gastrostomy tube presence, receipt of blood transfusion, and total parenteral nutrition [11]. Additional risk factors for candidal CLABSI in the adult literature include prolonged use of broad-spectrum antibiotics, hematologic malignancy, receipt of bone marrow or solid-organ transplant, and colonization due to Candida species at multiple sites [10]. The empiric addition of an antifungal such as an echinocandin or fluconazole should be considered in a septic patient with any of these risk factors when CLABSI is suspected.

The length of antibiotic therapy is dependent on the causative organism, the rapidity of clinical response to therapy, and if complications (such as septic thrombi, endocarditis, or seeding to distal organs) occur. In all situations, day 1 of therapy is defined as the first day that a sterile blood culture is obtained. For low-virulence organisms such as coagulase-negative Staphylococci, catheter removal and a short course (e.g. 5 to 7 days) of systemic antibiotics is adequate. If the catheter is salvaged, the length of antibiotic therapy is extended to 10 to 14 days.

CLABSI due to *S. aureus* is associated with a high risk of complication, including prolonged BSI, endocarditis, and septic embolization to organs such as skin brain, lung, liver, spleen. Over the past decade, the rate of CLABSI in United States ICUs have declined, with the exception of CLABSI specifically caused by *S. aureus* in PICUs; the reason for this is unknown [12]. Catheter removal is recommended when *S. aureus* is found to be the causative organism; replacement of a new catheter should be delayed until blood cultures are sterile for >48 hr. For uncomplicated *S. aureus* CLABSI, 14 days of systemic antibiotics is recommended; prolonged courses (4 to 6 wk) may be required if complications occur or if the patient has intravascular hardware.

CLABSI caused by Gram-negative bacilli typically require a 10 to 14 day course of antimicrobial therapy. A low threshold for catheter removal should be maintained, especially if the child has prolonged bacteremia or fever despite appropriate antibiotic therapy.

Candida sp. are the most common fungi to cause fungal CLABSI. Catheter salvage is associated with prolonged candidemia and dissemination. Treatment with an echinocandin or fluconazole for 14 days is sufficient for uncomplicated infections. Many infectious disease experts recommend a dilated ophthalmologic examination to rule out candidal endopthalmitis, an echocardiogram to evaluate for endocarditis, and a urine culture with renal ultrasound to rule out candida pyelonephritis or renal fungal ball.

Prompt catheter removal is recommended in the following situations: severe sepsis; tunnel infection; pocket infection; endocarditis; persistently positive blood cultures despite >72 hr of appropriate antimicrobial therapy; CLABSI due to *S. aureus*, fungi, *Pseudomonas aeruginosa*, or mycobacteria [10]. Persistently positive blood cultures despite appropriate antimicrobial therapy suggests that an endovascular focus of infection may be present (e.g. endocarditis, septic thrombophlebitis). In such cases, echocardiogram and venous Doppler ultrasonography is indicated, and a prolonged course of therapy is needed.

2.3. Prevention

Much effort has been invested in determining evidence-based strategies for pediatric CLABSI prevention. Many of these efforts have been combined into "prevention bundles," which have been evaluated in large multi-center collaborative programs. One collaborative of 29 PICUs implemented both insertion and line maintenance bundles [3]. The insertion bundle included hand hygiene before procedure; chlorhexidine skin antisepsis at insertion site; the use of an insertion cart/tray; an insertion checklist; full sterile barrier; and mandatory insertion education for all providers. The maintenance bundle included daily assessment of catheter need (and removal as soon as feasible); standardized care of catheter site, hub, cap,

and tubing. These bundles led to a 56% reduction in CLABSI rate over 36 mo [3].

Daily skin bathing with a chlorhexidine preparation in PICU patients over 2 mo of age is recommended for CLABSI prevention [13, 14]. No routine recommendation exists for infants younger than 2 mo of age; however, several studies have demonstrated routine use and tolerability of 4% chlorhexidine gluconate-containing skin antisepsis in young infants, including premature neonates [15–17].

3. CAUTI

Urinary tract infections (UTIs) are a common and important cause of HAIs in the PICU setting. Over 80% of hospital-acquired UTIs are associated with the use of urinary catheters [18]. In 2002, approximately 13,000 deaths were reported to be associated with UTIs in hospitals in the United States [19]. One quarter of all hospitalized patients may have a urinary catheter sometime during their hospitalization, and in a third of those patients, the catheter may actually be unnecessary [20]. CAUTI can be associated with serious morbidity including pyelonephritis, sepsis, prolonged ICU stay and increased hospital days [18]. The most important risk factors for developing a CAUTI are the presence of a urinary catheter and the length of time the catheter remains in place. CAUTI prevention guidelines list appropriate indications for a urinary catheter placement. These include: critically ill patients who require accurate measurement of urinary output; patients with urinary obstruction; perioperative use; use in patients who have immobilizing injuries; situations to assist with healing of sacral/perineal wounds; comfort during end of life care [21, 22].

3.1. Clinical manifestation and laboratory diagnosis

Fever may be the first sign of a CAUTI. Other symptoms may include suprapubic tenderness, costovertebral angle tenderness and/or pain, frequency, dysuria and urgency. Laboratory evaluation should include urinalysis and culture. Urinalysis findings must include at least one of the following: (1) positive leukocyte esterase, and/or nitrites, (2) pyruria with >/ = 10 WBC/mm^3 of unspun urine or >5 WBC/high power field of spun urine, (3) microorganisms present on Grams stain if unspun urine.

Urine cultures are considered positive if they contain 10^3–10^5 CFU/mL (with no more than two species of microorganisms present). Children <1 yr of age with CAUTI may lack abnormal findings on urinalysis; however, the urine sample should still yield a positive culture, confirming the diagnosis of a CAUTI. The presence of an indwelling urinary catheter for $\geq$2 days that remains in place or was removed no more than one day prior identifies the UTI as a CAUTI [23]. Asymptomatic bacteruria may be present without any other clinical indications of infection. In 2009, the CDC's National Healthcare Safety Network (NHSN) modified the definition of CAUTI to exclude asymptomatic bacteruria [21].

3.2. Management

CAUTIs are most often caused by *Escherichia coli* and Candida sp, followed closely by Enterococcus sp, *P. aeruginosa, Klebsiella pneumoniae*, and Enterobacter sp. Appropriate treatment includes removal of the catheter if possible. If urinary catheter removal is not possible, strong consideration for changing the urinary catheter to a new sterile device should be made, as catheters can become colonized with the causative organism [24]. Initial empiric therapy usually includes a third generation cephalosporin, which can eventually be modified based on urine culture results. A broader spectrum agent (e.g. carbapenem) may be indicated for patients who are known to be colonized or previously infected with a multi-drug resistant organism. There is no evidence asymptomatic bacteriuria should be treated with antibiotics [22]. Therapy for bacteriuria and infection should include remove of the catheter if possible. If the catheter is retained, infection often persists after completion of antimicrobial therapy [25].

3.3. Prevention

Prevention bundles to reduce CAUTI include education about placing urinary catheters only when indicated, and removing them as soon as possible. Several adult CAUTI reduction studies have demonstrated that implementing quality improvement protocols can significantly decrease the use of catheters and the incidence of CAUTI [26]. One children's hospital also conducted a successful quality improvement project that provided extensive staff education and implemented a CAUTI bundle. The bundle included: placing urinary catheters only for approved indications; strict

aseptic technique; the use of a checklist during catheter placement; ongoing maintenance using aseptic technique including free drainage of urine, daily review of catheter necessity (with prompt removal as soon as appropriate). This led to a 50% decrease in the CAUTI rate, even though the utilization of urinary catheters remained constant [4].

Other options for urinary drainage and monitoring that may decrease risk of CAUTI include intermittent catheterizations and use of condom catheters. When a patient needs an indwelling urinary catheter, it is important that it is placed using aseptic technique, by providers properly trained in insertion. It is also important to assure the catheter drainage system is closed. The drainage bag should always remain below the level of the bladder and be free of kinks in the tubing. Immobilization of the Foley catheter (to decrease traction and local trauma) and using the smallest bore catheter may also decrease the risk of infection [21, 22].

One study found that physicians were unaware that their patient had a urinary catheter in place more than 25% of the time [20]. It is reasonable then to assume that protocols and guidelines supporting nurse-directed daily assessment about the indication for urinary catheter and catheter removal could impact CAUTI rates. Indeed, studies have shown that nurse-directed assessments for removal of unnecessary urinary catheters can result in a significant decrease in CAUTI rates [26, 27].

4. Ventilator-associated pneumonia (VAP)

Pneumonia is the second most common cause of HAI in the PICU setting. A point prevalence study of 35 US PICUs found that 23% of HAIs were due to pneumonia [28]. In 2012, nearly 4,000 VAPs were reported to the CDC's NHSN [29]. Risk factors for VAP specific to the PICU include genetic syndrome, steroids, re-intubation, bloodstream infection, prior antibiotic therapy, and bronchoscopy [30]. Another study identified subglottic/tracheal stenosis, trauma, and tracheostomy as pediatric-specific risk factors for VAP [31].

4.1. Clinical manifestation and laboratory diagnosis

Diagnosing pediatric VAP is difficult, as there is a lack of consensus for both the clinical and surveillance NHSN definitions. An alternative term such as "ventilator associated infection" is sometimes used, which includes bacterial tracheitis, pneumonia, and other related lower respiratory tract infections. The challenge in defining VAP is reflected by the NHSN's 2013 nomenclature modification from VAP to VAE for adult surveillance. Infection-related VAEs include inflammatory or infectious ventilator associated condition, possible VAP, and probable VAP [32]. The new definitions of VAE intentionally broaden the focus of surveillance from pneumonia alone to include additional physiologically significant complications of mechanical ventilation. At present, VAP remains the NHSN's terminology for PICU, and incorporates clinical, radiographic, and microbiological findings [29]. This change in nomenclature has been implemented for adult surveillance, but not for pediatrics.

With the difficulty in defining VAP, this disease remains a diagnostic dilemma. Ideally, one would use direct examination and culture of lung tissue, but this is impractical in children for routine diagnosis. Currently, the use of clinical, radiographic, and microbiological data are used in diagnosing VAP. Clinical criteria include fever, leukocytosis, purulent secretions, cough, worsening gas exchange, and auscultatory crackles. Many of the clinical findings are nonspecific and may be associated with an inflammatory response caused by other non-infectious entities. Radiographic findings are also often difficult to interpret in this population given the frequent occurrence of atelectasis in mechanically ventilated children, which makes consolidation difficult to confirm.

Microbiological information is also often difficult to interpret. Willson et al. [33] found that 37–53% of endotracheal tube aspirates using sterile catheters were positive for $>10^4$ colony-forming units by day 4 and these findings did not correlate with NHSN clinical criteria for VAP. BAL findings are the microbiological results most consistent with autopsy findings, however, obtaining a BAL is often impractical in children. There exist techniques which may be more specific than blind tracheal aspirates that are often sent for culture, but none have become the accepted standard of care. These include protected brush specimens, and non-bronchoscopic BAL. If routine tracheal aspirates are used, a sterile suction catheter will improve the usefulness of results.

Similar to NHSN's approach of using clinical, radiologic, and microbiologic criteria, Pugin et al. [34] developed a clinical pulmonary infection score (CPIS)

using six clinical, radiographic and microbiologic criteria in a scoring system (ranging 0–12). Scores greater than six are considered consistent with the diagnosis of VAP. This score has been used in adults with varying success. This CPIS score has been modified for children and validated in a single center for diagnosis of VAP in the PICU [34].

Currently, much of the diagnostic criteria for VAP are subjective, increasing variability and likely resulting in increased and unnecessary antibiotic use. More research is needed to improve the diagnostic criteria for VAP in children. Thus, the CDC has convened a working group that is considering a modified VAE definition for infants and children [35].

4.2. Management

If ventilator associated pneumonia is suspected it is important to initiate broad antibiotic coverage until more information is known, since delayed treatment with VAP is associated with increased mortality in the adult population. Initial empiric therapy should be based on patient-specific factors: length of hospitalization, aspiration risk, known colonization with multi-drug resistant organisms, and pathogens identified from the patient's prior respiratory cultures. When microbiological information is available, it is important to narrow antibiotic coverage appropriately. For uncomplicated VAP, a short course of therapy (e.g. 7 days) may be sufficient. A common dilemma occurs when tracheal aspirates are sent for culture as part of a routine evaluation for "new fever without source," but the patient has no signs of a pulmonary infection. It is well-established that the endotracheal tubes rapidly become colonized; thus, positive tracheal aspirate cultures may not reflect true infection [33]. This often leads to confusion about the diagnosis, and likely overuse of antibiotics in the PICU population.

4.3. Prevention

Prevention bundles for VAP and VAE have been developed for adults. The four most consistent features are: (1) elevation of the head of the bed to 30–40 degrees, (2) peptic ulcer prophylaxis, (3) deep vein thrombosis prophylaxis, (4) daily evaluation of extubation readiness [36]. It is unclear if consistent deep vein thrombosis prophylaxis is associated with decreasing rates of VAP; however, this element continues to be included in the Institute for Healthcare Improvement bundle recommendations. The intent of the daily extubation evaluation readiness testing is to ensure extubation as soon as clinically appropriate. The Institute for Healthcare Improvement also developed a "how to guide" which includes a VAP prevention bundle; in addition to the four elements mentioned above, it also includes daily oral chlorhexidine care and a daily "sedation vacation" [36]. Some of these interventions have not been well studied or are not available for infants and young children. The Society of Healthcare Epidemiology of America recently published 2014 practice recommendations to prevent VAP in acute care hospitals, which include pediatric-specific strategies [35].

5. Healthcare-associated respiratory virus infections

Common respiratory viruses have been implicated in numerous pediatric healthcare facility outbreaks. When breaks in standard infection prevention policies occur, respiratory virus transmission can occur rapidly in an ICU setting. Viral respiratory infections may be potentially life-threatening; several reports in the literature illustrate the significant morbidity and mortality due to outbreaks in the PICU and neonatal ICU (NICU) settings [37, 38]. In 2002, a respiratory syncytial virus (RSV) outbreak in a PICU led to 15 nosocomial cases [37]. Four infants died (all with underlying congenital heart disease). A NICU experienced a severe influenza A virus outbreak in 1998 in which 19 of 54 infants (35%) in the unit became infected during the 18-day long outbreak, including one death [38]. In these outbreaks, notable risk factors included breaches in routine infection control practices (e.g. appropriate patient isolation, hand hygiene compliance, appropriate use of disposable gloves and gowns) and low influenza immunization rates among healthcare providers.

5.1. Clinical manifestations and laboratory diagnosis

During respiratory virus season, pediatric healthcare providers should have a low index of suspicion for identifying respiratory virus HAI. If a hospitalized child develops new-onset upper respiratory infection symptoms, the child should be promptly placed in appropriate isolation precautions and viral diagnostic

testing performed. Providers should be aware of the available viral diagnostic laboratory tests; polymerase chain reaction assay and rapid viral antigen detection (immunoassays) have improved turnaround times compared to viral culture.

5.2. Management

All children diagnosed with hospital-onset respiratory virus infection should receive supportive care. Children diagnosed with influenza should receive antiviral therapy, regardless of influenza immunization status, optimally within 48 hr of symptom onset.

Ribavirin has *in vitro* activity against RSV, and treatment with aerosolized ribavirin has been reported to yield a small but significant increase in oxygen saturation during acute infection [20]. However, aerosolized ribavirin has not been proven to cause a reduction in mechanical ventilation, PICU length of stay, or overall length of stay [39]. Ribavirin may be considered for selected patients with severe life-threatening disease, profound immunodefiency, or severe underlying cardiopulmonary disease.

Immunotherapy with RSV monoclonal antibody is not routinely recommended nor approved by the Food and Drug Administration for patients with RSV infection.

Cidofovir is an antiviral agent that has been used in a select patients with life-threatening adenovirus disease, usually in immunocompromised hosts (e.g. transplant recipients), but also in life-threatening community-acquired pneumonia [40, 41]. Cidofovir is highly nephrotoxic; the risk of kidney injury can be decreased with concominant probenecid and intravenous hydration [40].

5.3. Prevention

There are several approaches in preventing respiratory virus HAI in the PICU setting, but no standard guideline exists specific to the inpatient setting. Important components to successful prevention include: immediate isolation (e.g. contact plus droplet isolation precautions) at the time of symptoms onset; rapid laboratory confirmation of infection; systematic screening of hospital visitors (especially young siblings) prior to ICU entry; excellent hand hygiene compliance; proper use of personal protective equipment (e.g. disposable gowns, gloves), and healthcare worker adherence to ill provider/sick leave policies.

If a unit identifies a case of respiratory virus HAI, the hospital infection prevention and control department should be notified. If more than two cases are identified, further interventions may be required to halt further spread (e.g. cohorting staff, visitor restriction, and active surveillance of exposed patients).

Routine immunization of healthcare workers (HCWs) is a critical component of HAI prevention. Nosocomial outbreaks of vaccine-preventable disease have been documented extensively in the literature. Influenza virus is an easily transmissible pathogen known to be associated with higher morbidity and mortality in young children and those with underlying medical conditions. In addition, HCWs may shed (and transmit) virus for 1 to 2 days before the onset of symptoms. An epidemiologic outbreak investigation of a NICU influenza outbreak revealed that of 86 staff who responded to the questionnaire, only 13 (15%) had been immunized against influenza that season [38]. In addition, although 14 HCWs admitted to having an influenza-like illness during the outbreak period, only four reported taking sick leave [38]. In institutions where immunization is not mandatory, PICU leadership (both physicians and nursing representatives) should implement an annual seasonal influenza employee immunization campaign. Routine HCW influenza immunization should be regarded as standard practice for the protection of vulnerable patients, fellow HCWs, and HCW families to decrease the risk of occupational exposure to influenza virus.

In conclusion, HAIs in the PICU lead to increased patient morbidity, mortality, and costs. Over the past decade, more scrutiny has been placed on the occurrence of HAIs, and the National Quality Forum refers to some HAIs as "never events" [42]. As a result, more pediatric-specific strategies are needed to prevent hospital-onset infections in this specific patient population.

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