Presence of Invasive Devices and Risks of Healthcare-Associated Infections and Sepsis

Erin E. Bennett¹ John VanBuren¹ Richard Holubkov¹ Susan L. Bratton¹

¹Division of Critical Care, Department of Pediatrics, University of Utah, Salt Lake City, Utah, United States

Address for correspondence Erin E. Bennett, MD, MPH, 295 Chipeta Way, PO Box 581289, Salt Lake City, UT 84115, United States (e-mail: Erin.Bennett@hsc.utah.edu).

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Abstract

Keywords

- healthcare-associated infection
- sepsis
- catheter-associated infections

The present study evaluated the daily risk of healthcare-associated infections and sepsis (HAIS) events in pediatric intensive care unit patients with invasive devices. This was a retrospective cohort study. Invasive devices were associated with significant daily risk of HAIS ($p < 0.05$). Endotracheal tubes posed the greatest risk of HAIS (hazard ratio [HR]: 4.39, confidence interval [CI]: 2.59–7.46). Children with both a central venous catheter (CVC) and urinary catheter (UC) had over 2.5-fold increased daily risk (HR: 2.59, CI: 1.18–5.68), in addition to daily CVC risk (HR: 3.06, CI: 1.38–6.77) and daily UC risk (HR: 8.9, CI: 3.62–21.91). We conclude that a multistate hazard model optimally predicts daily HAIS risk.

Introduction

Healthcare-associated infection and/or sepsis (HAIS) events complicate the care of critically ill hospitalized patients leading to potential organ injury or failure, prolonged length of stay (LOS), increased medical costs, and death. Although sustained focus on infection prevention has decreased rates of catheter-associated infection, invasive medical devices still pose risks to intensive care patients.¹

Invasive devices including endotracheal tubes (ETT), urinary catheters (UC), and central venous catheters (CVC) are associated with increased infection rates in intensive care unit (ICU) settings.² Although previous studies evaluated multiple devices and increased risk of HAIS events in pediatrics, there are limited data evaluating the association of device use and infection.^{3–8} Few studies of pediatric ICU patients are available to assess catheter-associated risk.^{4,6}

The Critical Illness Stress-Induced Immune Suppression (CRISIS) Prevention Trial was a randomized, double blind placebo-controlled multicenter analysis that evaluated the occurrence of HAIS events in pediatric ICU patients receiving nutritional supplements versus patients receiving routine nutrition. There was no difference in HAIS events between the groups.⁹

We used this publicly available dataset to compare time-dependent patient exposure of invasive devices and risk of

HAIS events in pediatric ICUs using a multistate hazard model. We predicted that the risk of HAIS would increase with invasive device exposure but that the risk would vary by device type. Our aim was to assess the relationship between clinical/demographic factors and the development of HAIS.

Methods

We conducted a post-hoc analysis of the CRISIS Prevention Trial, which took place from April 2007 to November 2009 and included 293 subjects from eight tertiary care hospitals in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. The study was registered ClinicalTrials.gov, number NCT00395161.

Subjects

The CRISIS inclusion criteria included children aged 1 to 18 years, study enrollment within 48 hours of ICU admission, and presence of at least one of the following invasive devices: ETT, CVC, and UC. All enrolled subjects were included in this analysis. Subjects were described as immunocompromised if they had undergone a hematopoietic stem cell or solid organ transplantation, had cancer or human immunodeficiency virus, or were treated chronically with immunosuppressive therapy, which included antilymphocyte globulin and

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chemotherapeutic agents. As the primary study did not find any difference in the incidence or time to HAIS,⁹ the treatment groups were combined for the present analysis.

Study Design

Severity of illness was assessed using three different scoring tools. All subjects were assigned an admission Pediatric Risk of Mortality III (PRISM III) score and Organ Failure Index scores and Pediatric Logistic Organ Dysfunction scores.^{10–12} These measures were calculated at study initiation and on preset subsequent ICU days.

The primary endpoint of the original CRISIS trial was HAIS development at least 48 hours after pediatric ICU admission until 5 days after discharge from the ICU. Daily data were collected to identify HAIS events up to a maximum of 33 days. A panel of investigators adjudicated each case of HAIS with the presence of invasive devices. Definitions of infection and sepsis were specific to the original CRISIS trial. Infection was defined as identification of a pathogen by culture, antigen detection, or antibody in the setting of fever, hypothermia, chills, or hypotension. Ventilator-associated infection (VAI) included a respiratory specimen that was positive for a pathogen, though the sources of ventilator infections varied by subject and a new radiographic infiltrate was not required for the diagnosis of VAI. Central line-associated bloodstream infection (CLABSI) required a positive blood culture for diagnosis, and catheter-associated urinary tract infection (CAUTI) required a positive urinary culture for diagnosis. Clinical sepsis was defined as fever $\geq 38^{\circ}\text{C}$, systolic blood pressure ≤ 90 mm Hg, or oliguria ≤ 20 mL/h in patients with ETT, CVC, and/or UC, and antibiotics were initiated by the clinician but no microbiologic cause or alternate explanation was identified.⁹ Time to event was calculated in days from the time of admission to time of infection, sepsis, both, or time to discharge or study completion in those without HAIS.

Outcome Measures

The aim of this secondary analysis was to assess the relationship between covariates and time to HAIS development by invasive device type using Cox proportional hazard ratios in a multistate hazard model. Indicators for whether ETT, CVC, and UC were present/absent on each study day were used as time-varying covariates in the multistate hazard model. Demographic variables and interactions between the time-varying covariates were considered in the modeling.

Statistical Analysis

Subjects were grouped into those with and without HAIS events and further divided into subgroups based on clinical sepsis and positive testing for infection. Device study days were defined as days with invasive devices in situ until development of HAIS or study conclusion without HAIS. Descriptive statistics and nonparametric tests were used to compare demographic and clinical characteristics of subjects with and without HAIS. Pairwise comparisons between subgroups were tested with the Wilcoxon Rank Sum test. We applied the Bonferroni correction for multiple comparisons. Among patients without HAIS, events occurred at the end of ICU stay, discharge, or death.

A secondary sensitivity analysis was performed to identify risk factors in patients who developed sepsis. Analyses were completed with SPSS software version 24 and SAS version 9.4 (SAS Institute; Cary, North Carolina, United States); $p < 0.05$ was prespecified for statistical significance.

Results

Of 293 enrolled patients, 122 (42%) had a HAIS event and 29 developed a second HAIS event. All events by initial HAIS type are displayed in ►Fig. 1. There were 97 subjects with microbiologically documented infections and 25 had culture negative sepsis. Of the subjects with infections, 66 had

Fig. 1 Flow chart of all pediatric intensive care unit subjects with an initial healthcare-associated infection or sepsis (HAIS) event, distributed by event type.

infections only and 31 were also septic. Most subjects with infection had one identified source ($n = 60$), but six subjects had > 1 source.

Demographic and Clinical Data

► **Table 1** compares demographic and clinical features among subgroups of subjects classified by HAIS status: those who developed sepsis and infection with an identified pathogen ($n = 31$, 11%), culture negative sepsis ($n = 25$, 9%), infection without sepsis ($n = 66$, 23%), and subjects who did not develop

sepsis or infection ($n = 171$, 58%). Subjects with and without HAIS did not significantly differ by age, gender, ethnicity, or postoperative status. Approximately half of study subjects (47%) had a complex chronic condition (CCC) and most CCCs occurred in immune competent individuals.

► **Table 2** shows the comparison of clinical data between subjects who developed HAIS and those who did not. At baseline, 113 of 122 (93%) subjects in the HAIS group were immunocompetent, which was similar among study groups. PRISM III scores were similar for patients who developed

Table 1 Select demographic and clinical features compared by documented infection and clinical sepsis

Patient demographics and clinical features	Healthcare-associated sepsis with pathogen identified $N = 31$	Healthcare-associated clinical sepsis no pathogen identified $N = 25$	Healthcare-associated infection without clinical sepsis $N = 66$	No healthcare-associated infection or clinical sepsis $N = 171$
Age in years, median (IQR)	8.0 (3.5, 14.0)	3.0 (2.0, 10.0)	9.0 (3.5, 15.5)	6.8 (2.0, 13.0)
Gender				
Female, n (%)	12 (39)	12 (48)	38 (58)	86 (50)
Ethnicity				
Hispanic or Latino, n (%)	6 (19)	2 (8)	13 (20)	34 (20)
Not Hispanic or Latino, n (%)	22 (71)	19 (76)	50 (76)	131 (77)
Unknown	3 (10)	4 (16)	3 (6)	6 (4)
Race				
American Indian or Alaska Native, n (%)	–	–	2 (3)	3 (2)
Asian, n (%)	–	1 (4)	3 (4)	2 (1)
Black or African American, n (%)	11 (35)	5 (20)	19 (29)	45 (26)
White, n (%)	19 (61)	19 (76)	41 (62)	108 (63)
Reported unknown, n (%)	1 (3)	–	1 (1)	8 (5)
Other, n (%)	–	–	–	5 (3)
Chronic mechanical ventilation				
Yes, n (%)	2 (6)	1 (4)	1 (1)	18 (10)
Chronic conditions ^a				
Cancer, n (%)	–	–	1 (1)	4 (2)
Cerebral palsy, n (%)	2 (6)	3 (12)	7 (11)	8 (5)
Chromosomal anomalies, not hereditary, n (%)	2 (6)	1 (4)	6 (9)	4 (2)
Congenital heart disease, n (%)	1 (3)	1 (4)	2 (3)	5 (3)
Neurological impairment, n (%)	5 (16)	5 (20)	21 (32)	27 (16)
Transplantation, n (%)	1 (3)	1 (4)	–	4 (2)
Other, n (%)	11 (35)	13 (52)	32 (48)	97 (57)
No chronic conditions, n (%)	22 (71)	13 (52)	32 (48)	84 (49)

Abbreviation: IQR, interquartile range.

^aChronic diagnoses are based on total chronic diagnoses because some children had more than one.

Table 2 Clinical data compared by HAIS outcome groups

Clinical data	HAIS N = 122, (%)	No HAIS N = 171, (%)
Immune status		
Immune competent, n (%)	113 (93)	155 (91)
Immune compromised, n (%)	9 (7)	16 (9)
Baseline PRISM III score mean, (SD)	10 (6.8)	8.5 (6.5)
Invasive devices at study enrollment		
Urinary catheter, n (%)	105 (86)	143 (84)
Endotracheal tube, n (%)	108 (89)	156 (91)
Central venous catheter, n (%)	107 (88)	144 (84)
Invasive devices at end of study^a		
Urinary catheter, n (%)	89 (73)	9 (5)
Endotracheal tubes, n (%)	98 (80)	13 (8)
Central venous catheter, n (%)	100 (82)	39 (23)
Duration of invasive devices in days		
Urinary catheter, median (IQR)	10 (6, 16) ^b	4 (3, 7)
Endotracheal tube, median (IQR)	10.5 (7, 18) ^b	4 (2, 6)
Central venous catheter, median (IQR)	13.5 (8, 23.5) ^b	6 (4, 9)
Pediatric ICU data		
Hours from pediatric ICU admit to end of study, ^a median (IQR)	142 (92, 203) ^c	261 (162, 331)
Pediatric ICU days, median (IQR)	17(11, 26) ^c	7 (5, 11)
Antibiotic free days in the Pediatric ICU, mean (SD)	4 (3)	3 (4)
Subjects with multiple events, n (%)	6 (5)	–
Death, n (%)	11 (9)	13 (8)

Abbreviations: HAIS, healthcare-associated infection and sepsis; ICU, intensive care unit; IQR, interquartile range; PRISM III, Pediatric Risk of Mortality III; SD, standard deviation.

^aEnd of study = healthcare-associated sepsis or infection for subjects who had an event or the end of the study time period for subjects who did not have an event.

^bIndicates $p < 0.001$ for duration of invasive devices in HAIS versus no HAIS.

^cIndicates p for HAIS versus no HAIS is $0.05/3 = 0.015$.

HAIS versus those who did not (10 vs. 8.5). Invasive devices at study initiation were common and present in similar proportions by study group since this was an inclusion criterion, but they were significantly greater in the HAIS groups at the time of the event. Additionally, duration of all invasive devices was significantly longer in patients who developed HAIS versus those who did not ($p < 0.001$).

Time-to-Event Analysis

Median time to event was significantly shorter in those who developed HAIS (142 hours vs. 261 hours, respectively, $p < 0.001$). Median pediatric ICU LOS also was significantly longer in the group with HAIS compared with those without (17 vs. 7 days, $p < 0.001$). Despite differences in HAIS development and ICU LOS, mortality was similar (9 vs. 8%). The most common cause of death in both groups was pulmonary failure (45 vs. 38%, data not shown).

► **Table 3** highlights invasive device-associated infection rates. Device-associated infections per total study days were CAUTIs 8 per 1,000 days, CLABSI 6 per 1,000 days, and VAI 42 per 1000 days.

Hazard Model for Risk Association

The hazard model results measuring risk of HAIS for the time-dependent variables are presented in ► **Table 4**. Neither

Table 3 Infection rates per invasive device use

Catheter type	Number of catheter-associated infections	Total device study days	Infections per device ^a 1,000 study days
Urinary catheter, n	14	1,747	8
Central venous catheter, n	12	2,156	6
Endotracheal tube, n	73	1,730	42

^aInfections are based on number of study days for which an invasive device was used.

Table 4 Risk of developing HAIS with invasive devices

Parameter	Hazard ratio (95% CI)	p-Value
Age (years)	1.02 (0.98, 1.05)	0.323
Number of chronic diagnoses		
One chronic diagnosis	0.49 (0.3, 0.77)	0.015
Two or more chronic diagnoses	0.8 (0.52, 1.24)	
No chronic diagnoses	Reference	
Endotracheal tube		
Yes	4.38 (2.58, 7.44)	< 0.001
Central venous and urinary catheter status^a		
CVC only	3.04 (1.38, 6.74)	0.006
UC only	8.9 (3.62, 21.91)	< 0.001
CVC and UC	2.59 (1.18, 5.68)	0.018

Abbreviations: CI, confidence interval; CVC, central venous catheter; ETT, endotracheal tube; HAIS, healthcare-associated infection and sepsis; UC, urinary catheter.

^aThe reference groups for the categories "Endotracheal Tube" and "Central Venous and Urinary Catheter Status" are the absence of ETT, CVC, and UC, respectively.

Note: "Reference" refers to the "No chronic diagnoses" row as being the "reference group" for this section to compare the "one chronic diagnosis" and "two or more chronic diagnoses."

the number of chronic diagnoses nor immunosuppression were independent risk factors for HAIS after adjusting for duration of invasive devices. Specific findings with each invasive device revealed that daily exposure to an ETT was the most consistent factor associated with greater than a fourfold daily increased risk of any HAIS development (hazard ratio [HR] of 4.39, 95% confidence interval [CI] 2.59, 7.46, $p < 0.001$) compared with children without an ETT and all other model factors being identical. Having a CVC alone increased the daily risk for any HAIS greater than threefold (HR: 3.06, 95% CI: 1.38–6.77, $p = 0.006$), and UC alone increased the daily risk over eightfold (HR 8.9, 95% CI 3.62–21.91, $p < 0.001$). While the HR for UC was over eightfold, the clinical occurrence of having a CVC was rare (only 199 study days) compared with the 2,182 study days observed in individuals with ETTs, thus ETT posed a greater risk factor for developing HAIS. Over and above the effect of ETT per se, we did not find an additional increased daily risk for relationships between ETT and CVC, ETT and UC, or all three present at the same time. However, having both a UC and CVC at the same time significantly increased the risk of developing HAIS on any given day > 2.5 -fold (HR: 2.59, 95% CI: 1.18–5.68, $p = 0.018$).

Secondary Sensitivity Analysis

The secondary sensitivity analysis that evaluated time to event for all subjects who developed sepsis at any point is shown in ► **Table 5**. Despite a limited number of subjects with the event of interest ($n = 56$), presence of an ETT continued to be the factor most significantly associated with developing sepsis with a 2.3-fold increase in daily risk (CI 1.12–4.75, $p = 0.024$). While CVC and UC tended to increase the risk of sepsis by approximately 1.5-fold daily, neither were statistically significant (HR: 1.62, 95% CI: 0.69–3.8), and UC increased the risk by (HR: 1.46, 95% CI: 0.72–2.93).

Discussion

This multistate analysis identified that presence of an invasive device was the biggest risk factor for the development of HAIS. We included primarily immune competent pediatric ICU patients with invasive devices of whom 42% developed HAIS. This population was at high risk of HAIS because study

eligibility required at least one invasive device for enrollment, and the hazard model determined that the most important factor in developing HAIS was presence of an invasive device. ETT posed the greatest risk factor for developing HAIS, and risk increased with the daily use of a CVC and/or UC. VAI was the most common adjudicated infection or sepsis event followed by CAUTI and CLABSI. As expected, HAIS led to longer pediatric ICU and hospital LOS.

Severity of illness scores, presence of CCC, and immunosuppression were not significantly associated with HAIS risk in our study. This differs from past reports of risk factors for HAIS.^{3,8,13–15} This may be because they did not account for the duration of invasive device use prior to the study. Pediatric patients with medical complexity have been shown to consume disproportionate pediatric ICU days and services such as invasive vascular monitoring, infusions or vasoactive medications, mechanical ventilation, dialysis, and extracorporeal membrane oxygenation,¹⁶ so chronic illness was likely collinear with both the use and the duration of invasive devices.

Our hazard model was consistent with other analyses that showed longer intubation time as a risk factor for VAI,^{17–24} and our time-dependent analysis showed a fourfold increase in incidence of HAIS for every day that an ETT was present. Pulmonary infections occurred in 68% of mechanically ventilated subjects, which are extremely high but consistent with some previous reports.^{17,18,25} Our rate of 42 VAI per 1,000 ventilation study days was almost 10 times higher than some reports,^{20,25} though current estimates range from 3 to 45 VAI per 1,000 ventilation days,^{21,22} and most reports acknowledge that VAI diagnostic criteria and sources of respiratory cultures are variable.^{18,20,23,24} Though the infections in our study were all adjudicated, there is no “gold standard” for VAI diagnosis, and the current clinical diagnosis differs substantially by both critical care providers and centers and leads to inconsistent reporting.

Indwelling CVCs increased the daily risk of HAIS over threefold in our hazard model. Our rate of 6 CLABSI per 1,000 CVC study days is similar to rates of CLABSIs at the time the CRISIS study was completed and to current reports of very high-risk burn and oncology patients^{6,8,26–29} but greater than most contemporary reports of hospitalized pediatric patients of 4–5/1000 day.^{22,30–32} Until recently, CLABSIs were the most common healthcare-associated infection;³³ however, multiple reports document dramatically decreased rates in both pediatric and adult patients when multidisciplinary teams adhere to insertion and maintenance care bundles.^{30,33,34} CLABSIs have a multivariable risk profile and depend on placement conditions, operator experience, catheter and site care, and other factors, though we were unable to explore these details in our study. However, longer duration of catheter use is consistently associated with higher risk of infection, and some studies also note greater severity of illness and/or multiple catheters as risk factors for catheter-associated infection.^{6,8,35}

Several factors may account, in part, for the relative high CLABSI rate in our study. First, CRISIS enrolled a relatively ill subset of pediatric ICU patients. Second, we calculated rates

Table 5 Risk of developing secondary sepsis with invasive devices

Parameter ^a	Hazard ratio (95% CI)	p-Value
Endotracheal tube	2.3 (1.12, 4.75)	0.024
Central venous catheter	1.62 (0.69, 3.8)	0.266
Urinary catheter	1.46 (0.72, 2.93)	0.293

Abbreviation: CI, confidence interval; CVC, central venous catheter; ETT, endotracheal tube; UC, urinary catheter.

^aThe reference groups for the categories “Endotracheal Tube” and “Central Venous Catheter and Urinary Catheter Status” are the absence of ETT, CVC, and UC, respectively.

based on CVC study catheter days rather than total catheter days because we do not know total catheter days. If patients had the CVC placed prior to ICU admission or multiple CVCs, this could count for some of our elevated CLABSI rate since the exposure would be longer. Although all participating centers had implemented insertion bundles for CVCs prior to this study, the timing was likely soon after study initiation and we do not have information on compliance with the bundle components.

While ETT posed the highest risk for HAIS, indwelling UCs posed the largest daily risk of HAIS. Our hazard model showed a ninefold increase in incidence of HAIS for every day that a UC was present. Our study rate of 8 CAUTI per 1,000 UC study days falls in the middle range of current reports. Davis et al and Dueñas et al reported CAUTI rates of < 6 per 1,000 UC days while Zavalkoff et al and Hatachi et al reported higher CAUTI rate of > 11 per 1,000 UC days.^{21,22,31,36} Implementation of insertion and maintenance bundles for CVCs increased attention to CAUTI prevention, which occurred after the initial success of decreasing CLABSI rates in pediatric patients. Quality improvement initiatives to decrease CAUTI concur that optimal CAUTI prevention techniques are a work in progress.³⁶ Our CAUTI rate may also be slightly increased due to our reliance on study days to calculate rates rather than total catheter days.

We also found increased risk of HAIS among patients when both a UC and CVC were present compared with the sum of the individual daily catheter risk, which is consistent with prior reports.^{37,38} As both CVC and UC are commonly used as monitors among patients with hemodynamic instability, it is not surprising that we found additional daily risk of HAIS in subjects who were treated with both invasive devices. However, the explanation for this increased risk (effect modification) other than increased severity of illness and risk of bacteremia from UTIs is not well described. Therefore, ICU patients will benefit from continual evaluation of potential for all inserted invasive device removal on a regular and frequent basis to decrease HAIS.

The number of pulmonary infections/VAI was high, so we performed a secondary sensitivity analysis to determine risk factors for developing sepsis alone. Our secondary analysis was consistent with the main analysis showing that the presence of an ETT was the most significant factor in developing sepsis, while the presence of a CVC or UC was no longer independently significant. Use of mechanical ventilation and invasive catheters is associated with organ failure and illness severity.

Creating a multistate hazard model allowed us to evaluate device exposure over time and predict daily risk of HAIS development. Beyersmann et al published previous reports on the benefits of creating multistate models to account for control subjects (i.e., subjects with an invasive device) who become case subjects (i.e., subjects who develop HAIS) over time, which therefore reduce the risk for the overestimation of HAIS.^{39–41} After implementation of the model, the most important factor for developing HAIS event was the number of catheter study days for CVC, UC, and ETT.

Our analysis has several limitations. First, CVC device information, including number of lumens, number of catheters in place, insertion site, impregnation with silver, heparin, or antibiotic coating, is unknown. We did not know if lumens were frequently used for blood testing or infusions of intralipids or high concentration dextrose. Second, we used the Center for Disease Control definitions of clinical sepsis and infection as referenced in the original CRISIS study from 2012, which differ from the current definitions. Third, diagnosing VAI is somewhat subjective, which makes it difficult to analyze. Fourth, we do not know if the centers had VAI and CAUTI bundles in place nor center compliance with the bundles. Fifth, we did not evaluate the effect of other invasive devices on HAIS development. Lastly, though the data are older and practices have been implemented to mitigate HAIS, current trends remain similar.

In future analyses, using a multistate hazard model is a superior method to quantify daily risk of invasive device association with HAIS development. Additionally, if a patient has multiple CVCs, current expert opinion suggests the catheter study days should be counted according to the number of invasive devices in each patient, as their recent study showed that the rate of CLABSI decreased after catheter study days were counted according to the number of invasive devices.³⁵ The hazard model developed for this analysis is a sufficient method to account for multiple invasive devices in the assessment of cumulative daily risk of HAIS.

Conclusion

Our multistate time-dependent analysis showed that the biggest daily risk factor for the development of HAIS was presence of any invasive device. The percent of HAIS in subjects with invasive devices in this study was high, especially when invasive devices were present for longer periods of time. The presence of any of these invasive devices did not increase mortality but did increase ICU and hospital LOS. Our findings emphasize the need for daily and frequent assessment of patient need for invasive medical devices.

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Conflict of Interest

None.

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