Inherent Risk Factors for Nosocomial Infection in the Long Stay Critically Ill Child Without Known Baseline Immunocompromise

A Post Hoc Analysis of the CRISIS Trial

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Background: Nosocomial infection remains an important health problem in long stay (>3 days) pediatric intensive care unit (PICU) patients. Admission risk factors related to the development of nosocomial infection in long stay immune competent patients in particular are not known.

Methods: Post-hoc analysis of the previously published Critical Illness Stress induced Immune Suppression (CRISIS) prevention trial database, to identify baseline risk factors for nosocomial infection. Because there was no difference between treatment arms of that study in nosocomial infection in the population without known baseline immunocompromise, both arms were combined and the cohort that developed nosocomial infection was compared with the cohort that did not.

Results: There were 254 long stay PICU patients without known baseline immunocompromise. Ninety (35%) developed nosocomial infection, and 164 (65%) did not. Admission characteristics associated with increased nosocomial infection risk were increased age, higher Pediatric Risk of Mortality version III score, the diagnoses of trauma or cardiac arrest and lymphopenia ($P < 0.05$). The presence of sepsis or infection at admission was associated with reduced risk of developing nosocomial infection ($P < 0.05$). In multivariable analysis, only increasing age, cardiac arrest and existing lymphopenia remained significant admission risk factors ($P < 0.05$); whereas trauma tended to be related to nosocomial infection development ($P = 0.07$).

Conclusions: These data suggest that increasing age, cardiac arrest and lymphopenia predispose long stay PICU patients without known baseline immunocompromise to nosocomial infection. These findings may inform pre-hoc stratification randomization strategies for prospective studies designed to prevent nosocomial infection in this population.

Key Words: nosocomial infection, pediatric intensive care unit, immune competent host

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Despite widespread implementation of *Centers for Disease Control (CDC)* recommendations, including hand washing and infection prevention bundles, hospital acquired nosocomial infection remains an important problem in critically ill children.[1] It is well established that hospital acquired infections are more common in long stay patients who are in the pediatric intensive care unit (PICU) for longer than three days with concomitant invasive measures.[2,3] Up to 40% of these children acquire nosocomial infection and/or sepsis after being in the PICU for 14 days. Among this population, children with known immunocompromise at baseline are at the greatest risk for acquiring nosocomial infection related in part to their inability to fight infection; however, this group of children accounts for at most 10% of the population in thePICU.[3] An important knowledge gap exists as to what factors predispose to, or protect against development of nosocomial infection in the other 90% of long stay PICU patients without known baseline immunocompromise.

Many randomized interventional nutritional studies have been performed to determine whether nutriceuticals can prevent nosocomial infections in critically ill premature neonates, children and adults. In this regard, we completed the Critical Illness Stress induced Immune Suppression (CRISIS) prevention comparative effectiveness trial in which long stay PICU patients were stratified according to baseline immune status and randomized to one of the 2 nutriceutical strategies: whey protein with essential amino acids and lactoferrin, or zinc, selenium, glutamine and the prolactin secretagogue metoclopromide.[3] There were no differences in time

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to nosocomial infection or rate of nosocomial infection between treatment arms in the population without known immunocompromise at baseline. In order to identify risk factors for the development of nosocomial infection and to inform future interventional trials in long stay PICU patients without known baseline immunocompromise, we performed a retrospective cohort analysis of this trial's database comparing patients in this group who did and did not develop nosocomial infection.

METHODS

Patients were recruited from and enrolled in the PICUs of 8 centers in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. These sites included Arkansas Children's Hospital, Children's Hospital of Los Angeles, Mattel Children's Hospital of UCLA, Seattle Children's Hospital and Harborview, Children's Hospital of Michigan in Detroit, Children's National Medical Center in Washington DC and Children's Hospital of Pittsburgh. Entry criteria in the randomized trial were an expected stay greater than 3 days with indwelling invasive devices including mechanical ventilation, central venous catheters and indwelling urinary catheters, and age >1 year but <18 years. Exclusion criteria included the following; (1) had a known allergy to metoclopramide, (2) were expected to have planned removal of endotracheal tube, central venous and urinary catheters, within 72 hours after study enrollment, (3) had suspected intestinal obstruction, (4) had intestinal surgery or bowel disruption, (5) had other contraindications to the enteral administration of drugs or nutrients, (6) received chronic metoclopramide therapy before enrollment, (7) had a known allergy to whey (cow's milk) or soy based products, (8) had been discharged from the PICU in the previous 28 days, (9) had been previously enrolled in this study or (10) had a positive pregnancy test. Patients were also excluded if their parents indicated a lack of commitment to aggressive intensive care therapies.

In this exploratory analysis, long PICU stay is defined as more than 3 days in the PICU. Therefore, we included all PICU patients who were not known to have baseline immunocompromise, and who were followed for more than 3 days after PICU admission in our previously published randomized, double-blinded, comparative effectiveness trial for the prevention of CRISIS-related nosocomial infection.[3] Children were considered to have no known baseline immunocompromise if they were not found to have an admission diagnosis of cancer, acquired immune deficiency syndrome, solid organ transplantation, stem cell transplantation, autoimmune disease, primary immunodeficiency syndromes or chronic use of immune suppressant therapies. In this analysis, patient study records were reviewed in detail for these characteristics, and thus numbers differ slightly from the previously reported "as-randomized" immune competent stratum (3). Specifically, 266 of the 293 enrolled children were considered to have no known baseline immunocompromise in this review, with 254 meeting, the long PICU stay criterion and therefore analyzed in this report.

Nosocomial infection was defined according to *CDC* criteria. Infection was defined by a positive culture, polymerase chain reaction assay or antigen test identifying an organism in a patient with fever, systolic blood pressure < 90 mm Hg, or urine output < 20 mL/h considered to be the cause of these symptoms for which the primary clinician chose to treat the patient with antimicrobial therapy if available. Nosocomial infections were identified by the site principal investigators and clinical research coordinators. All identified nosocomial infections were then adjudicated by the network steering committee which included the site principal investigators, representatives of the data coordinating center (University of Utah) and the network scientific research officer (National Institutes of Child Health and Development). Nosocomial infection events were defined as occurring at least 48 hours after PICU admission during the hospital stay until 5 days after discharge from the PICU. For children remaining in the PICU for >28 days, events were counted for up to 33 days.

As this trial showed no difference in the time to development of or rate of nosocomial infection between treatment arms (beneprotein vs. zinc, selenium, glutamine and metoclopramide) we included both treatment arms of the study in our post hoc analysis of the population without known baseline immunocompromise. For these analyses, the patients were grouped into two cohorts those who developed nosocomial infection, and those who did not. Baseline characteristics were compared in order to evaluate the role of inherent preexisting risk factors.

Three scoring systems were used to assess severity of illness as a risk factor for later development of nosocomial infection. The Pediatric Logistic Organ Dysfunction (PELOD) score, an organ dysfunction severity scale designed to predict population mortality risk in the PICU, was collected on study day 1.[4] The Pediatric Risk of Mortality version III (PRISM III) score, a physiologic function scale designed to predict population mortality risk in the PICU, was collected in the first 12 hours of PICU admission.[5] The organ failure index, an organ failure scale designed to count the number of organ failures, was collected on study day 1.[6] Study day 1 was defined as the first day study drug administration was attempted and it varied from 0 to 3 days following PICU admission (median = 2 days following PICU admission).

Existing lymphopenia was defined as an absolute lymphocyte count $\leq 1000/mm^3$ from PICU admission until the first study treatment (median = 2 days following PICU admission). Existing neutropenia was defined as an absolute neutrophil count $\leq 1000/mm^3$ from PICU admission until the first study treatment (median = 2 days following PICU admission).

Statistical Analyses

We compared PICU admission characteristics between the 2 cohorts. Categorical variables are summarized as absolute counts and percentages. Continuous variables are summarized as means, standard deviations, medians and ranges. The statistical significance of association between the development of nosocomial infection and each characteristic was assessed by the Pearson χ^2 test or Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Reported significance levels are not adjusted for multiple comparisons as this analysis is considered exploratory.

Multivariable logistic regression was also used to evaluate the potential association between PICU admission characteristics and the development of nosocomial infection. Multivariable analyses were restricted to those with available lymphopenia data (208 of 254 patients). Variables with $P < 0.1$ in univariable analysis were considered for inclusion in the logistic regression model. The final model was determined using stepwise selection, with significance level of 0.1 for entry and 0.1 to remain in the model. Adjusted odds ratios with 95% confidence intervals and significance level from the Wald $\chi 2$ test are provided for each variable in the final model.

RESULTS

Two hundred and fifty-four long stay PICU patients were identified in the database to have no known baseline immunocompromise. Ninety (35%) subsequently developed nosocomial infection whereas 164 (65%) did not develop nosocomial infection. The number of days in the PICU at the time of developing nosocomial infection was a mean of 8.5 with a standard deviation of 5.3.

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The entire PICU stay was longer in the children who developed nosocomial infection (mean 23.4 days; standard deviation 19.6 days) compared with those who did not (mean 10.0 days; standard deviation 8.1 days). There were 146 total nosocomial infections and coinfections with 40% of the patients with nosocomial infection (n = 36) having multiple infections. By far the respiratory tract was the most common site of nosocomial infection (n = 92 lower tract; n = 3 upper tract), with urinary tract (n = 17), skin soft tissue (n = 12) and blood stream (n = 16) being similar at less than 20% of the incidence of the respiratory tract. Six patients had other sites of nosocomial infection. Table 1 shows the nosocomial infection and coinfection species identifications. There were a total of 197 infecting organisms with 35 fungi, 80 Gram-negative bacilli, 2 Gram-positive bacilli, 4 Gram-negative cocci, 67 Gram-positive cocci, 5 viruses and 4 undetermined. Most infections were consistent with a hospital acquired organism ecology rather than a community acquired organism ecology with only 13 being *Haemophilus influenza*, 1 being *Haemophilus parainfluenza* and 4 being *Moraxella catarrhalis*.

Table 2 shows the admission and baseline characteristics of the cohorts of children who did and did not develop nosocomial infection. Because only 3 patients had baseline neutropenia, this characteristic was not assessed in statistical analysis. In univariable analysis, increased age in years, increased severity of illness as indicated by higher PRISM III score, the primary or secondary diagnosis of Cardiac Arrest or Trauma, and the presence of lymphopenia (≤1000/mm^3) were all associated with the development of nosocomial infection ($P < 0.05$). Severity of illness measured by the PELOD score tended to be associated with increased risk ($P = 0.09$). By contrast, the presence of infection or sepsis at admission was associated with protection against the subsequent development of nosocomial infection ($P < 0.05$).

Table 3 shows the final multivariable model of factors independently associated with development of nosocomial infection. In this model, increasing age, cardiac arrest and lymphopenia continued to be significant risk factors ($P < 0.05$) whereas trauma tended to be a risk factor ($P = 0.07$) for development of nosocomial infection. Among these, the greatest risk was associated with cardiac arrest (adjusted odds ratio of 6.7 and a 95% confidence interval of 1.6–28.1). The most prevalent risk factor was lymphopenia, which was present in 78/208 (38%) of patients without known baseline immunocompromise (adjusted odds ratio of 2.0 and 95% confidence interval of 1.1 to 3.8). Ten patients developed lymphopenia ≥7 days of whom 5 developed nosocomial infection (50%) compared with the 78 patients with baseline lymphopenia of whom 37 developed nosocomial infection (47%). For every 10 years of age, the odds of developing nosocomial infection nearly doubles (for a child 1 year older than another, the estimated odds ratio was 1.06 with 95% confidence interval of 1.01–1.12).

TABLE 1. Nosocomial Infection Identification

Total number of infecting organisms	N = 197
Fungi	35
Candida albicans	9
Candida tropicalis	6
Yeast	7
Candida glabrata	4
Candida lusitanae	4
Other fungi: *Aspergillus niger* (2), *Candida* (1), *Candida parapsilosis* (1), *Cryptococcus* (1)	5
Gram-negative bacilli	80
Pseudomonas aeruginosa	27
Haemophilus influenzae	13
Stenotrophomonas maltophilia	7
Enterobacter cloacae	6
Klebsiella pneumoniae	6
Other Gram-negative bacilli: *Serratia marscescen* (4), *Acinetobacter baumannii* (3), *Citrobacter freundii* (3), *Escherichia coli* (3), *Klebsiella oxytoca* (2), *Haemophilus parainfluenza* (1), *Enterobacter aerogenes* (1), *Eikenella* species (1), *Acinetobacter species* (1), *Pantoea agglomerans* (1), *Enterobacter* species (1)	21
Gram-positive bacilli	2
Clostridium difficile	2
Gram-negative cocci	4
Moraxella catarrhalis	4
Gram-positive cocci	67
Staphylococcus aureus	31
Staphylococcus coagulase negative	9
Enterococcus faecalis	4
Staphylococcus epidermidis	4
Other Gram-positive cocci: *Enterococcus* species (3), methicillin-resistant *Staphylococcus aureus* (3), *Viridans streptococci* (2), *Streptococcus pneumoniae* (2), vancomycin-resistant *Enterococcus faecium* (1), *Enterococcus raffinosis* (1), *Enterococcus aerogenes* (1), *Enterococcus cloacae* (1), *Staphylococcus* (1), *Streptococcus* species (1), *Micrococcus* species (1), *Streptococcus viridans* group 2 (1), *Streptococcus* serogroup F (1)	19
Virus	5
Undetermined	4

DISCUSSION

To our knowledge this cohort analysis is the first study to ask the question whether there are inherent clinical factors which are associated with an increase or decrease in the risk of developing nosocomial infection in the long stay PICU population that does not have known baseline immunocompromise. Studies have previously shown that long stay PICU patients have increased rates of hospital acquired infections compared with short stay patients, with a 40% incidence of nosocomial infection observed by 14 days.[1–3] Our present cohort analysis represents the first study to evaluate what inherent characteristics determine risk among long stay critically ill children without known baseline immunocompromise. In this regard, we have attained several previously unappreciated insights. Primary or secondary admission diagnoses of cardiac arrest or trauma were associated with or tended to be associated with the development of nosocomial infection, and the presence of lymphopenia or increasing age further increased this risk. These findings inform future clinical investigations of nosocomial infection prevention strategies in critically ill children without known baseline immunocompromise.

The occurrence of nosocomial infections in children without known baseline immunocompromise in the CRISIS prevention trial was common, happening in over a third of the children. Multiple episodes of nosocomial infection and coinfections were not uncommon. The organisms identified were for the most part characteristic of hospital acquired ecology. Children who developed nosocomial infections were on average in the PICU for 8.5 days before infection onset. On average, their time in the PICU was increased out nearly 2 weeks compared with children who did not develop nosocomial infection, who on average had a length of stay just over 1 week.

Cardiac arrest was associated with 6-fold increased odds of developing nosocomial infections. This is biologically plausible for several reasons. First, regurgitation and aspiration pneumonia occur commonly among adults successfully resuscitated from cardiac arrest and might also occur in chidlren.[7–9] Second, cardiac arrest may impair bowel wall barrier integrity as a result of ischemia-reperfusion injury leading to bacterial translocation and nosocomial infection. Third, cardiac arrest survivors usually need continued invasive mechanical ventilation and hemodynamic monitoring with arterial and venous catheters that increase their risk for hospital acquired infections. The

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TABLE 2. Admission Factors in Patients Who Did and Did Not Develop Nosocomial Infection

	No Nosocomial Infection N = 164	Nosocomial Infection N = 90	*P*
Age (years)			
Min, max	1, 17.9	1, 17.9	
Mean (SD)	7.4 (5.5)	9.2 (5.8)	
Median (Q1, Q3)	5.1 (2.1, 12.6)	8.7 (3.6, 15.1)	0.01
Female	80 (49%)	48 (53%)	0.49
PELOD score			
Min, max	0, 50	0, 41	
Mean (SD)	9.8 (7.8)	12.2 (10.2)	
Median (Q1, Q3)	11 (2, 12)	11 (2, 21)	0.09
PRISM III score			
Min, max	0, 28	0, 34	
Mean (SD)	8.2 (6.3)	10 (6.8)	
Median (Q1, Q3)	7 (3, 12)	8 (5, 13)	0.04
Organ failure index score			
Min, max	0, 5	0, 6	
Mean (SD)	1.7 (1)	1.8 (1.1)	
Median (Q1, Q3)	2 (1, 2)	2 (1, 3)	0.24
Postoperative	45 (27%)	28 (31%)	0.54
Infection or sepsis	113 (69%)	49 (54%)	0.02
Lymphopenia (ALC ≤ 1000 mm^3)	41 (31%) [N = 134]	37 (50%) [N = 74]	0.01
Primary or secondary diagnosis			
Asthma	8 (5%)	2 (2%)	0.50
Cardiac arrest	4 (2%)	9 (10%)	0.01
Cardiovascular disease acquired	1 (1%)	3 (3%)	0.13
Cardiovascular disease congenital	13 (8%)	4 (4%)	0.29
Chromosomal abnormality	2 (1%)	3 (3%)	0.35
Diabetes	1 (1%)	0 (0%)	1.00
Drug overdose	2 (1%)	0 (0%)	0.54
Hypoxic ischemic encephalopathy	3 (2%)	0 (0%)	0.55
Meningitis	4 (2%)	2 (2%)	1.00
Pneumonia/bronchiolitis	46 (28%)	23 (26%)	0.67
Seizure	14 (9%)	9 (10%)	0.70
Sepsis	22 (13%)	8 (9%)	0.29
Shock	18 (11%)	6 (7%)	0.26
Trauma	32 (20%)	29 (32%)	0.02
Other	75 (46%)	47 (52%)	0.32
Chronic diagnoses	78 (48%)	38 (42%)	0.41

TABLE 3. Multivariate Logistic Regression Results for Nosocomial Infection Admission Risk Factors

Variable	Adjusted Odds Ratio (95% Confidence Intervals)	*P*
Age (per 1-year increase)	1.06 (1.01, 1.12)	0.03
Cardiac arrest (primary or secondary diagnosis) vs. no cardiac arrest	6.74 (1.62, 28.08)	0.01
Lymphopenia (ALC ≤ 1000 mm^3) vs. no lymphopenia	2.03 (1.10, 3.76)	0.02
Trauma (primary or secondary diagnosis) vs. no trauma	1.91 (0.96, 3.79)	0.07

very high risk of nosocomial infections among these critically ill children post cardiac arrest indicates that this group deserves special attention for monitoring and prompt treatment. Trauma tended to increase nosocomial infection risk. This is also biologically plausible because trauma and tissue injury destroy physical barrier defenses against bacterial and fungal infections. Skin lacerations allow for direct infection with skin and soil flora.[10–13] Lymphopenia was the most common risk factor in the development of nosocomial infection as it occurred in one-third of the children with available data. Lymphopenia is a recognized risk factor for the development of nosocomial infection in trauma and surgery patients.[14–16] This may be related to a heightened stress response leading to lymphocyte apoptosis and impaired immune function.[17,18] Felmet et al[18] previously reported increased risk of nosocomial infection in critically ill children when lymphopenia persisted beyond seven days. In our present study, we observed that the incidence of developing nosocomial sepsis in patients with baseline lymphopenia was similar to the incidence we observed in patients with prolonged lymphopenia. The mechanism by which increasing age might increase proclivity to nosocomial infection is not known although some have suggested that preexisting or ICU acquired dental and gingival biofilms can predispose to nosocomial pneumonia with age.[19]

The protective effect of having infection or sepsis at admission on subsequent development of nosocomial infections fell out

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in multivariable analysis. It appears paradoxical in the univariable analysis because severe sepsis is known to induce a secondary immune suppression period in approximately one-third of hosts who have sepsis induced multiple organ failure syndrome.[18,20,21] It is possible that the treatment of all patients who had infection or sepsis at admission with antibiotics prevented the onset of nosocomial infection through an unintended antibiotic "prophylaxis" effect. The harmful effects of increased severity of illness as measured by the PRISM III and PELOD also fell out in multivariable analysis.

There are several important limitations to consider in evaluating our study. First, we used the CDC pediatric criteria for diagnosing nosocomial infection at the time that this comparative effectiveness study was performed. We did this because we considered the CDC to be an authority on definitions of hospital acquired infection in children; however, there is no consensus among pediatric critical care infectious disease experts regarding these CDC criteria. This lack of a true gold standard for diagnosing infection in this population makes it quite possible that the sensitivity and specificity of our findings are negatively affected by over-estimation of true infection incidence. Second, 10 years have passed since beginning the CRISIS study and subsequent implementation of national and international initiatives using care bundles to reduce nosocomial infection from central lines, ventilators and urinary catheters. This also supports the likelihood that our nosocomial infection incidence represents an overestimate compared with today's true nosocomial infection incidence. Third, the patient population sample in this study received either daily enteral whey protein, or daily enteral zinc, selenium, and glutamine and intravenous metoclopramide as part of a comparative effectiveness trial. Because neither treatment arm affected the time to development or the rate of nosocomial infection in our population of interest, we grouped them together for the purposes of this exploratory analysis. Although this may seem reasonable, patients who agree to be part of a randomized interventional trial may be different from other long stay PICU patients in ways we do not know. A fourth limitation is that the clinical characteristics evaluated were designed for the purposes of the comparative effectiveness trial, not for the purpose of this cohort analysis. The small sample size attained in the randomized interventional trial also provides the possibility of a type II error. These limitations could be overcome by looking at larger databases; however, our purpose in doing this post-hoc analysis was to inform planning of future trials of nutriceuticals to prevent nosocomial infection in the long stay PICU patient without known baseline immunocompromise. For our purposes, these limitations can be viewed as strengths, because the type of patients and families who agreed to enrollment and the data collected in future interventional trial efforts will likely be similar to the patient population enrolled and data collected in the CRISIS prevention comparative effectiveness trial.

In future, interventional nutriceutical trials designed to prevent nosocomial infection in hosts without known baseline immunocompromise, investigators can be informed by the findings observed in this post-hoc analysis. Increasing age, cardiac arrest and lymphopenia predispose to nosocomial infection, whereas children with trauma have an increased tendency towards nosocomial infection. Consideration can be given to stratified randomization according to the presence or absence of lymphopenia because fully one-third of subjects will be expected to be lymphopenic with 2-fold increased odds of developing infection. Consideration can also be given to excluding cardiac arrest patients because they have more than 6-fold increased odds and represent only 5% of the population. Increasing age can be adjusted for using an a priori analytical strategy. The trauma populations can be evaluated separately or similarly adjusted for using an a priori analytical strategy. Future interventional trials aimed at reducing nosocomial infection risk in long stay PICU patients without known baseline immunocompromise should consider strategies controlling for these risk factors.

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