Utility of Clinical Biomarkers to Predict Central Line-associated Bloodstream Infections After Congenital Heart Surgery

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Background: Central line-associated bloodstream infections is an important contributor of morbidity and mortality in children recovering from congenital heart surgery. The reliability of commonly used biomarkers to differentiate these patients has not been specifically studied.

Methods: This was a retrospective cohort study in a university-affiliated children's hospital examining all patients with congenital or acquired heart disease admitted to the cardiovascular intensive care unit after cardiac surgery who underwent evaluation for a catheter-associated bloodstream infection.

Results: Among 1260 cardiac surgeries performed, 451 encounters underwent an infection evaluation postoperatively. Twenty-five instances of central line-associated blood stream infections (CLABSI) and 227 instances of a negative infection evaluation were the subject of analysis. Patients with CLABSI tended to be younger (1.34 vs. 4.56 years, $P = 0.011$) and underwent more complex surgery (RACHS-1 score 3.79 vs. 3.04, $P = 0.039$). The 2 groups were indistinguishable in white blood cell, polymorphonuclears and band count at the time of their presentation. On multivariate analysis, CLABSI was associated with fever (adjusted odds ratio: 4.78; 95% CI: 1.6–5.8) and elevated C-reactive protein (CRP; adjusted odds ratio: 1.28; 95% CI: 1.09–1.68) after adjusting for differences between the 2 groups. Receiver-operating characteristic analysis demonstrated the discriminatory power of both fever and CRP (area under curve 0.7247, 95% CI: 0.42 to 0.74 and 0.58, 95% CI: 0.4208 to 0.7408). We calculated multilevel likelihood ratios for a spectrum of temperature and CRP values.

Conclusions: We found commonly used serum biomarkers such as fever and CRP not to be helpful discriminators in patients after congenital heart surgery.

Key Words: cardiac intensive care, CRP, fever, WBC, congenital heart surgery

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Central line-associated blood stream infections (CLABSI) are theoretically preventable hospital-acquired conditions that contribute importantly to morbidity, mortality and health care costs across all age groups and diagnoses.[1,2] Although nationwide preventive efforts have reduced CLABSI rates, recent studies demonstrate that CLABSI remain highly prevalent.[2] Current estimates suggest between 15,000 and 41,000 CLABSI occur per year in non-neonatal hospitalized patients[1,3,4] and incidence rates as high as 48,600–80,000 cases per year affect patients in intensive care units (ICUs).[5] Owing to the inflammatory and immune-modulating effects of cardiopulmonary bypass, infants and children recovering from cardiac surgery are thought to be uniquely vulnerable to CLABSI.[6]

Owing to the injurious consequences associated with CLABSI in critically ill children, pediatric intensivists are motivated to react expeditiously to any indications of infection. Unfortunately, unlike other hospital-acquired infections such as surgical site infection (SSI) and ventilator-associated pneumonia (VAP), which often are associated with localized findings, CLABSI often present nonspecifically. Thus, a combination of fever, leukocytosis and elevated acute phase reactants, such as C-reactive protein (CRP), are commonly used to evaluate for CLABSI and represent important determinants for the empiric initiation of antimicrobial therapy. The diagnostic utility of these traditional biomarkers of infection to forecast CLABSI accurately in the pediatric cardiovascular intensive care unit (CVICU) has not been described previously. Furthermore, the wide variation in antimicrobial administration and treatment approaches to fever within pediatric ICUs suggests that these traditional biomarkers are not applied in a standardized fashion to accurately predict a bloodstream infection in this population.[7,8] The aim of our study was to investigate the ability of commonly used infection biomarkers (fever, leukocytosis and CRP) to accurately identify CLABSI in patients undergoing a sepsis evaluation after cardiac surgery.

MATERIALS AND METHODS

We designed the study to be a retrospective, single-center, cohort study performed at Lucile Packard Children's Hospital (LPCH) at Stanford University Medical Center. All patients admitted to the pediatric CVICU between September 1, 2009 and December 31, 2012 were evaluated for inclusion. Patients who were admitted for reasons other than postoperative care after corrective or palliative congenital heart surgery were excluded. Patients without a central venous or arterial catheter were also excluded. Within the remaining population, all patients who had a blood culture (sepsis evaluation) were examined. At our institution, patients recovering from cardiac surgery in the CVICU do not prophylactically undergo evaluation for bloodstream infection. Thus, any order to obtain a blood culture is a direct result of a clinical concern for infection. Blood cultures are obtained utilizing a standard process with a minimum blood volume of 0.5–1 mL per aerobic and anaerobic culture mediums. We identified patients by the presence of a positive blood culture, and the diagnosis of CLABSI was made utilizing the National Healthcare Safety Network (NHSN) criteria[9] in effect during the defined study period. To understand the relationship of postoperative day with CLABSI, we excluded patients who experienced more than 1 CLABSI in a single hospital encounter from the analysis. Patients with a central line who had a blood

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culture drawn but ultimately did not have an infection were used as the comparator cohort. Thus, any patient who had an identified infection other than CLABSI (eg, VAP, urinary tract infection, SSI and/or secondary blood stream infection that did not meet NHSN criteria for CLABSI) was excluded from the analysis.

Demographic features (age, gender), peak temperature and surgical complexity [as defined by the Risk Adjusted Congenital Heart Surgery Score[10] (RACHS-1)] were recorded. The peak temperature, highest total white blood cell (WBC), polymorphonuclear (PMN) and band count, and quantitative CRP concentration obtained within 72 hours preceding the time that an investigation for infection (blood culture) commenced were recorded and analyzed as mean values. In addition, the greatest change in total WBC (ΔWBC) within 5 days preceding the infection investigation was calculated. The postoperative day the infection investigation originated was recorded. Clinical outcomes were compared between the case and control groups including in-hospital mortality rates, CVICU length of stay (LOS) and total hospital LOS. The study protocol was approved by the Institutional Review Board at Stanford University Medical Center.

All patients requiring intensive care after congenital heart surgery are admitted to the CVICU at LPCH. Patients requiring cardiopulmonary bypass (CPB) empirically receive methylprednisolone sodium succinate [30 mg/kg (max 1 g)] at the initiation of the CPB. Other intraoperative support strategies, including deep hypothermic circulatory arrest and modified ultrafiltration, are not customarily utilized by our pediatric cardiac surgeons. Perioperatively, patients recovering from cardiac surgery routinely receive 3 prophylactic doses of intravenous cephazolin (50 mg/kg (max 1 g)] (or vancomycin [15 mg/kg (max 500 mg)] in the setting of cephalosporin hypersensitivity). Central venous catheters included percutaneous catheters placed in the operating room or CVICU; typically these are intracardiac catheters placed under direct visualization via open sternum, internal jugular or femoral venous catheters and peripherally inserted central venous catheters.

Statistical Analysis

We used descriptive statistics to compare patients with and without CLABSI with variables expressed as mean with standard deviation (SD) or median [with interquartile ranges (IQR)] according to their parametric distribution. χ^2 analysis was used to assess the association between gender and CLABSI. The ranksum test was used to assess the association between CLABSI and age, postoperative day, temperature, total WBC, ANC, band count, CRP, CVICU LOS and hospital LOS. Fisher's exact test was used to assess the association of CLABSI and in-hospital mortality. Generalized linear model was used in the multivariate analysis to identify independent predictors of CLABSI. We constructed a receiver-operating characteristic (ROC) curve for variables significantly associated with CLABSI. Optimized sensitivity and specificity profiles for important features were constructed based on the ROC curves. Statistical analyses were performed using R stats package, version 2.15.2, ROCR packages, version 1.0-5.

RESULTS

Between September 1, 2009 and December 31, 2012, 1260 encounters consisted of patients admitted after congenital heart surgery. A total of 31 CLABSI occurred in 28 postoperative patients during the study period. Three patients had 2 CLABSI during their encounter and were therefore excluded leaving 25 single instances of CLABSI per encounter for inclusion in the analysis. Coagulase negative *Staphylococcus* (21.7%) and *Enterobacter* species (19.6%) represented the most common microorganisms identified, respectively. A total of 312 encounters underwent a sepsis evaluation that resulted in a negative blood culture. Among these patients, 85 investigations yielded an identified infection (SSI, urinary tract infection, endocarditis and pneumonia) leaving 227 patients, or 49% of all sepsis investigations, who had a negative sepsis evaluation (defined by a negative blood culture without an identified source). These 227 patients comprise the comparison cohort. Figure, Supplemental Digital Content 1, http://links.lww.com/INF/C72, displays the study design and inclusion/exclusion criteria.

Demographic and outcome characteristics for patients with and without CLABSI are shown in Table 1. Patients who had a CLABSI were younger (0.36 vs. 1.4 years, $P = 0.01$), underwent a more complex cardiac operation (median RACHS-1 score 3.8 vs. 3.0, $P = 0.04$), and were evaluated for infection later in their postoperative course (median postoperative day 25.5, $P < 0.01$). Both Total and CVICU LOS was longer in patients who developed CLABSI than in those who did not (median 61 vs. 13 days, $P < 0.001$ and 42 vs. 8 days, $P < 0.001$, respectively). There were no differences in mortality in children who developed CLABSI (14.3% vs. 6.4%, $P = 0.11$).

A comparison of commonly used biomarkers for infection between the patients with and without CLABSI is shown in Table 1. There were no significant differences in WBC, ΔWBC, PMN count, band count or CRP between the 2 groups. However, higher mean temperatures were recorded in patients with CLABSI (38.8°C ± 0.8 vs. 37.8°C ± 0.9, $P < 0.001$).

In the multivariate analysis, CLABSI was associated with fever [Adjusted odds ratio 4.78 (95% CI: 1.62, 5.76), $P < 0.04$] and CRP [Adjusted odds ratio 1.28 (95% CI: 1.09, 1.68), $P = 0.04$] after controlling for important differences in cohort (age, postoperative days). In selecting covariates for inclusion, we did not include RACHS-1 because of co-linearity with hospital LOS.[11,12] The diagnostic properties of patient temperature were further analyzed using a ROC curve (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/C73). The area under the curve is 0.72 [95% CI: (0.86,0.58)] for fever and 0.58 [95% CI: (0.74,0.42)] for CRP. A multilevel likelihood ratio table of varying temperature thresholds, along with sensitivity, specificity, likelihood ratio, positive predictive value and negative predictive value are shown in Table 2.

DISCUSSION

We found traditional acute phase biomarkers such as WBC count, band and PMN count do not have diagnostic utility in differentiating CLABSI from no CLABSI when there is a concern for sepsis in patients recovering from congenital heart surgery. In addition, we found fever and CRP to be weak markers to differentiate those with CLABSI in patients undergoing evaluation for suspected bloodstream infection.

After cardiac surgery, factors that confound the accurate differentiation of CLABSI include routine exposures to the proinflammatory and immune-modulating effects of cardiopulmonary bypass, mechanical ventilation, perioperative antibiotics and systemic glucocorticoids. While the epidemiology of CLABSI in the PICU and pediatric CVICU have been well characterized with the identification of clear risk factors,[6,7,13] these reports did not include the full array of common clinical biomarkers evaluated in our study, including fever and CRP. In a review of risk factors for CLABSI in a pediatric CVICU, Costello et al.[6] found that an ANC <5000 cell/μL was an independent risk factor, but they were unable to characterize other markers of the systemic inflammatory response syndrome. Similar to our findings, Wylie et al.[14] found that lowest and highest WBCs were no different between patients with CLABSI and matched patients without a CLABSI in a pediatric medical-surgical ICU. However, both

TABLE 1. Characteristics of Patients Undergoing Sepsis Evaluation With and Without CLABSI After Congenital Heart Surgery

Characteristic	CLABSI (N = 25)	Non-infected† (N = 227)	*P* Value
Age (yrs)—median (IQR)	0.36 (0.01, 1.6)	1.4 (0.2, 6.2)	0.01*
Gender (Female)—number (%)	15 (62.5)	98 (43.2)	0.11
Chromosome 22q11 deletion, number (%)	1 (4)	18 (8)	0.7
RACHS-1 score—median (IQR)	3.8 (3, 5)	3 (2, 4)	0.04*
Postoperative day‡—median (IQR)	25.5 (13.8, 34)	4.5 (2, 5)	< 0.01*
In-hospital mortality, number (%)	6 (14.3)	29 (6.4)	0.11
CVICU LOS (days)—median (IQR)	42 (21.2, 86.8)	8 (5, 15)	<0.01*
Total Hospital LOS, days—median (IQR)	61 (32.8, 120)	13 (7, 23)	<0.01*
Highest Temperature (°C)—mean (SD)	38.7 (0.9)	37.8 (0.9)	<0.01*
WBC (K/μL)—mean (SD)	17.5 (8.2)	17.2 (6.1)	0.94
ΔWBC§ (K/μL)—mean (SD)	9.0 (6.8)	7.9 (5.1)	0.45
Polymorphonuclear cells (%)—mean (SD)	57.4 (19.6)	58.9 (15.4)	0.9
Band count (%)—mean (SD)	19.3 (16.8)	17.1 (13.2)	0.7
CRP (mg/dL)—mean (SD)	6.8 (6.7)	6.8 (5.6)	0.91

*Statistically significant.

†Excluding patients with SSI, endocarditis, pneumonia and urinary tract infection.

‡Day after surgery that the infection investigation occurred.

§Measured as the greatest difference in WBC from the preceding 5 days before the investigation evaluation.

SD, standard deviation; RACHS-1, risk adjusted congenital heart surgery score-1; LOS, length of stay; IQR, interquartile range; °C, degrees Celsius; WBC, white blood cell; ΔWBC, change in white blood cell count; CRP, C-reactive protein.

studies compared patients with CLABSI to matched controls that were not suspected of having an infection. We found that, under the condition where the decision was already made to undergo a sepsis evaluation, all of the biomarkers did not perform well in discriminating patients with a CLABSI from patients who were "ruled out" from an infection—a dilemma intensivists regularly face to determine appropriate usage of antimicrobials and continued need for hospitalization.

Although the utility of acute phase proteins such as CRP and neutrophil counts are well described in outpatient and emergency room settings,[15,16] the data describing their ability to predict infections in the inpatient setting are limited. Earlier pediatric studies have suggested that CRP may be superior to WBC in detecting occult or overt infections.[17–19] However, we found that quantitative serum CRP had little clinical value in differentiating patients with CLABSI after congenital heart surgery. We hypothesize that the induction of inflammatory biomarkers such as CRP by exposure to cardiopulmonary bypass reduces its value as a useful prediction tool for infection in this patient population. Multiple studies have demonstrated altered levels of CRP, in addition to other proinflammatory and anti-inflammatory cytokines, in children undergoing cardiopulmonary bypass.[20–23] Most reports demonstrate peak elevations in plasma CRP concentrations 24–48 hours after cardiopulmonary bypass.[20–22] Interestingly, we found that the average serum concentration of CRP in patients with CLABSI compared with those without were values that exceed what has been reported as more typical elevations found after cardiopulmonary bypass[21] suggesting that CRP is elevated due to other postoperative factors. We speculate that the postoperative course after cardiac surgery exposes pediatric patients to ongoing proinflammatory triggers separate from that of bypass itself (eg, prolonged mechanical ventilation, atelectasis, venous thrombosis and red blood cell transfusions) and that such events are commonly misinterpreted as clinical infection.

In addition, our study demonstrates that fever is only marginally better for distinguishing patients with CLABSI from those without an infection. Although a peak temperature of 38.5°C concurrently exploits both sensitivity and sensitivity profiles, this specific value may not necessarily be the most clinically relevant. Several delineations of fever cutoffs were analyzed and provided in both ROC and multilevel likelihood ratios, allowing us to interpret fever in varying clinical situations, depending on whether it is more important to be empiric or conservative in management. Different cutoff points for fever may aid the intensivist in deciding whether the risk to benefit calculation favors empiric utilization of antibiotics or observation alone. However, given the relative insensitive performance of fever, the utility of this biomarker as a stand-alone test is not likely to be clinically meaningful. A more standardized approach of evaluating for potential sepsis in the patient recovering from cardiac surgery may support efforts to reduce unnecessary exposure to antimicrobial agents and extended ICU days.

One notable finding in our results was the important differences in demographic characteristics between patients with CLABSI and those without. Not surprisingly, infected patients were younger, underwent more complicated cardiac surgery and

TABLE 2. Multilevel Likelihood Ratios for Fever and CRP

Variable	Cut Off	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio (95% CI)	PPV (95% CI)	NPV (95% CI)
Fever (°C)	38	0.79 (0.49, 0.95)	0.5 (0.43, 0.58)	1.59 (1.17, 2.16)	0.1 (0.05, 0.17)	0.97 (0.92, 0.99)
	38.5	0.79 (0.49, 0.95)	0.69 (0.62, 0.75)	2.5 (1.78, 3.52)	0.15 (0.08, 0.25)	0.98 (0.94, 1)
	39	0.57 (0.29, 0.82)	0.89 (0.84, 0.93)	5.3 (2.9, 9.67)	0.27 (0.12, 0.46)	0.97 (0.93, 0.99)
	39.5	0.29 (0.08, 0.58)	0.96 (0.92, 0.98)	6.48 (2.28, 18.43)	0.31 (0.09, 0.61)	0.95 (0.91, 0.98)
CRP (mg/dL)	1	0.84 (0.64, 0.95)	0.20 (0.07, 0.41)	1.05 (0.81, 1.36)	0.51 (0.35, 0.71)	0.56 (0.21, 0.86)
	5	0.44 (0.24, 0.65)	0.64 (0.43, 0.82)	1.22 (0.62, 2.42)	0.55 (0.32, 0.77)	0.53 (0.34, 0.72)
	10	0.20 (0.07, 0.41)	0.88 (0.69, 0.97)	1.67 (0.45, 6.24)	0.62 (0.24, 0.91)	0.52 (0.36, 0.68)
	15	0.08 (0.01, 0.26)	0.96 (0.80, 1.00)	2.00 (0.19, 20.67)	0.67 (0.09, 0.99)	0.51 (0.36, 0.66)

°C, degrees Celsius; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

experienced their infection later after their operation. These observations may guide clinicians to better interpret clinical biomarkers that, alone, are insufficient for prediction. For example, from our analysis, a fever of >39°C in patients who are younger, farther out from their operation and after more complex congenital heart surgery is more likely related to CLABSI than a false positive outcome. Similarly, a fever <38.5°C in a patient who recently underwent cardiopulmonary bypass after a low complexity operation is more likely to be unrelated to CLABSI. Better understanding of these patient and surgical characteristics associated with infection may define future opportunities for clinicians and investigators to define more effective algorithms to improve the value of commonly used clinical biomarkers as predictors of CLABSI.

There are a number of important limitations to our study that deserve discussion. First, this is a retrospective study design from a single institution and may not be generalizable to other hospitals. Institutions that adopt a more standardized approach to evaluating and managing infection could find improved clinical value of serum and clinical biomarkers we analyzed. However, to our knowledge there are no published reports that demonstrate a standardized protocol to sepsis evaluation in the pediatric intensive care units that reliably identifies patients who are infected with CLABSI. Second, the observational design raises concern for a potential referral bias as the biomarkers under study may have influenced providers' decision to obtain a blood culture, which may confound the discriminative power of the studied biomarkers. However, this report does not attempt to study the discriminatory ability of these biomarkers to exclude patients from undergoing an investigation for infection. Instead, we found that once the decision was made to undergo an investigation for CLABSI, most of the biomarkers performed poorly, whereas fever and CRP performed only fairly in discriminating patients with a CLABSI from patients where an infection was ultimately excluded. Finally, we excluded patients with other sources of infection such as pneumonia and SSI where CRP and other biomarkers may be more diagnostically valued. We excluded these patients because other diagnostic adjuncts such as physical examination and radiography are useful in localizing the infection, whereas CLABSI often present without focal findings.

In conclusion, serum biomarkers that have been used traditionally to identify infections were not reliable in distinguishing patients with CLABSI during a sepsis evaluation after congenital heart surgery. Further research should focus on identifying patterns of biomarkers or clinical practice parameters that can distinguish patients who are infected. Improvements in detection methodologies could lead to more tailored antibiotic therapy, improved antibiotic stewardship and reduced antibiotic resistance.

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