Culture Negative Sepsis after Pediatric Cardiac Surgery: Incidence and Outcomes

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Abstract

**Background**: A significant proportion of children after cardiac surgery with clinical features of bloodstream sepsis do not have a positive blood culture and are managed as presumed ‘culture negative sepsis (CNS)’. There is little information on outcomes of CNS early after pediatric cardiac surgery. We sought to describe the incidence, outcomes and antibiotic utilization pattern of culture negative sepsis in children undergoing cardiac surgery.

**Methods**: 437 consecutive children who underwent cardiac surgery were studied. CNS was empirically defined as those in whom antibiotics were upgraded based on clinical and/or laboratory suspicion of bloodstream sepsis with eventual negative blood culture. Outcomes were compared between three groups: normal controls, CNS and Culture Positive Sepsis (CPS).

**Results**: Incidence of CNS was 16% (71/437). The mortality was highest in CPS group (10.7%, 3/29); intermediate for CNS (2.9%, 2/71) and least for the normal group (1.2%, 4/337). Similarly, duration of ventilation and intensive care unit (ICU) length of stay (in hours) was highest for CPS (116 [45-271]; 288 [156-444]), intermediate for CNS (63 [23-112]; 192 [120-288]) and least for the normal group (18 [6-28]; 72 [48-120]). Third-tier antibiotics were initiated for 27 (40%) with CNS and 23 (92%) with CPS. Although the mean antibiotic duration for CNS (6.3±3.0 days) was less than CPS (9.09±5.12); p=0.022, 27.3% of CNS received antibiotics for more than one week.

**Conclusion**: The high incidence of CNS points towards the need for accurate biomarkers of bacterial sepsis after cardiac surgery. The relatively better outcomes of CNS merits consideration to rapidly de-escalate antibiotics for presumed sepsis after cardiac surgery.

Introduction

Advances in diagnostic precision, cardiac surgical expertise and intensive care practices have contributed to prodigious advancement in outcomes after pediatric cardiac surgery globally. These advances have also recently impacted pediatric cardiac surgery outcomes in Low Middle Income Countries (LMICs) [1, 3]. However, bacterial sepsis is identified as the prime impediment for further progress in LMICs centers with reported incidence of 7–21% [4–8]. Perioperative sepsis influences immediate surgical outcomes with an increased morbidity, mortality, prolonged ventilation and ICU stay [2, 7, 8]. While prompt diagnosis and treatment is the key to improving survival, particularly in neonates and young infants, the systemic inflammatory response syndrome (SIRS) after cardiopulmonary bypass (CPB) can cloud the clinical and laboratory diagnosis of sepsis and there is often considerable difficulty in diagnosing sepsis early after cardiac surgery [9].

Because of the complexity of the clinical situation and the overall vulnerability of these patients, the threshold for antibiotic initiation or escalation is low in most units especially for neonates. Once started, the antibiotic regimen is often continued despite a negative culture report [7]. A relatively high proportion of those who receive antibiotics for presumed sepsis in neonatal intensive care units in LMICS have
negative blood cultures and this entity is labelled as ‘Culture Negative Sepsis (CNS)’ [10]. The outcomes of the neonates with CNS have been identified as better than those with positive blood cultures in previous studies from general neonatal ICU settings [10].

While, it is clear that broad spectrum antibiotics are administered frequently because of presumed sepsis, the clinical outcomes of CNS in pediatric cardiac units have not been systematically evaluated. Given the rapid emergence of multi-drug resistant organisms from widespread use of broad-spectrum antibiotics [11], there is a need to maximize opportunities to reduce the overall usage of high-end antibiotics in the pediatric cardiac ICU. This study seeks to systematically examine the incidence and clinical outcomes and antibiotic usage pattern in children identified as CNS in a busy pediatric cardiac surgical unit in a tertiary referral hospital in Southern India.

Methods

Study Design

Retrospective review of institutional data base of a single center.

Study Setting

The study center is located in Southern India and receives patients from a population of ~ 30 million in the state of Kerala and neighbouring regions. A detailed description of the study setting and the manner in which care is organized in the unit has been published previously [2].

Data Source: The study centre is a member of the International Quality Improvement Collaborative for Congenital Heart Disease (IQIC; https://iqic.chboston.org/) since 2010 [1]. A database that includes key pre-operative, operative and postoperative variables is collected as a part of this initiative. Additionally, data was abstracted from the Medical Records Information was collected regarding demographics, diagnosis, laboratory results, culture results and antibiotic tier, dosage and duration. Those with incomplete medical records were not included in study. Permissions for collecting and publishing the data was obtained from the hospital institutional ethics committee.

Definitions

We defined CPS when a pathogenic organism grew in the blood culture. Respiratory fluid, urine and sternal wound swab positivity were not included in this group. Patients who required escalation of antibiotics beyond what was used for perioperative prophylaxis for suspected blood borne sepsis based on clinical and laboratory criteria (see below) but with negative culture reports after 5 days were considered as CNS. A patient growing same organism more than once in sequential blood cultures during the ICU stay was considered as single episode of CPS. Those patients where the perioperative antibiotic was not escalated were classified as ‘normal controls.’
Antibiotics are classified into three tiers; 1st tier is cefuroxime, used as primary surgical prophylaxis for 48 hours perioperatively. We consider aminoglycosides, fluoroquinolones, macrolides, penicillins, cefoperazone-sulbactam, piperacillin tazobactam, metronidazole, trimethoprim- sulfamethoxazole as 2nd tier and meropenem, imipenem-cilastatin, tetracycline, aztreonam, minocycline, vancomycin and colistin as 3rd tier antibiotics.

**Blood Culture Technique and Validation**

A single blood sample was obtained by venipuncture site after careful disinfection of the skin and not from a pre-existing intravascular catheter whenever clinical sepsis was suspected prior to empirical upgrading of antibiotics on all instances. 1 to 3 ml of blood was inoculated each time into BACTEC PEDS PLUS Culture vial and stored at 2-to-25-degree Celsius. The site of collection, volume of blood collected, prior antibiotic administration with duration and dosage if any was documented in the blood culture investigation form and was transferred at the earliest to microbiology team. The BACTEC automated culture has superior bacterial isolation rate with lesser detection time in comparison to conventional methods [12]. The microbiology team provisionally declares it as negative culture if no growth identified in the initial 48 hours, subsequent delayed positivity was also reported promptly.

**Patients**: All children of the age group 1 day to 18 years who underwent corrective or palliative cardiac surgical procedures from January 2020 through December 2020 were included. This study was limited to those patients in whom antibiotics were initiated specifically for presumed or proven blood stream sepsis. The common reasons to upgrade antibiotics included one or more of the following: fever (rectal temperature ≥ 38°C [100.4°F]) beyond 48 hours after surgery, unexplained hemodynamic instability in the form of hypotension, reduced tissue perfusion in the absence of any residual cardiac lesions or ventricular dysfunction, persistent lactic acidosis, leukopenia (< 4000/mL), marked leukocytosis (> 25000/mL), thrombocytopenia (platelet count < 50,000/ mL) and, persistent hypoglycemia. Subjects with antibiotic initiation for pneumonia, urinary infection or surgical site infection were excluded.

**Outcome Variables**

The outcome variable that were tested included, in-hospital mortality, duration of mechanical ventilation, duration of ICU stay and total duration of hospital stay.

**Statistical Analysis**

Categorical variables were presented as frequency and percentage and normally distributed continuous variables were presented as mean ± SD. In situation where the continuous variables were skewed we presented the median and IQR. Pearson Chi-Square test or Fisher’s exact test was used to compare categorical variables. Independent sample t-test was used to compare the duration of antibiotics between culture negative and positive groups. Kruskal-Wallis test followed by Mann Whitney test for subgroup was used to compare the demographic variables and continuous outcome variables. Multiple binary logistic regression (Enter) method was used to estimate the odds ratio (OR) with 95% CI of risk factors for
postoperative mortality. Multiple ordinary least square (OLS) linear regression model was used evaluate the relation between culture negative, culture positive, age and weight with duration of postoperative mechanical ventilation, adjusting for confounding variables. Since the postoperative stay variables were highly skewed, they were log-transformed to meet the normality assumptions required by the OLS linear regression method. The resulting parameter estimates were then back transformed to their original scale to facilitate the interpretation of the results. The back-transformed parameters can be interpreted as “median ratio”. Statistical analyses were conducted using SPSS Version 20.0 for Windows (IBM Corporation ARMONK, NY, USA).

Results

Out of 437 children who were operated during the study period, 14 were excluded due to incomplete medical records. There were 29 (7%) patients with a positive blood culture report and 71 (16%) patients with clinical features of sepsis along with a negative culture report were classified as having CNS. Patients with CPS were significantly younger and accordingly weighed less (Table 1). The proportion of neonates and infants was also higher in CPS intermediate in culture negative and least in the normal control group (Table 1). Associated medical illness and syndromes and surgical risk category (RACHS-1) were equally distributed in the three groups.

The overall surgical mortality was 2.05% and highest in those with positive cultures (3/29; 10.7%); intermediate for those with CNS (2.9%, 2/71) and least for the normal control population (1.2%, 4/337). (Table 1) Multivariable regression analysis identified only CPS as a significant independent predictor of mortality with an odds ratio of 8.6 (1.7–44.9; p = 0.010) adjusted by culture negative group, age and weight at surgery.

The remaining outcome variables, duration of mechanical ventilation, length of ICU and hospital stay was the least in the normal controls, intermediate in the those with CNS and highest in those with CPS. (Table 1). Multivariable linear regression analysis identified CPS (Median Ratio: 3.1 (2.3–4.1), p < 0.001), CNS (Median Ratio 5.6 (3.7–8.4), p < 0.001) and weight (kg) (Median Ratio 0.98 (0.96–0.99), p = 0.009) as the only independent associations of duration of mechanical ventilation.

In those with CPS escalation to 3rd line antibiotics was done in 92% of cases. In CNS, 59.7% were managed with 2nd tier antibiotics, for the rest of 40.3% cases further escalation to 3rd line antibiotics was done even in the absence of a positive culture.

The culture negative group as a whole received antibiotics for shorter duration in comparison to the culture positive group (6.3 ± 3 days vs, 9.1 ± 5.1 days; p = 0.022). However more than a quarter of the patients in the culture negative category received antibiotics for over a week and in two patients the antibiotics were continued beyond 14 days (Fig. 1)

Discussion
This study demonstrates a high proportion of children with presumed sepsis in the early postoperative period after congenital heart surgery that was not confirmed through a positive blood culture. It is possible or even likely that many of these patients were never infected in the first place and antibiotics were administered empirically. A significant proportion of these patients (40.3%) received third tier antibiotics and nearly a quarter of them received antibiotics for more than a week indicating a reluctance to de-escalate.

We believe that our findings are likely to be observed in other pediatric cardiac units as well [6, 7, 13]. Many clinical and laboratory features of bacterial sepsis overlap with the early postoperative systemic inflammatory response and cardiac failure. The threshold to upgrade to a higher grade of antibiotic is understandably low [7].

The outcomes of the groups with CNS are intermediate between those with CPS and the normal. In hospital mortality of the culture positive group was significantly higher than the rest (10.9%) but that of the intermediate group (2.9%) was not significantly different from the rest (1.2%). The morbidity parameters (mechanical ventilation, ICU stay) showed a similar gradient across the three categories and CPS had the longest duration of ICU stay. Given the large number of potential confounders in this retrospective cohort, these differences may not attributable to infection alone notwithstanding the demonstrable independent association of CPS with mortality as well as independent association of culture positive and negative sepsis on morbidity. Those with CPS were youngest and smallest and a significant proportion of these patients were neonates and patients with CNS were also younger than the normal counterparts. However, age and weight were not independently associated with mortality or duration of mechanical ventilation.

Studies from neonatal ICUs in LMICs have also demonstrated a significantly lower mortality among CNS as compared to CPS.10 Antibiotic stewardship programs should target a reduction in antibiotic usage in this category of CNS. The absence of reliable biomarkers of bacterial sepsis in the early postoperative period is an important barrier [9]. Standard inflammatory markers such as C Reactive Protein (CRP) and procalcitonin are often of little value after cardiac surgery [14]. While leukocytosis and thrombocytopenia consistently accompany sepsis there are no reliable cut-off values that specifically point toward bacterial sepsis [9]. However, the demonstration of relatively better outcomes in this category can provide a basis for early antibiotic de-escalation in a number of patients after careful assessment of the overall clinical situation.

Limitations

Our study is limited by its retrospective nature. A single blood culture was obtained and it is possible that multiple samples may have identified a few more culture positive cases. The exact basis for decision to escalate the antibiotic was not systematically recorded. The potential role of confounding factors could not be precisely identified. Ventilator associated pneumonia, urinary tract infections and surgical site infections were excluded from the study. However, this analysis provides the basis for a prospective multi-
center study that seeks to capture the exact reasons for escalation to higher antibiotics as well as identification of specific combination of clinical and laboratory variables that best correlate with positive blood cultures.

**Conclusions**

This study sought to systematically explore the mysterious entity of ‘culture negative sepsis’ following pediatric cardiac surgery. The relatively frequent perceived need to upgrade antibiotics without eventual positive blood cultures may indicate antibiotic overuse and is a target for antimicrobial stewardship. Additionally, the continued administration of empirical antibiotics for more than a week in over a quarter of patients points towards a reluctance to de-escalate. The significantly better outcomes in culture negative sepsis may provide a stronger basis to consciously reduce antibiotic usage in the pediatric cardiac intensive care unit. Prospective multi-center studies can enable identification of more precise indicators of sepsis in this setting.

**Declarations**

The authors declares that there is no conflict of interest

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**References**


Tables
Table 1
Intergroup comparisons on demographics and outcomes in the three groups of patients

<table>
<thead>
<tr>
<th>Demographic and Outcome variables</th>
<th>Culture positive sepsis (a) n = 29 (7%)</th>
<th>Culture negative sepsis (b) n = 71 (16%)</th>
<th>Controls (c) n = 337 (77.1%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (IQR)*</td>
<td>0.07 [0.04, 0.29]</td>
<td>0.33 [0.05, 1]</td>
<td>0.5 [0.17, 1]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight (Kg), Median (IQR)*</td>
<td>3.18 [2.55, 4.46]</td>
<td>4.35 [2.95, 6.79]</td>
<td>5.5 [3.6, 9.2]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Proportion of neonates (&lt; 30 days)</td>
<td>16 (55.2)</td>
<td>20 (28.2)</td>
<td>48 (14.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Proportion of infants (&lt; 1 year)</td>
<td>28 (96.6)</td>
<td>53 (74.6)</td>
<td>223 (66.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Other medical illness/ Syndromes</td>
<td>3 (10.3)</td>
<td>7 (9.9)</td>
<td>29 (8.6)</td>
<td>0.909</td>
</tr>
<tr>
<td>In- Hospital Mortality</td>
<td>3 (10.7)</td>
<td>2 (2.9)</td>
<td>4 (1.2)</td>
<td>0.030</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (hours), Median (IQR)*</td>
<td>116 (45–271)</td>
<td>63 (23–112)</td>
<td>18 (6–28)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU length of stay (hours), Median (IQR)*</td>
<td>288 (156–444)</td>
<td>192 (120–288)</td>
<td>72 (48–120)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Intergroup comparisons revealed significant differences between groups

Figures
Figure 1

Antibiotic duration comparison between culture negative group (CNS) and culture positive group (CPS)