# Risk Factors of Sepsis and Prevalance of Multi-Drug Resistant Organisms in Pediatric Cardiac Surgery in Tertiary Care Teaching Rural Hospital In India: Retrospective, Observational Study

Short running title: Risk Factors of Sepsis and Prevelance of Multi-Drug Resistant Organisms

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The data that support the findings of this study are openly available in[Authorea]at

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## Abstract

### Background and Aims

Cardiac surgery and cardiopulmonary bypass lead to an immunoparalyzed state in children which makes them susceptible to sepsis and other hospital acquired infections. Identification of risk factors of sepsis would lead to appropriate management

### Objective

The present study was conducted to assess the prevalence of sepsis and risk factors associated with sepsis in pediatric cardiac surgical patients and the subsequent prevalence of multidrug resistant organisms.

### Methods

A retrospective, single-center observational study was conducted on 100 pediatric patients admitted to the PICU after cardiac surgery between January,2017 and February, 2018. All the data of the patients were collected from the medical record department of the hospital. Patient case report form consisted of demography, surgery details, Pre-operative & post-operative haematological reports and clinical details. After collecting the data, chi-square test and logistic regression analysis were used to find the risk factors associated with sepsis.

## Results

The prevalence of sepsis in our population was 27 % and mortality rate due to sepsis was 1 %. The only statistically significant risk factor for sepsis we found in this study was prolonged ICU (intensive care unit) stay for more than 5 days. Total 8 patients had blood culture positive for bacterial infection. The alarming finding was that all 8 were multi-drug resistant organisms, requiring the last line of antibacterials.

## Conclusion

Our study implies that special clinical care is required when ICU stay is prolonged to mitigate the risk of sepsis. These new and upcoming infections not only lead to high mortality and morbidity rates but also contribute to increased cost of care due to the use of newer broad-spectrum antibiotics and longer hospital stay. The high prevalence of multi-drug resistant organisms is unacceptable in the current scenario and hospital infection and prevention control play a critical role in minimizing such infections.

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**Key Words:** sepsis, pediatric cardiac surgery

## Introduction

The survival rate for neonates, infants, and children with congenital heart disease (CHD) has increased significantly with improved surgical techniques, cardiopulmonary bypass (CPB) and post-operative care. However, CPB elicits a complex, systemic inflammatory response that is characterized by activation of the complement cascade, release of endotoxin, activation of leukocytes and release of pro-inflammatory cytokines. This complex humoral and cellular-mediated immune response results in a transient and relative state of immune suppression, often referred to as "immunoparalysis". [1,2] This state of immunoparalysis may result in an increased risk of sepsis in children undergoing cardiac surgery. [3,4] In addition, chronic hypoxia, low cardiac output syndrome and other co-morbid conditions associated with CHD, [3-5] as well as invasive devices may also increase the risk of sepsis in this population.

Despite wide spread adoption of healthcare guidelines & sepsis prevention bundles,the frequency of healthcare acquired infection remains high, at 6 % to 30.8 % in pediatric cardiac surgical patients.Sepsis is a significant and independent risk factor for increased duration of mechanical ventilation, cardiac intensive care unit length of stay, healthcare costs, and mortality in children with CHD.

Very few case series of sepsis prevalance in pediatric cardiac surgical patients, in a rural tertiary care hospital from India has been published. None of them has highlighted the lurking threat of increasing prevalence of multi-drug resistant organisms.

## Materials & Methods

### Study Design and Setting:

This was a retrospective, single-center observational study conducted at Cardiac Pediatric Intensive Care Unit(CPICU) of Bhanubhai and Madhuben Patel Cardiac Centre, Shree Krishna Hospital, Karamsad, India after getting approval of the research project from the Institutional Ethics Committee (IEC-2) of the Bhanubhai and Madhuben Patel Centre for Medical Care and Education, Anand, Gujarat, India, vide approval No. (IEC/BU/2021/Ex.03/44/2023 dated 24.01.2023

### Inclusion Criteria -

- Consecutive Pediatric Patients less than or equal to 14 years old admitted to the CPICU after pediatric cardiac surgery between January, 2017 and February, 2018.

Exclusion Criteria -

- Older patient & patient undergoing any major non-cardiac surgical intervention was excluded from surgery.
- Also patients discharged against medical advice, having pre-admission infection or patient transferred from other hospital department or other center with infection were excluded from the study.

**Data collection**

The study was initiated after receiving approval from the Institutional Ethics Committee of the hospital. It was a retrospective observational study so in need of Informed Consent form was waived off by Institutional Ethics Committee.

An observational retrospective study was conducted on one hundred pediatric patients(less than 14 years) who had undergone cardiac surgery between January, 2017 & February, 2018. All the data of the patients were received from the medical record department of the hospital. Case report form was prepared in English.

To look for the associated risk factors for sepsis patients clinical and laboratory analyses were recorded in case report form. Such data are patient's demographic data including sex, age, weight, height, cardiac and non-cardiac abnormalities, major medical history. Preoperative sepsis screen & risk factors of immune-supression like severe mal-nutrition, chromosomal disorders, HIV infection and use of pre-operative antibiotics & hospital stay was recorded.

Surgery data recorded were - surgery type, Risk adjustment for congenital heart surgery (RACHS) score for evaluating surgical complexity, CPB duration, hypothermia or total circulatory arrest, delayed sternal closure, intubation & ventilation duration, need of re-intubation, central catheter lines & its duration, length of ICU (intensive care unit) stay, blood transfusion, inotropic support,renal support, tracheostomy.

Haematology data included were preoperative & postoperative haemoglobin level, leukocytes count, c-reactive protein, procalcitonin & culture report were recorded from the medical records of the

patients.In case of positive culture report, antibiotics sensitivity pattern & their minimum inhibitory concentration were recorded. Mortality with its cause were also noted.

Definition of sepsis, septic shock was confirmed as per definition mentioned in Sepsis-3. Suspected sepsis was labelled when a patient was managed as sepsis, based on clinical & laboratory parameters.

## Statistical Analysis

Variables were evaluated using the chi-square test. Logistic regression analysis were used to find the risk factors associated with sepsis.

## Results and Discussion

One hundred and three pediatric patients with age less than 14 years, had undergone cardiac surgery during January, 2017 to February, 2018. Three patients who was discharged against medical advice or transferred to other centers were excluded from study

One hundred (100) pediatric cardiac surgical patients, aged less than 14 years old, were included in study and were observed retrospectively for the incidence of sepsis after cardiac surgery.

Out of 100 pediatric patients 55 patients were male and 45 patients were female.

## Table 1 - Demographic and Surgical Characteristics

| Characteristics | Mean(SD) | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| Age (year) | 2.39 | 3.29 | 0.9 | 1 (day) | 14 (year) |
| Weight (kgs.) | 8.14 | 5.72 | 5.93 | 1 | 28 |
| Height (cms.) | 78.02 | 25.34 | 70 | 43 | 144 |
| RACHS | 1.85 | 0.74 | 2 | 1 | 4 |
| Surgery duration (minute) | 89.43 | 39.69 | 83 | 28 | 230 |
| Duration of intubation(hours) | 40.62 | 51.07 | 24 | 1 | 336 |
| Pre-operative length of stay (days) | 1.93 | 3.10 | 1 | 0 | 28 |
| Total no. of hospital stay (days) | 9.58 | 5.61 | 8 | 3 | 35 |
| Length of ICU stay (days) | 3.91 | 4.46 | 2 | 0 | 26 |

Out of 100 patients weight of 58 patients was more than 5 kgs and 36 patients were in-between 2.5 to 5 kgs while only 6 patients had weight less than 2.5 kgs.

8 patients were in the age group of < 30 days (neonates), 44 patients were in the age group of 30 days-1 year (infants), 30 patients were in the age group of 1 year-5 years while 18 patients were in the age group of 5 years-14 years.

In the study group 8 patients had blood culture proven sepsis. Another 8 patients had suspected sepsis which developed after surgery, while

11 had suspected sepsis developed pre-operatively during hospital stay.

## Table - 2 Infection and Mortality

| Infection | N=100 | % |
|---|---|---|
| Proven Sepsis | 8 | 8 |
| Suspected Sepsis | 19 | 19 |
| No Infection | 73 | 73 |
| Mortality | - | 2 |

## Table – 3 Mortality in the Study Group

| Mortality | Sepsis | RACHS | Cause of death |
|---|---|---|---|
| Patient 1 | Yes | 4 | Acute respiratory distress syndrome with Sepsis |
| Patient 2 | No | 3 | Cardiogenic shock |

In our study group there was no case of mediastinitis or endocarditis. Although 6 patients had sternal wound gaping. Swab culture from these patients was sterile. They improved on oral antibiotics.

Among type of surgery - VSD (ventricular septal defect) closure surgery had higher prevalance.While total 14 patients had VSD closure, 4 (28%) of them had sepsis.

## Table - 4 Clinical Characteristics of the Patient Population and Risk Factors for Sepsis in Bivariate Analysis (Chi-Square Statistics)

| Variable | Level | Total (N= 100) | Overall % | Number with sepsis (n=27) | % with sepsis | Number with no sepsis (n=73) | % with no sepsis | p Value |
|---|---|---|---|---|---|---|---|---|
| **Pre-operative assessment** | | | | | | | | |
| RACHS category | 1 | 34 | 34 | 5 | 18.52 | 29 | 39.73 | 0.236 |
| | 2 | 49 | 49 | 16 | 59.26 | 33 | 45.21 | |
| | 3 | 15 | 15 | 5 | 18.52 | 10 | 13.70 | |
| | 4 | 2 | 2 | 1 | 3.70 | 1 | 1.37 | |
| | 5 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | 6 | 0 | 0 | 0 | 0 | 0 | 0 | |
| **Demographics** | | | | | | | | |
| Age | <30 days | 8 | 8 | 5 | 18.52 | 3 | 4.11 | ***0.005** |
| | 30 days-1 year | 44 | 44 | 16 | 59.26 | 28 | 38.26 | |
| | 1 year-5 year | 30 | 30 | 5 | 18.52 | 25 | 34.25 | |
| | 5 year-14 year | 18 | 18 | 1 | 3.70 | 17 | 23.29 | |
| Weight | <2.5 kg | 6 | 6 | 4 | 14.81 | 2 | 2.74 | ***0.004** |
| | 2.5-5 kg | 36 | 36 | 14 | 51.85 | 22 | 30.14 | |
| | >5 kg | 58 | 58 | 9 | 33.33 | 49 | 67.12 | |
| Sex | Male | 55 | 55 | 15 | 55.56 | 40 | 54.79 | 0.946 |
| | Female | 45 | 45 | 12 | 44.44 | 33 | 45.21 | |
| **Risk factors** | | | | | | | | |
| Preoperative length of stay (days) | 0 | 9 | 9 | 5 | 18.52 | 4 | 5.48 | 0.156 |
| | 1 | 60 | 60 | 13 | 48.15 | 47 | 64.38 | |
| | 2 | 14 | 14 | 5 | 18.52 | 9 | 12.33 | |
| | >3 | 17 | 17 | 4 | 14.81 | 13 | 17.81 | |
| Surgery | <30 | 1 | 1 | 1 | 3.70 | 0 | 0 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| duration (minute) | 30-90 | 62 | 62 | 8 | 29.63 | 54 | 73.97 | ***0.000** |
| | 90-200 | 35 | 35 | 18 | 66.67 | 17 | 23.29 | |
| | >200 | 2 | 2 | 0 | 0 | 2 | 2.74 | |
| Length of ICU stay (days) | 1 | 34 | 34 | 1 | 3.70 | 33 | 45.83 | ***0.000** |
| | 2-4 | 37 | 37 | 9 | 33.33 | 28 | 38.89 | |
| | 5-9 | 19 | 19 | 10 | 37.04 | 9 | 12.50 | |
| | 10-30 | 9 | 9 | 7 | 25.93 | 2 | 2.78 | |
| Duration of intubation (hours) | 3 | 21 | 21 | 1 | 3.70 | 20 | 27.40 | ***0.001** |
| | 8 | 9 | 9 | 1 | 3.70 | 8 | 10.96 | |
| | 9-120 | 64 | 64 | 20 | 74.07 | 44 | 60.27 | |
| | >120 | 6 | 6 | 5 | 18.52 | 1 | 1.37 | |
| Duration of central venous catheterization (hours) | 3 | 21 | 21 | 1 | 3.70 | 20 | 27.40 | ***0.001** |
| | 8 | 9 | 9 | 1 | 3.70 | 8 | 10.96 | |
| | 9-120 | 64 | 64 | 20 | 74.07 | 44 | 60.27 | |
| | >120 | 6 | 6 | 5 | 18.52 | 1 | 1.37 | |
| Re-intubation | Yes | 10 | 10 | 4 | 14.21 | 6 | 8.22 | 0.329 |
| | No | 90 | 90 | 23 | 85.19 | 67 | 91.78 | |
| Inotropic Support | Yes | 63 | 63 | 21 | 77.78 | 42 | 58.33 | 0.073 |
| | No | 36 | 36 | 6 | 22.22 | 30 | 41.67 | |
| Delayed sternal closure | Yes | 7 | 7 | 6 | 22.22 | 1 | 1.37 | ***0.001** |
| | No | 93 | 93 | 21 | 77.78 | 72 | 98.63 | |
| Hypothermia | Yes | 47 | 47 | 17 | 62.96 | 30 | 41.10 | 0.052 |
| | NO | 53 | 53 | 10 | 37.04 | 43 | 58.90 | |

As we inserted risk factors data in chi-square statistics we got 7 significant p values which are < 0.05. Such as age (0.005), weight (0.004), surgery duration (0.000), length of ICU stay (0.000), duration of intubation (0.001), duration of central venous catheterization (0.001) and delayed sternal closure (0.001) respectively.

## Table – 5 Risk Factors for Sepsis in Multivariable Analysis (Logistic regression analysis)

| Variable | Level | Number with sepsis (n=27) | % with sepsis | Number with no sepsis (n=73) | % with no sepsis | OR | (95%CI) | P-value |
|---|---|---|---|---|---|---|---|---|
| Age | <30days-1 year | 16 | 59.26 | 28 | 38.26 | 1.18 | [0.14,9.70] | 0.87 |
| | 1 year- 5 year | 5 | 18.52 | 25 | 34.25 | 0.82 | [0.05,12.5] | 0.89 |
| | 5 year-14 year | 1 | 3.70 | 17 | 23.29 | 0.40 | [0.01,11.3] | 0.59 |
| Weight | 2.5–5 kg | 14 | 51.85 | 22 | 30.14 | 0.66 | [0.07,5.5] | 0.70 |
| | >5 kg | 9 | 33.33 | 49 | 67.12 | 0.68 | [0.06,7.3] | 0.75 |
| Length of ICU stay (days) | 2-4 | 9 | 33.33 | 28 | 38.89 | 9.03 | [0.82,98.8] | 0.07 |
| | 5-9 | 10 | 37.04 | 9 | 12.50 | 19.0 | [1.5,226.8] | ***0.02** |
| | 10-30 | 7 | 25.93 | 2 | 2.78 | 50.4 | [2.56,994.] | ***0.01** |
| Duration of intubation (hours) | 8 | 1 | 3.70 | 8 | 10.96 | 1.24 | [0.05,28.9] | 0.89 |
| | 9-120 | 20 | 74.07 | 44 | 60.27 | 4.45 | [0.46,42.9] | 0.19 |
| | >120 | 5 | 18.52 | 1 | 1.37 | 9.52 | [0.29,311.] | 0.20 |
| Delayed sterna closure | Yes | 17 | 62.96 | 30 | 41.10 | 0.36 | [0.003,43.] | 0.68 |
| | No | 10 | 37.04 | 43 | 58.90 | 0.3 | [0.001,1.0] | 0.054 |

Multivariate logistic regression analysis was performed to analyze the risk factors of sepsis. The analysis concluded that the risk factors were associated only with the length of ICU stay. Prolonged Duration of ICU (intensive care unit) stay more than 5 days (<0.05) which is moderately significant.

Total 8 patients had blood culture positive for bacterial infection – mostly were nosocomial gram negative bacteria. One was Enterococcus faecium. Alarming finding is that except one, all other are multi-drug

resistant organism requiring last line of anti-bacterials as shown in chart.

## Discussion

Infections in children are frequent (incidence, 13% to 31%) after cardiac surgery [3,6]. Many are surgical site infections (incidence, 2.3 % to 8 %) [7]. Some are more serious, such as septicemia (incidence,6.3 % to 15 %) [8,9,10], mediastinitis (incidence, 0.2 % to 3.3 %) [6-14], and endocarditis (incidence, 0.2 %) [11].

Pollock and associates [4] reported blood-stream infections (BSIs) in 21 (6.8 %) of 310 children after cardiac surgery.In our study, prevalence of sepsis was 27 % with 1 % mortality.There was no incidence of mediastinitis or endocarditis in the study group. 6% patients had surgical site infection.

Dicky Fakhri et al. [12] reported in their study that duration of cardiopulmonary bypass ≥ 90 minutes was associated with 5.538 increased risk of post-surgical sepsis in comparison to those ≤90 minutes. Our study was insufficiently powered to prove it, although trends suggested it.

Rosanova et al. [13] concluded that longer hospitalization and inotropic support were risk factors for infections in their study.

Takeshi Hatachi et al. [14] concluded that mechanical ventilation greater than or equal to

3 days, dopamine use, genetic abnormality, and delayed sternalclosure were associated with healthcare-associated infections after pediatric cardiac surgery.

Risk factor which was significant in our study was longer duration of ICU (intensive care unit) stay (more than 5 days). Multi-variate analysis of our study group did not find other independent risk factors that may be because of inadequate numbers to have statistical significance.

However, the alarming finding of our study is very high prevalence of multi-drug resistant nosocomial bacterial infection (7 out of 8 culture positive sepsis). They required last line of anti-bacterials. Inspite of this, mortality rate due to sepsis was only 1 %. However, this may worsens if we lose sensitivity to last line of anti-bacterials. This scenario is unacceptable in pediatric cardiac patients who may encounter precarious hemodynamics due to cardiac surgery.

Other studies have also highlighted prevalence of resistant organism in pediatric cardiac septic patients. This reflects deficiencies in anti-sepsis measures in many pediatric cardiac department.

## Conclusion

The prevalence of sepsis in the study population was 27 % which is comparable with other studies. With implementation of proper asepsis guideline the prevalence of sepsis can be reduced further to 5% as in recent study.

There is high incidence of multi drug resistance organisms in culture positive septic patients. If urgent steps are not taken to contain it, we may lose many patients because of sepsis with resistant bacteria. Misuse & overuse of antibiotics may further aggravate the problem

Prolonged ICU (intensive care unit) stay was statistically significant as a risk factor for sepsis, in current study. It implies that special clinical

care is required when ICU stay is prolonged to mitigate the risk of sepsis.

**Limitations of the Study**

As it is a retrospective study some data discrepancy cannot be ruled out. Although care has been taken to minimize it. Many other risk factors were not statistically significant as the study group was not sufficiently powered in this study population. As it is a single center study, its result cannot be generalized for entire pediatric cardiac surgery patients in the region or country.

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