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ORIGINAL ARTICLE

Stenotrophomonas maltophilia Infection Among Young Children in a Cardiac Intensive Care Unit: A Single Institution Experience

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Abstract *Stenotrophomonas maltophilia* can present as bacteremia, respiratory tract infection, urinary tract infection, soft tissue and wound infections, bone and joint infections, meningitis, and endocarditis especially in immunosuppressed patients and those with underlying medical conditions. The incidence and impact of *S. maltophilia* in young children with heart disease are poorly defined. A single center retrospective observational study was conducted in infants <180 days of age with positive *S. maltophilia* cultures over a period of 5 years. The overall incidence for *S. maltophilia* infection was 0.8 % ($n = 32$/3656). Among 32 identified infants, there were 47 episodes of *S. maltophilia* infection 66 % of infants had prior exposure to broad spectrum antibiotics. 97 % of positive isolates were susceptible to trimethoprim/sulfamethoxazole and 91 % to levofloxacin as well as ticarcillin/clavulanate. Ventilator-free days and absolute lymphocyte count prior to acquiring infection were significantly lower in non-survivors than in survivors. 100 % of survivors had clearance of positive cultures compared to 50 % in non-survivors ($p < 0.05$). The crude all-cause mortality rate was 37.5 %. All non-survivors had increased length of ICU stay and duration of mechanical ventilation and had delayed clearance of infection and required longer duration of treatment.

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Introduction

Stenotrophomonas maltophilia (S maltophilia) is a non-fermenting, gram-negative bacillus which in recent years, has emerged as an opportunistic pathogen in human host. It increasingly causes nosocomial human infections particularly among patients who are immunosuppressed and have an underlying debilitating medical condition [7, 10, 12, 13, 15–17]. It causes a variety of clinical syndromes like bacteremia, respiratory tract infection, urinary tract infection, ocular infections, skin, soft tissue and wound infections, bone and joint infections, meningitis, and endocarditis [6, 25, 29]. Although it was initially thought to be of lower virulence, several studies [7, 10, 14, 17] indicate that the mortality rates from *S. maltophilia* infection have been rising especially in patients with malignancy, organ transplant, and among those admitted in intensive care units (ICU).

Currently, among children, there are only a few reports describing *S. maltophilia* infection [6, 14, 16, 21, 32]. The majority of these studies have focused on *S. maltophilia* in cystic fibrosis patients [1, 8, 9, 19], in patients with hematological malignancies/bone marrow transplant [2, 23, 25, 28], and in the neonatal ICU population [6, 16, 21, 32]. However, there are no studies which describe the clinical characteristics of *S. maltophilia* infections among children with heart disease cared for in the cardiac ICU.

Therefore, our objective was to investigate the incidence, clinical characteristics, and outcome of *S. maltophilia infection* among children 0–6 months of age with underlying cardiac disease. We hypothesized that unique

risk factors are associated with poor outcome with *S. maltophilia* infection in this patient population.

Materials and Methods

Study Design and Setting

This single center, retrospective, observational study was conducted in the cardiovascular ICU (CVICU) at Arkansas Children's Hospital, a 330 bedded urban tertiary care children's hospital. The study was approved by the Institutional Review Board (IRB) and waiver was obtained for informed consent from the IRB.

Study Population

The study included all children between 0 and 6 months of age hospitalized in CVICU for at least 48 hours and had positive cultures for *S. maltophilia* at any biologic site between the period of January 1st, 2006 and December 31st, 2010. All study patients were identified by querying the institutional medical records and microbiology records. Subjects were excluded if they were admitted to non-ICU units or transferred from an outside facility with *S. maltophilia* infection.

Study Definitions

Infection was defined as recovery of *S. maltophilia* from blood, cerebral spinal fluid (CSF), urine, eye, wound, or bronchio-alveolar lavage (BAL). All hospital acquired-health-care associated infections were defined using the standard Centers for Disease Control/National Healthcare Safety definition criteria [15]. For the purposes of the study, (a) ventilator-associated pneumonia (VAP) was defined as per the CDC guidelines for VAP criteria, i.e., patients with new or progressive and persistent infiltrate on $\geq$2 Chest x-rays along with desaturations or increased oxygen requirement or increased ventilator settings and with temperature instability (fever or hypothermia) OR leukocytosis and left shift or leukopenia (<4,000/>15,000) OR bradycardia or tachycardia OR apnea, tachypnea or retractions were defined as having infection and patients who did not qualify this criteria were defined as colonized. We defined bloodstream infection as isolation of *Stenotrophomonas* from blood and urinary tract infection as >50,000 colony count of *Stenotrophomonas* from catheterized urine sample and wound infection as isolation of *Stenotrophomonas* without any mixed growth from wound along with clinical features of wound infection, (b) Prolonged ICU and hospital length of stay (LOS) was defined as the LOS above the 75th percentile cutoff for LOS for the entire study cohort, (c) A day for the study was defined with a cutoff of 12 midnight while defining outcomes, (d) Ventilator-free days were defined as twenty-eight days minus number of days the subjects were not on mechanical ventilator via tracheostomy or oral endotracheal tube, (e) Days of infection was defined as number of days from first positive culture for *S. maltophilia* to first day of negative culture, (f) Broad spectrum antibiotics duration was defined as days of usage of extended spectrum beta-lactams, carbapenems, or intravenous quinolones about 4 weeks prior to first positive *S. maltophilia* culture, (g) Negative culture during hospitalization was defined as negative culture present before death or discharge, (h) Treatment duration days were defined as days treated with appropriate antibiotics till the presence of first negative culture in subjects with one infection and till last negative culture during hospitalization in subjects with multiple infections, and (i) Lymphopenia was defined as absolute lymphocyte count (ALC) less than 1500 cells/microliter of blood.

Data Variables

Data abstracted include: demographic variables, ICU outcomes (mortality, ICU length of stay (LOS), hospital LOS), underlying medical/surgical condition(s), and laboratory parameters. Additional *S. maltophilia* infection- specific data collected were site, days to first positive culture, broad spectrum antibiotic use (type and duration) 30-days prior to infection, presence, type and number of invasive indwelling catheters (central line, surgical drains, urinary catheter), resistance pattern of infection, and other bacterial/viral infections.

Statistical Analysis

All the data were analyzed using R v2.15.0 (R Development Core Team, Vienna, Austria). Descriptive statistics were expressed as median (interquartile range) for continuous variables and frequency and percentage for categorical variables. Mann–Whitney *U* tests were carried out to compare the distributions of continuous variables between the survivors and non-survivors to hospital discharge, while the proportions of categorical data were compared between the two groups using χ^2 tests. A histogram was plotted to represent the distribution of the ALCs (Fig. 1). Kaplan–Meier curves were plotted for the time from day of hospital admission to *S. maltophilia* infection and time from start of mechanical ventilation to *S. maltophilia* infection among survivors and non-survivors, respectively (Figs. 2 and 3). Log-rank tests were performed to evaluate the difference in the survival curves between survivors and non-survivors. *p*-values less than 0.05 were considered to indicate statistical significance.

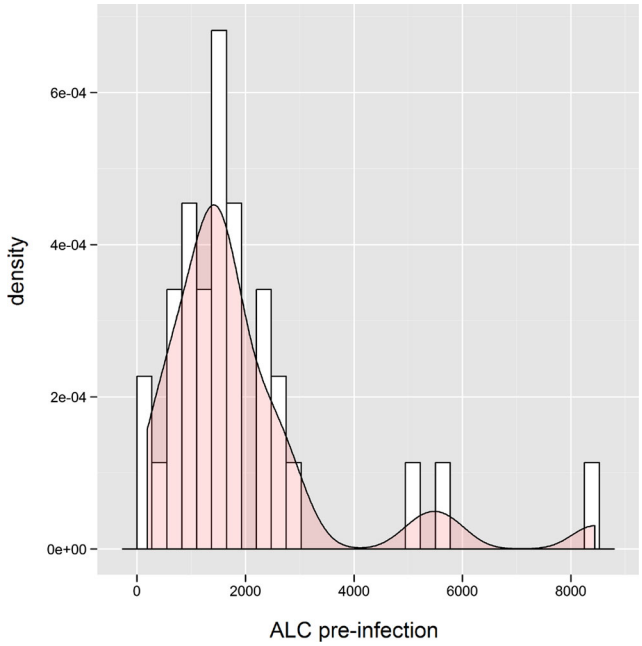

Fig. 1 Distributional plot of ALC prior to infection

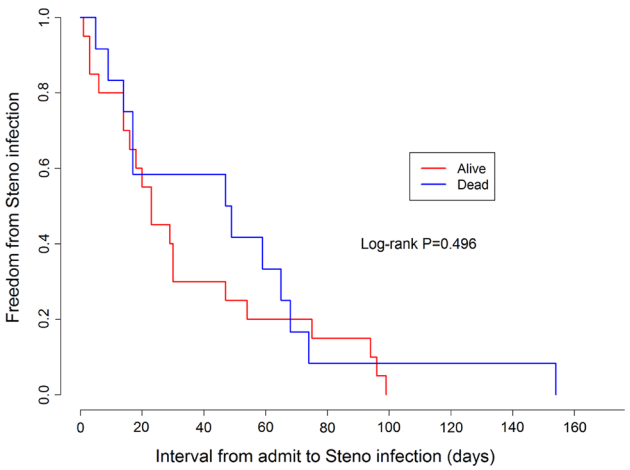

Fig. 2 Kaplan Meier plot for time from hospital admission to *Stenotrophomonas* infection stratified by death

Results

Patient Characteristics

We identified a total of 38 patients between the ages of 0–6 months hospitalized in CVICU for ≥48 hours with positive culture for *S. maltophilia.* Six of these patients were excluded from the study as they did not fulfill the CDC criteria for VAP and were considered to be colonized with *S. maltophilia.* The overall incidence for the 5-year study period was 0.8 % ($n = 32/3656$) with an incidence of 0.7 % in 2006 ($n = 5/713$), 1.05 % in 2007 ($n = 7/662$), 1.4 % in 2008 ($n = 10/729$), 1.06 % in 2009 ($n = 8/755$), and 0.25 % in 2010 ($n = 2/794$). Among 32 eligible patients, there were 47 *S. maltophilia* infections, including 44 episodes of VAP, one blood stream infection, one sternal wound infection, and one urinary tract infection.

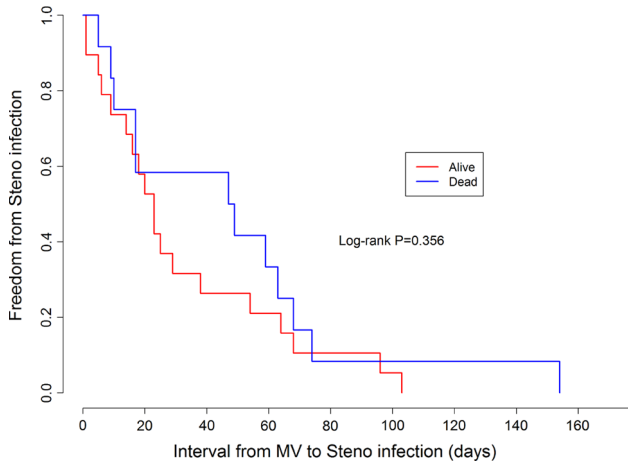

Fig. 3 Kaplan Meier plot for time from mechanical ventilation to *Stenotrophomonas* infection stratified by death

Demographics of study patients are shown in Table 1. The median age of the overall study population was 60 days. Among those who acquired *S. maltophilia* infection after admission in CVICU, 21.8 % were admitted in neonatal ICU and one (3.1 %) was admitted in pediatric ICU prior to transfer to the CVICU. The overall in-hospital all-cause mortality for the study group was 37.5 % ($n = 12/32$).

Comparison of Survivors and Non-survivors with *S. maltophilia*

Survivors had 56 ventilator-free days when compared to 15.5 days among non-survivors (p value = 0.006). Number of days with positive cultures for *S. maltophilia* was 30 days in non-survivors compared to 11 days in survivors (p value = 0.008).

The ALC immediately prior to *S. maltophilia infection* was significantly higher in survivors versus non-survivors (1,665 vs 960/mm^3; p value = 0.01) (Fig. 1). All patients ($n = 32$) had leukocytosis prior to infection with *S. maltophilia* but there was no statistical differences between survivors and non-survivors. Among the comorbid conditions, the need for renal dialysis (67 %; $n = 8/12$ among non-survivors vs 30 %; $n = 6/20$; p value = 0.04) and presence of stroke (17 %; $n = 7/12$ among non-survivors compared to 0 % in survivors; p value = 0.05) were found to be significantly different among survivors and non-survivors.

Table 1 Comparison of demographics between survivors and non-survivors

Demographics	*N*	Survivors ($N = 20$)	Non-survivors ($N = 12$)	*p*
Age (days)	32	67.5 (56.2, 97.5)	60.0 (56.2, 90.0)	0.601
Gender				
Male	32	85 % (17/20)	58 % (7/12)	0.092
Race				
White	32	65 % (13/20)	58 % (7/12)	0.852
Black		25 % (5/20)	25 % (3/12)	
Other		10 % (2/20)	17 % (2/12)	
Prematurity	32	15 % (3/20)	17 % (2/12)	0.9
Gestational age (weeks)	32	38.0 (38.0, 38.0)	38.0 (38.0, 38.2)	0.843
Mechanical ventilation	32	100 % (20/20)	100 % (12/12)	
Co-morbidities				
Chronic lung disease	32	5 % (1/20)	8 % (1/12)	0.706
Necrotizing enterocolitis	32	10 % (2/20)	0 %	0.258
Intra-ventricular hemorrhage	32	10 % (2/20)	0 %	0.258
Stroke	32	0 %	17 % (2/12)	0.059
Seizures	32	10 % (2/20)	17 % (2/12)	0.581
Renal failure	32	35 % (7/20)	67 % (8/12)	0.082
Dialysis	32	35 % (7/20)	67 % (8/12)	0.083
Nitric oxide	32	55 % 11/20	50 % (6/12)	0.784
Neurologic injury	32	25 % 5/20	33 % (4/12)	0.612
Laboratory Variables				
ANC at admission	32	6900.0 (4981.0, 8662.0)	9275.0 (6962.0, 13026.0)	0.083
ALC at admission	32	2517.0 (1575.0, 4380.0)	3535.0 (3094.0, 4068.0)	0.301
ANC prior to infection	32	7971.0 (6685.0, 11862.0)	7468.0 (5807.0, 8932.0)	0.581
ALC prior to infection	32	1665.0 (1318.0, 2320.0)	960.0 (588.0, 1507.0)	*0.015*

Italic value indicates statistically significance $p < 0.05$

All continuous variables are depicted as median (inter-quartile range) and all categorical variables are depicted as percentage (*N*)

ANC absolute neutrophil count, *ALC* absolute lymphocyte count

A majority of positive cultures for *S. maltophilia* were poly-microbial in 75 % ($n = 9/12$) of non-survivors compared to 55 % ($n = 11/20$) among the survivors. The most common bacteria which were involved in poly-microbial infection were pseudomonas ($n = 10/32$), enterobacter ($n = 8/32$), and klebsiella ($n = 7/32$). 95 % of survivors ($n = 19/20$) had negative culture during hospitalization in contrast to 50 % ($n = 6/12$) among non-survivors (p value = 0.003).

The median time between ICU admission and ICU acquired *S. maltophilia* and the median time from mechanical ventilation to ICU acquired infection in survivors and non-survivors are depicted as Kaplan–Meier plots in Figs. 2 and 3.

Antibiotic Therapy

The median duration of antibiotic therapy among survivors was 10 days versus 24 days among non-survivors (p value = 0.011). 97 % ($n = 31/32$) of *S. maltophilia* strains were sensitive to TMP-SMX therapy and 91 % ($n = 29/32$) to levofloxacin and ticarcillin/clavulanate. Resistance pattern in our patient cohort was low and it did not change over time even in patients who had multiple episodes of infection with S. *maltophilia.*

Broad spectrum antibiotic use prior to infection with *S. maltophilia* was noted in 75 % of non-survivors ($n = 9/12$) versus 60 % ($n = 12/20$) of survivors. The median duration of broad spectrum antibiotics before S. *maltophilia* infection was noted to be 7.5 days in non-survivors and 6 days in survivors. 50 % of all patients ($n = 16/32$) and 66.6 % of non-survivors ($n = 8/12$) had prior treatment with carbapenem about 2–4 weeks before *S. maltophilia* infection. Clinical characteristics of patients are demonstrated in Table 2 and outcome of study patients is demonstrated in Table 3.

There were two patients who were older than 6 months of age who qualified for diagnosis with *S. maltophilia* VAP based on criteria. One of them was 5 years of age, had ALC of 2,370 and 3,600 at admission and prior to infection, respectively, was treated with trimethoprim/sulfamethoxazole for 16 days, was on broad spectrum antibiotics for about a month prior to infection, had multiple positive cultures, the isolate was resistant to ticarcillin/clavulanate and did not survive. The second patient was 18 months of age, had ALC of 553 and 1,440 at admission

Table 2 Infection and antimicrobial-related characteristics

	N	Survivors($N = 20$)	Non-survivors($N = 12$)	Combined ($N = 32$)	*p*
Duration of broad spectrum antibiotics (days)	32	6.0 (0.0, 15.5)	7.5 (0.0, 12.5)	6.0 (0.0, 15.5)	0.81
Sensitivity to trimethoprim/sulfamethoxazole	32	100 % 20/20	92 % 11/12	97 % 31/32	0.19
Sensitivity to levofloxacin	32	85 % 17/20	100 % 12/12	91 % 29/32	0.16
Sensitivity to ticarcillin/clavulanic acid	32	90 % 18/20	92 % 11/12	91 % 29/32	0.88
Negative culture during hospitalization	32	95 % 19/20	50 % 6/12	78 % 25/32	0
Treatment duration(days)	32	10.0 (10.0, 16.2)	24.0 (15.2, 32.5)	12.0 (10.0, 27.8)	*0.01*
Broad spectrum antibiotics prior to *stenotrophomonas* infection	32	60 % 12/20	75 % 9/12	66 % 21/32	0.39
Presence of Central venous line or Foley catheter	32	95 % 19/20	100 % 12/12	97 % 31/32	0.43
Interval from admission to first positive *Stenotrophomonas* culture (days)	32	23.0 (14.0, 48.8)	48.0 (16.2, 65.8)	26.0 (14.0, 60.5)	0.46
Interval from mechanical ventilation to first positive*Stenotrophomonas* culture (days)	31*	23.0 (11.5, 46.0)	48.0 (15.2, 64.2)	23.0 (12.0, 61.0)	0.37

Italic value indicates statistically significance $p < 0.05$

All continuous variables are depicted as median (inter-quartile range) and all categorical variables are depicted as percentage (*N*)

*In one patient, *stenotrophomonas* culture was done prior to mechanical ventilation

Table 3 Comparison of outcomes between survivors and non-survivors

Outcomes	*N*	Survivors ($N = 20$)	Non-survivors ($N = 12$)	*p*
Mechanical ventilation (days)	32	67.5 (27.5, 95.8)	68.0 (45.0,116.8)	0.433
Ventilator free days	32	56.0 (24.0, 61.8)	15.5 (10.0, 21.2)	*0.006*
Length of stay in ICU (days)	32	132.0 (60.0, 172.0)	85.0 (55.0, 176.0)	0.761
Length of stay in hospital (days)	32	132.0 (67.5, 171.8)	85.0 (55.0, 176.2)	0.704

Italic value indicates statistically significance $p < 0.05$

All continuous variables are depicted as median (inter-quartile range) and all categorical variables are depicted as percentage (*N*)

and prior to infection, respectively, was treated with ticarcillin/clavulanate for 10 days, was on broad spectrum antibiotics for 21 days prior to infection, cleared the positive culture, the isolate was susceptible to trimethoprim/sulfamethoxazole, ticarcillin/clavulanate, and levofloxacin and survived.

Discussion

This is the first study to characterize *S. maltophilia* nosocomial infection exclusively among infants (0–6 months) with heart disease hospitalized in a dedicated CVICU. The resistance to TMP-SMX was low and the resistance pattern did not change over 5-year study period, even in patients with multiple episodes of documented infections.

The overall incidence rate of *S. maltophilia nosocomial infection* was 0.8 % over the study period of 5 years and there were no significant increase in the incidence at our institution despite recent trends of increase in the overall incidence of *S. maltophilia* infection in ICUs. Earlier reports from the late 1990 s indicated an incidence of 0.6–0.9 %. However, in recent years, several studies have indicated a much higher incidence of up to 8 %. However, unlike these studies which included adults as well as children our study focused specifically on infants with complex heart disease.

Lymphopenia prior to *S. maltophilia* infection was noted to be significantly more frequent among non-survivors compared to survivors. It is possible that lymphopenia conferred a degree of immunosuppression among non-survivors and may have contributed for them to have longer duration of positive cultures and to be treated for longer duration with antibiotics. In contrast to our report, however, Mazzoni et al. have noted that neutropenia was an associated risk factor for developing *S. maltophilia* bacteremia among adult patients with malignancy. Even though we found lymphopenia more frequently among our non-surviving subjects, this study is limited in defining it as a risk factor for acquiring *S. maltophilia* infection.

The use of broad spectrum antibiotics prior to *S. maltophilia* infection in two-thirds of the study cohort is consistent with other studies which mention antibiotic exposure as a risk factor for infection with *S. maltophilia*. Furthermore, carbapenem use in only 50 % of all infected patients in our study is similar to some those reported by

other studies [35]. It appears that rather than exposure to one particular antibiotic, exposure to broad spectrum antibiotics is important in *S. maltophilia* infection. However, in contrast, prior use of TMP-SMX which was identified to be associated with an increased risk for bacteremia [4] was only used in 15.6 % of our patient population. We found 97 % of the isolates were sensitive to TMP-SMX and 91 % of the isolates to levofloxacin and ticarcillin/clavulanate. The other antibiotics were not tested for susceptibility at our institution. The resistance rate is much less when compared to one article [4] which mentioned 10 % resistance rate to TMP/SMX and 54 % to ticarcillin/clavulanate but similar rates to TMP/SMX as another article [27]. The resistance pattern did not change significantly even in isolates from the same patient with recurrent episodes of infection. In more than half of the patients in our study (62.5 %), bacterial co-pathogens were isolated from the respiratory tract when *S. maltophilia* infection was diagnosed. This frequency of polymicrobial infections is slightly higher than previously reported data in patients with *S. maltophilia* pneumonia and *S. maltophilia* bacteremia [[27], [31], [23] and [9]].

S. maltophilia infection in our cohort was associated with significant morbidity (prolonged need for mechanical ventilation, prolonged ICU-LOS, and hospital LOS). It was also associated with poor outcomes as non-survivors had longer duration of positive cultures and antibiotics therapy and it took longer to clear the infection. The findings are consistent with several other studies [[10], [32], [33], [5], [23], and [9]] which showed a similar increase in morbidity in patients with *S. maltophilia infection* who have severely debilitating underlying illness and/or immunosuppression. These data suggest that acquisition of *S. maltophilia may* be a marker of severity of underlying illness than of it being a pathogen with high virulence. Most studies which suggest high attributable mortality rates from *S. maltophilia* infection [1, 5, 17, 18, 20, 27] had large incidence of *S. maltophilia* bacteremia than localized respiratory tract involvement [8, 23, 26, 30]. In our study, the majority of *S. maltophilia* infections were localized as pneumonia with only one episode of bacteremia noted.

The crude all-cause mortality was 37.5 % which may be related to their underlying medical/surgical condition rather than to *S. maltophilia* infection. This study is limited to calculate infection-attributed mortality rate as we did not include matched controls without *S. maltophilia infection*. Prior studies indicate infection-attributed mortality rate in the range of 14.7–37.5 % [1, 5, 11, 13, 17, 18, 20, 22, 27] and infection-attributed mortality rate for bacteremia to be as high as 51 % [8, 9, 11, 22–24, 26, 30, 34]. Risk factors for increased mortality described in the literature include bacteremia, shock, thrombocytopenia, neutropenia, multi organ dysfunction, ICU admission, underlying pulmonary disease, pulmonary source of isolate, polymicrobial cultures, delayed effective treatment, prior use of carbapenem, renal failure, and liver failure in the ICU [1, 3, 5, 9, 11, 18, 24, 27]. Our study population is unique as it only included infants with congenital heart disease but shared some of the common risk factors noted in other studies like ICU admission and pulmonary source of isolate. However, in our cohort we did not find bacteremia, shock, polymicrobial cultures, neutropenia or thrombocytopenia to be higher among non-survivors compared to survivors.

Our study has several potential limitations related to its retrospective observational study design, and a small sample size from a single study center. Since molecular typing of *S. maltophilia* isolates was not performed in clinical routine, we cannot provide data on potential transmission of *S. maltophilia* isolates in our study. The small sample size as well as the absence of a comparison group precluded us from being able to conduct a multivariate analysis for risk factors.

Conclusion

To our knowledge, this is the first study in the literature looking at incidence, clinical characteristics and outcomes related to ICU-acquired *S. maltophilia* infection in pediatric population. *S. maltophilia* infection is found to be rare in this particular patient cohort at our institution during the study period over 5 years. Lymphopenia was noted prior to infection in non-survivors and these patients took a longer time to clear the infection and needed prolonged duration of antibiotic therapy. The all-cause in-hospital mortality was found to be 37.5 % and *S. maltophilia* infection was associated with increased morbidity with increased length of stay in ICU, increased length of hospitalization, increased duration of mechanical ventilation, and longer duration of treatment with antimicrobials similar to another article [4]. Prospective, multi-center, case–control studies among larger pediatric ICU population will be important to further define risk factors for acquiring *S. maltophilia* infection among children with cardiac disease.

Conflict of interest None.

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