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Original Article

Streptococcus mitis/*oralis* Causing Blood Stream Infections in Pediatric Patients

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SUMMARY: Viridans streptococci are still under investigation concerning epidemiology, pathogenesis and clinical presentations. We aimed to investigate the clinical presentations and outcomes of pediatric patients infected with *Streptococcus mitis*/*oralis*. Based on the accumulation of bloodstream infections (BSI) caused by *S. mitis*/*oralis* in 4 patients in our Hematology and Bone Marrow Transplantation Department at a particular time, a review of the medical and microbiological records of pediatric patients with positive blood cultures for *S. mitis*/*oralis* in the entire hospital was performed. In addition, a retrospective case-control study was conducted. Pulsed-field gel electrophoresis of *S. mitis*/*oralis* in 4 patients displayed unrelatedness of the strains. A total of 53 BSI (42 BSI and 11 catheter-related BSI) were analyzed. Thirty-four percent of patients with BSI caused by *S. mitis*/*oralis* had febrile neutropenia. Clinical and microbiological outcomes were favorable and infection-related mortality was not observed. Although not significant, previous antibiotic use and trimethoprim-sulfamethoxazole prophylaxis were more common in the case group. *S. mitis*/*oralis* seems likely an important agent in bacteremic children who are particularly neutropenic because of the underlying hematologic and oncologic diseases. Prompt management of infections with appropriate antimicrobials, regarding antibiotic susceptibilities of organisms, may facilitate favorable outcomes.

INTRODUCTION

Viridans streptococci (VS) are part of the normal flora of the oral cavity, respiratory tract, and gastrointestinal tract. Although they reside commensally in these anatomic locations, under immunocompromised conditions, they may cause invasive diseases such as endocarditis, meningitis, and pneumonia (1,2). They are important emerging pathogens which are still under investigation concerning epidemiology, pathogenesis and clinical presentations. Recently there has been an apparent increase in the incidence of VS infections (3,4), especially in neutropenic patients, which has been attributed to improvements in microbiological identification methods, use of chemotherapeutics which cause mucosal damage, prophylactic regimens, and a host of other factors.

Consequences of infections with VS are inconsistent; some patients present with minimal symptoms while some present with shock syndrome (5). Classification based on colony size, molecular profiling by DNA, RNA, and chemical reactions are currently preferred methods of diagnosis. *S. mitis* and *S. oralis* are classified under the *S. mitis* group (6). Based on the accumulation of bloodstream infections (BSI) caused by *S. mitis*/*oralis* in a group of patients hospitalized in Hematology and Bone Marrow Transplantation Inpatient Clinics at a particular time, we investigated the clinical presentations and outcomes of the patients infected with *S. mitis* group.

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METHODS

Study setting: A flow chart of the study design is shown in Fig. 1. From March to April 2016, 4 pediatric cases with febrile neutropenia in the Department of Hematology and Bone Marrow Transplantation were identified as having catheter-related BSI caused by *S. mitis*/*oralis*. This hospital has 270 beds and serves as a tertiary care children's hospital. The Department of Hematology and Bone Marrow Transplantation ward consists of 8 rooms with 1–2 beds for leukemia patients and 4 single rooms for transplantation patients in a separate hall. Isolates of *S. mitis*/*oralis* obtained from blood cultures of 4 patients were assessed via pulsed-field gel electrophoresis (PFGE). Subsequently, a review of medical and microbiological records of pediatric patients with positive blood cultures for *S. mitis*/*oralis* between January 2015 and March 2017 in the entire hospital was performed. A standardized data collection form was used to extract clinical data from the electronic records of patients with positive blood cultures for *S. mitis*/*oralis*. Data regarding demographic characteristics, underlying diseases, concomitant infections, laboratory evaluation (WBC [white blood cell] count, CRP [C-reactive protein], and platelet counts), presence of central venous catheter (permanent or temporary), presence of febrile neutropenia (absolute neutrophil count $\leq 0.5 \times 10^9$/L), and mucositis at the time of BSI, length of stay in hospital before infection, and treatment duration were evaluated. For the outcome analysis, response to treatment (clinical and microbiological) and mortality (infection-related and overall)

were stated at the end of the study period.

Clinical findings of BSI were defined as the presence of at least one of fever, chills, or hypotension (7) in addition to isolation of *S. mitis*/*oralis*. Catheter-related BSI was defined as the presence of clinical manifestations of infection (fever, chills, and/or hypotension, etc.) with an in-situ central venous catheter for more than 48 h, and no other apparent source of infection (8). Clinical response at the end of therapy was stated as the resolution of fever, leukocytosis, and signs and symptoms of infection. Microbiologic response was specified as the eradication of the organism that caused the infection, which was evidenced in control blood cultures after initiation of treatment. The study protocol was approved by the local ethical committee (no: GO 17/452).

Case-control study: To identify risk factors for *S. mitis*/*oralis* BSI, a case-control study was conducted. A case was defined as a patient with signs of BSI and positive blood culture for *S. mitis*/*oralis*. Controls were all patients without positive blood cultures for *S. mitis*/*oralis* from the Department of Hematology and Bone Marrow Transplantation who were hospitalized for at least 48 h from March to April 2016. The 2 groups were compared concerning age, gender, underlying diseases, presence of central venous catheter, presence of febrile neutropenia, absolute neutrophil counts, presence of mucositis, use of antacids or histamine receptor antagonists, previous antibiotic use (glycopeptides [vancomycin or teicoplanin], carbapenems [meropenem], and third-generation cephalosporins) in the 15 days preceding the analysis period, and antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ) or ciprofloxacin.

Microbiological and molecular assays: Identification of *S. mitis*/*oralis* in blood culture was achieved by matrix-assisted laser desorption ionization-time of flight mass spectrometry, and antimicrobial susceptibility testing of *S. mitis*/*oralis* was performed using the VITEK 2 system (bioMérieux, Marcy l'Etoile, France). For antimicrobial susceptibility testing, our bacteriology laboratory switched from the guideline of the Clinical and Laboratory Standards Institute (CLSI) to that of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in September 2016, in accordance with Europe, in order to ease the epidemiological surveillance. The date of switch coincided with the period of retrospective analysis. Therefore, in the present study, the results of antimicrobial susceptibility tests were interpreted according to the CLSI recommendations between January 2015 and September 2016 (9). After September 2016, antimicrobial susceptibilities were evaluated according to the EUCAST guideline (10).

For molecular typing of *S. mitis*/*oralis* isolated from 4 patients in the Hematology and Bone Marrow Transplantation ward, PFGE of *Sma*I-digested genomic DNA was performed using the CHEF-DRII system (Bio-Rad, Hercules, CA, USA) (Fig. 1) and PFGE patterns were compared visually, according to the aforementioned criteria (11).

Statistical analyses: Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were

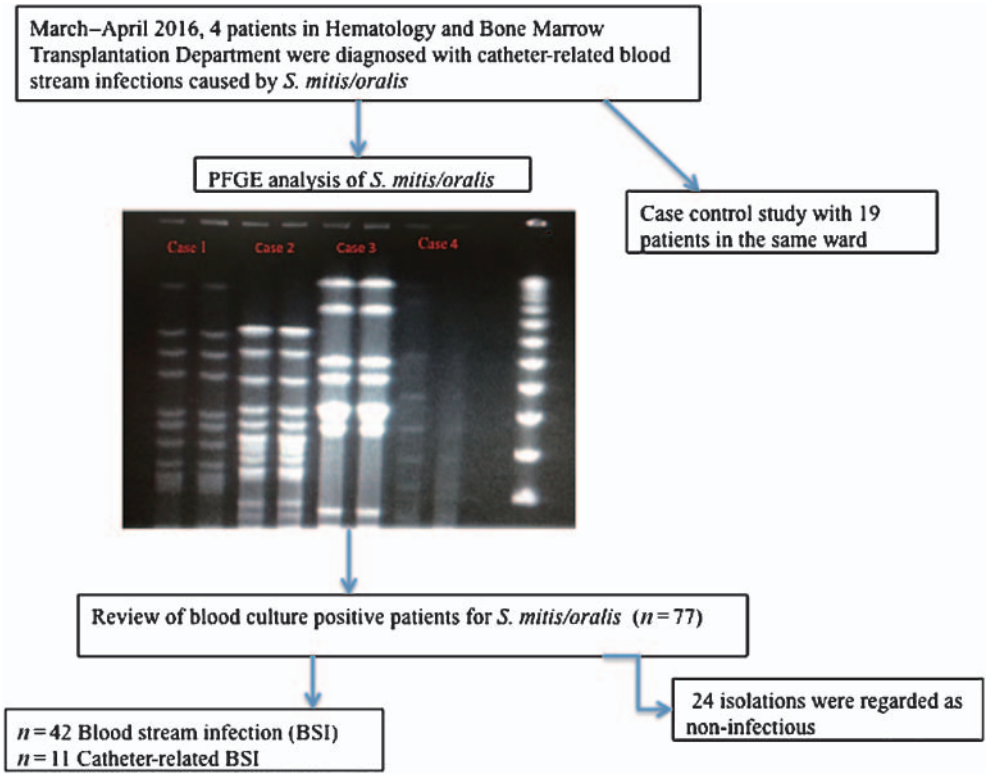

Fig. 1. (Color online) Flow chart of the study design. Pulsed-field gel electrophoresis (PFGE) analysis of 4 patients is shown in the figure. Case 1: 9 years of age, male, AML; Case 2: 2 years of age, male, AML; Case 3: 13 years of age, male, AML; Case 4: 7.5 months of age, male, osteopetrosis and bone marrow transplantation.

used to summarize the participants' baseline characteristics, including medians, interquartile ranges (IQRs) for continuous and frequency distributions for categorical variables. The normality of quantitative variables was tested using the Kolmogorov-Smirnov test. For continuous variables, the independent-groups *t*-test was used for normally distributed variables or the nonparametric Mann-Whitney *U* test, if the normality assumption was violated. In all analyses, 2-tailed p-values < 0.05 were regarded as statistically significant.

RESULTS

During the study period, 4 patients had catheter-related BSI caused by *S. mitis*/*oralis*. Case 1 was a 9-year-old male patient with acute myeloid leukemia (AML); case 2 was a 2-year-old male patient with AML; case 3 was a 13-year-old male patient with AML; and case 4 was a 7.5-month-old male patient who underwent bone marrow transplantation on account of osteopetrosis. All of the 4 patients had febrile neutropenia. PFGE analysis of *S. mitis*/*oralis* bacteria isolated from blood cultures of the 4 patients displayed unrelatedness of the strains (Fig. 1).

A total of 53 pediatric patients fulfilling the criteria were enrolled in the study; 42 (79.2%) had BSI and 11 (20.8%) had catheter-related BSI. Demographic and clinical characteristics of the study population are summarized in Table 1. There were 28 (52.8%) male patients. The median age was 27 (IQR: 4.8–99.8) months. The underlying diseases included hematologic malignancy ($n = 12$, 22.6%), oncologic malignancy ($n = 9$, 17%), post-bone marrow transplantation ($n = 3$, 5.7%), congenital heart disease ($n = 6$, 11.3%), gastrointestinal disease ($n = 5$, 9.4%), neurometabolic disease ($n = 3$, 5.7%), nephrologic diseases ($n = 3$, 5.7%), and primary immunodeficiency ($n = 1$, 1.9%). All patients had underlying diseases. Nine patients had concomitant infections such as pneumonia ($n = 4$), urinary tract infection ($n = 3$), mediastinitis ($n = 1$), and meningitis ($n = 1$). In the entire group, 3 patients had mucositis (5.7%) and the *S. mitis*/*oralis* isolates of these patients were included in the PFGE analysis. The median WBC count was 7.9 (IQR: 1.45–13.3) $\times 10^9$/L, the median platelet count was 160 (IQR: 50.5–246) $\times 10^9$/L, and median CRP concentration was 2.86 (IQR: 0.32–7.2) mg/dL. Febrile neutropenia was present in 18 (34%) of patients at the time of *S. mitis*/*oralis* infection. The median duration of hospitalization before infection and total duration of treatment were 9 (IQR: 2–42) and 15 (IQR: 10–22) days, respectively. In the outcome analysis, the clinical and microbiological response rates were 100%, and no infection-related mortality was observed.

Table 2 demonstrates the in vitro susceptibility of *S. mitis*/*oralis* isolates from the entire cohort of patients to selected antimicrobial agents. During the study period, according to timeline, 2 different guidelines (CLSI till September 2016 and EUCAST after September 2016) were utilized for antimicrobial susceptibility interpretations. For both periods, no resistance to vancomycin and linezolid was observed. The penicillin resistance rate was 45.2 and 44.4%, respectively. The proportions of resistance to cefotaxime and ceftriaxone were 41.8 and 39.5% according to the CLSI guideline while it was 50% for both according to the EUCAST guideline.

Table 3 shows the results of the case-control study conducted including cases and controls from the same

Table 1. Characteristics of pediatric patients with BSI caused by *S. mitis/oralis*

$n = 53$	
Age, months (median, [IQR])	27 [4.8–99.8]
Male*	28 (52.8)
Underlying diseases*	
Hematologic malignancy	12 (22.6)
Oncologic malignancy	9 (17)
Post-BMT	3 (5.7)
Congenital heart disease	6 (11.3)
Gastrointestinal disease	5 (9.4)
Neurometabolic disease	3 (5.7)
Nephrologic disease	3 (5.7)
Primary immunodeficiency	1 (1.9)
Other	11 (20.8)
Concomitant infection*	
Pneumonia	4 (7.5)
Urinary tract infection	3 (5.7)
Mediastinitis	1 (1.9)
Meningitis	1 (1.9)
Presence of central venous catheter*	18 (34)
Mucositis*	3 (5.7)
Febrile neutropenia (ANS $< 0.5 \times 10^9$/L)*	18 (34)
Laboratory analysis (median, [IQR])	
WBC ($\times 10^9$/L)	7.9 [1.45–13.3]
Platelet counts ($\times 10^9$/L)	160 [50.5–246]
CRP (mg/dL)	2.86 [0.32–7.2]
Length of stay in hospital before infection, days (median, [IQR])	9 [2–42]
Treatment duration, days (median, [IQR])	15 [10–22]
Outcome*	
Clinical response	53 (100)
Microbiological response	53 (100)
Infection-related mortality	—
Overall mortality	5 (9.6)

*: *n* (%).
WBC, white blood cell count; CRP, c-reactive protein.

Table 2. In vitro susceptibility of *S. mitis/oralis* isolates from whole group of patients to selected antimicrobial agents

	January 2015–August 2016[1)] $n = 43$	September–December 2016[2)] $n = 10$
	Susceptibility breakpoint μg/mL resistant strains (%)	Susceptibility breakpoint μg/mL resistant strains (%)
Ampicillin	8/41.8	2/60
Penicillin	4/45.2	2/44.4
Levofloxacin	8/9.3	-/0
Linezolid	-/0	-/0
Cefotaxim	4/41.8	0.5/50
Ceftriaxone	4/39.5	0.5/50
Vancomycin	-/0	2/0

[1)]: According to CLSI.
[2)]: According to EUCAST.

Table 3. Characteristics of cases and control patients

Characteristics	Case $n = 4$	Control $n = 19$	p
Age (months) [median, IQR]	71 [13.4–152.4]	78 [48–150]	0.5
Male*	4 (100)	7 (36)	0.55
Underlying diseases			NA
ALL	—	15	
AML	3	3	
Osteopetrosis-BMT	1	—	
MDS	—	1	
Mucositis*	2 (50)	7 (36.8)	0.5
Presence of central venous catheter*	4 (100)	10 (52.6)	0.12
Presence of febrile neutropenia*	4 (100)	10 (52.6)	0.12
Absolute neutrophil count $< 100 \times 10^9$/L*	4 (100)	13 (68.4)	0.53
Absolute neutrophil count, $\times 10^9$/L [median, IQR]	150 [25–350]	200 [100–600]	1.0
Use of antiacids or histamine receptor antagonists*	2 (50)	9 (52.6)	0.6
Previous antibiotic use*			
Glycopeptide	3 (75)	6 (31.5)	0.6
Carbapenem	3 (75)	6 (31.5)	0.26
3rd generation cephalosporin	0	2 (10.5)	NA
Antimicrobial prophylaxis with*			
TMP–SMZ	3 (75)	13 (68.4)	1.0
Ciprofloxacin	2 (50)	1 (5.8)	NA

*: *n* (%).
ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; MDS, myelodysplastic syndrome; BMT, bone marrow transplantation; TMP–SMZ, trimethoprim-sulfamethoxazole.

ward in the same period of time. The 2 groups displayed no significant difference concerning the presence of a central venous catheter, presence of febrile neutropenia, absolute neutrophil counts, presence of mucositis, use of antacids or histamine receptor antagonists, previous antibiotic use in the preceding 15 days, and antimicrobial prophylaxis with TMP-SMZ or ciprofloxacin. Although not significant, previous antibiotic use was more common in the case group (75% vs. 31.5 % for glycopeptide and carbapenem use). The proportion of TMP-SMZ prophylaxis was 75% for the case group and 68.4% for the control group.

DISCUSSION

In the present study, it was demonstrated that *S. mitis*/*oralis* was one of the microbiological causes of BSI in pediatric patients; thirty-four percent of patients with BSI caused by *S. mitis*/*oralis* had febrile neutropenia; and half of the patients had hematologic malignancies, oncologic malignancies, and bone marrow transplantation. Clinical and microbiological outcomes were favorable, and infection-related mortality was not observed. In previous studies, particularly adult data, the mortality rate varied between 4 to 22% among patients with VS infections (12–15). In the present study, despite similar antimicrobial susceptibility results to those found in the literature, immediate availability of preliminary microbiological results and collaboration with microbiologists in our hospital enabled early and accurate interventions for the patients, which may be the reason for the good outcomes.

Four patients, whose *S. mitis*/*oralis* strains were included in the PFGE analysis, had different strains from each other and the presence of mucositis in these patients supported the causal relationship for BSI as reported in the previous literature (16–18). However, in the present study, 34% of patients had central venous catheters and 20.8% of the patients were considered as having catheter-related BSI. In a report of adult patients, Shelburne et al. showed that a significant percentage of VS BSI isolates had a high central venous catheter / peripheral blood culture colony forming unit ratio, supporting the concept of VS as the causative agent of central venous catheter-related BSI (19). These findings call for an evaluation of central catheter insertion as a risk factor for acquisition of these bacteria in larger studies.

VS commonly exist in the oral cavity but also live in the upper respiratory tract, the female genital tract, and all regions of the gastrointestinal tract. These organisms can invade sterile body sites and lead to life-threatening infections. Currently, VS are considered as major bacterial pathogens both in pediatric and adult patients with malignancy (1,5). They caused 21–32% of all cases of bacteremia among hospitalized neutropenic patients with malignancy (3,13). Recently, it was reported that approximately 80% of patients with VS positive blood cultures had neutropenia and hematologic malignancies (20). In addition, among patients undergoing bone marrow transplantation, 12–17.5% had VS associated bacteremia during episodes of severe neutropenia (17,18). In the pediatric group, neutropenic patients with hematologic malignancies had VS positive blood cultures with a predominance of *S. mitis* strains followed by *S. oralis* (20). In this group, compared with strains of other VS, *S. mitis* strains were significantly more likely associated with moderate or severe disease states. As a result, it was stated that *S. mitis* strains might have inherently virulent

properties compared with other VS. In the present study, due to the unavailability of microbiological methods, we were unable to differentiate the patients with *S. mitis* and *S. oralis* isolates; the clinical outcomes were still pleasing.

Since the recognition of VS as causes of bacteremia with cancer, a number of risk factors were studied. Besides profound neutropenia, antimicrobial prophylaxis with TMP-SMZ and fluoroquinolone was recognized as a risk factor for the development of VS associated bacteremia (18,21,22). Moreover, it was shown that the emergence of VS as causes of bacteremia in patients with neutropenia coincided with the increased use of broad-spectrum antibiotics (6). Via reduction of Gram-negative flora, broad-spectrum antibiotics may facilitate the proliferation of VS and other commensals relatively resistant to these agents. In the present case-control study, although prophylaxis with these agents was not found to be a risk factor statistically, the patients with BSI associated with *S. mitis*/*oralis* were more commonly under prophylaxis.

Kennedy et al. studied the effect of a change in empirical antibiotic treatment from ceftazidime plus amikacin to piperacillin-tazobactam plus amikacin in pediatric febrile neutropenia (23). They displayed the change in geometric mean MIC values of all β-lactams tested against blood culture isolates in accordance with the change in empirical treatment, as evidence of selection of VS with diminished susceptibility in case of repeated courses of certain agents. In relation to these findings, we sought the effect of previous glycopeptide and carbapenem use in the case-control study. Although not statistically significant, our case patients in the Hematology and Bone Marrow Transplantation Department were more frequently treated with glycopeptides and carbapenems previously.

In the present study, *S. mitis*/*oralis* was also identified as a causative agent in non-neutropenic pediatric patients. Our center is a tertiary hospital which takes care of many clinically high-risk groups of pediatric patients with immunocompromised states other than malignancies and patients in need of long-term intensive care unit support. These groups require a variety of interventions, accompanying long-term and combined therapies during their hospital stay. Many factors which were reported as risk factors for *S. mitis*/*oralis* infections, such as destruction of mucosal integrity with interventions, intravenous hyperalimentations (6), colonization with VS (24), and use of antacids (6), may be contributory factors to bacteremia in this group of patients. Further analyses of these factors in non-neutropenic patients are necessary with a larger group of patients.

Despite early initiation of appropriate antimicrobial treatment, the mortality rate due to bacteremia caused by VS in neutropenic patients with malignancy ranged from 0% to 18% (12,14,16,17,25). Shelburne et al. observed that most patients with VS bacteremia had clinically mild infections, but 25% had moderate to severe infections including 11 patients who had VS shock syndrome associated with *S. mitis* (20). Bacteremia may not always be the only factor causing mortality, especially in patients with comorbidities. In our present series of pediatric patients, infection-related mortality was not observed, and the clinical and microbiological response rates were 100%. Length of hospital stay until bacteremia was 9 days, which had not been reported before. The median treatment duration was relatively long for Gram-positive bacteremia treatment which was probably due to accompanying problems.

None of the *S. mitis*/*oralis* isolates displayed in vitro vancomycin resistance in the present study, consistent with the literature (6). The penicillin resistance rate was 45% which was higher than 5% resistance from all VS isolates reported in the SENTRY Antimicrobial Surveillance Program data (25). Similar with Marron et al's report about VS resistance to ceftazidime (53%) and cefepime (34%) (26), our analysis showed 39–50% resistance to cefotaxime and ceftriaxone, changing according to the guideline used during the study period. As a result, for high-risk patients, use of empirical vancomycin for treating fever seemed wise in our patient population.

Our study has certain limitations. We could only include the data of a relatively small number of patients. There is the potential for bias and inaccurate data collection due to the retrospective nature of this study. We were unable to evaluate *S. mitis*/*oralis* isolates for molecular analysis and toxin-production evaluations. Lu et al. in a major outbreak report of *S. mitis*-associated toxic shock-like syndrome showed highly pyrogenic endotoxin production of *S. mitis* strains which were clonally identical in PFGE analysis (27). In order to assess the behavior of these bacteria in different patient populations and disease states, further molecular studies are necessary for bacteremia caused by the *S. mitis* group. Despite these limitations, we believe that our data will guide physicians because of the scarcity of pediatric data in this field. Further prospective studies with larger patient populations involving multiple centers are necessary to identify optional management strategies for *S. mitis*/*oralis* infections in children.

In conclusion, *S. mitis*/*oralis* seems likely an important agent in bacteremic children who are particularly neutropenic because of underlying hematologic and oncologic diseases. Previous use of extended-spectrum antimicrobial treatments apart from prophylactic ones might be evaluated profoundly in pediatric wards. Prompt management of infections with appropriate antimicrobial agents regarding antibiotic susceptibilities of organisms may facilitate favorable outcomes, as in our study.

Conflict of interest None to declare.

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