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Original Article

Clinical features and complications of viridans streptococci bloodstream infection in pediatric hemato-oncology patients

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Background and Purpose: Viridans streptococci (VS) are part of the normal flora of humans, but are fast emerging as pathogens causing bacteremia in neutropenic patients. The clinical features, outcomes, and antibiotic susceptibilities of VS bloodstream infections in children with hemato-oncological diseases are reported in this study.
Methods: A retrospective chart review of pediatric patients (≤18 years) diagnosed with VS infections between January 1998 and December 2004 was conducted at the National Taiwan University Hospital.
Results: Among the 26 episodes noted in 25 pediatric patients, the incidence rate of VS bacteremia was found to be significantly higher in pediatric patients with acute myeloid leukemia compared with other hemato-oncological conditions. Most of the patients had profound neutropenia related to chemotherapy for a median of 5 days on the day of positive blood culture. Eight of the 25 patients had undergone stem cell transplantations. *Streptococcus mitis* was the most common bloodstream isolate and only 12 (44%) of the 27 isolated strains of VS were penicillin-susceptible. Empirical antibiotic treatments were not effective in half of the episodes, but did not affect overall mortality. Isolated bacteremia (63%) and pneumonia (22%) were the two leading clinical presentations. Complications were recognized more frequently in patients with pneumonia. Hypotension and mechanical ventilation each developed in 8 patients (31%). The overall mortality rate was 23%.
Conclusions: Penicillin non-susceptible VS infection has emerged as a threat in children with hemato-oncological diseases, especially those with acute myeloid leukemia. *S. mitis* is the most common spp. of VS causing bacteremia in children and is associated with serious complications. The development of pneumonia resulted in clinical complications and higher mortality. Empirical antibiotic treatments with activity against the infecting strains did not reduce the overall mortality rate in this study.

Key words: Hematology; Neoplasms; Penicillins; Viridans streptococci

Introduction

Gram-positive bacteria have emerged as important pathogens of bloodstream infections in neutropenic patients with cancer over the last decade [1]. Alpha-hemolytic viridans streptococci (VS) are part of the commensal flora in human respiratory and gastrointestinal tracts [2], and are considered to be of low virulence because VS has rarely been reported in immunocompetent hosts. In contrast, since the first cases of VS bacteremia in neutropenic patients with cancer were described in 1978 [3,4], the isolation of these microorganisms has become more frequent in immunocompromised individuals.

Bloodstream infections with VS usually come with serious complications, such as endocarditis [2,5,6], toxic shock-like syndromes, adult respiratory distress syndrome, pneumonia [7,8], and meningitis [2,9]. Severe neutropenia, prophylactic antibiotic treatment, chemotherapy involving high doses of cytosine arabinoside, and the presence of oropharyngeal mucositis were the most frequent risk factors noted [8,10,11].

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VS were considered to be uniformly susceptible to beta (β)-lactams, macrolides, and tetracyclines in the past. However, their growing resistance to penicillin and the other β-lactam antimicrobial agents is increasingly being recognized as a matter of concern [8,10,12,13]. Recent trends of prophylaxis with quinolones or trimethoprim-sulfamethoxazole have been shown to be a risk factor for VS bacteremia [10,13,14]. Some data suggest that mortality due to VS bacteremia in the neutropenic host may be higher in patients not initially treated with vancomycin [11,15]. The emergence, as well as the spread of multidrug-resistant strains of VS, has complicated both the selection of empirical antibiotic therapies in neutropenic fever and the prevention of these infections.

Gram-positive bacteria account for 32% of bloodstream isolates from febrile neutropenic adults with hematological malignancies in Taiwan, and 4% of these are accounted for by VS [16]. The incidence of VS bacteremia was reported to be 6.5% in the febrile neutropenic episodes of children with malignancies [17]. However, the clinical course and complications associated with VS bacteremia in children have not been described in detail. This retrospective study aimed to investigate the clinical features, outcomes, and antibiotic susceptibilities of VS bloodstream infections in Taiwanese pediatric hemato-oncology patients.

Methods

Subjects and bacterial isolates

We reviewed all strains of VS isolated from the bloodstream of the pediatric population (defined as age ≤18 years) between January 1998 and December 2004 at the National Taiwan University Hospital (NTUH). This study focused on patients with hemato-oncological diseases. Demographic data of patients and the characteristics of their VS isolates, including results of routine susceptibility tests were analyzed. Drug susceptibilities of blood isolates of VS were assayed by the disk diffusion method (penicillin) and Etest (AB Biodisk, Solna, Sweden) [cefotaxime]. The National Committee for Clinical Laboratory Standards criteria recommended for viridans group streptococci were used to interpret susceptibilities [18].

Episodes of infection

All bloodstream isolates were judged as infections based on their clinical courses. Bacteremia was defined as "isolated bacteremia" (possibly catheter-related), if there were no obvious infectious foci and the blood specimen was sampled from the catheter. Catheter-related infections were diagnosed when catheter tip cultures revealed a confluent growth of bacteria identical to that of the bloodstream isolate. Pneumonia was defined as the presence of abnormalities in chest radiography, including obvious infiltration, patchy lesions or consolidations, with compatible clinical symptoms or signs. Meningoencephalitis was defined when VS was grown from the bloodstream or cerebrospinal fluid together with cerebrospinal fluid pleocytosis or on the new onset of central nervous system symptoms and signs. Patients with radiological evidence of intracranial hemorrhage or laboratory-confirmed etiologies of central nervous system infection with pathogens other than VS were excluded from the category of meningoencephalitis.

Statistical analysis

The association between VS bacteremia, and the various demographic and nominal variables was examined using the Fisher's exact tests and chi-squared tests with Yate's correction. A p value <0.05 was considered significant.

Results

Twenty six episodes of VS bacteremia were identified in 25 pediatric hemato-oncology patients (13 males and 12 females) whose median age was 8.6 years (range, 1.4-17.7 years) [Table 1]. The incidence rate of VS bacteremia was significantly higher in patients with acute myeloid leukemia (AML) when compared to other hemato-oncology patients (2.4% per hospitalization vs 0.4% per hospitalization, $p<0.001$), and most of the episodes (17/26, 65%) occurred within the first 12 months of disease. Seventeen of the 26 episodes (63%) were isolated bacteremia without recognizable clinical foci. Pneumonia was present in 22% of the cases and other infrequent manifestations, including meningoencephalitis, endocarditis, mastoiditis, and necrotizing fasciitis were also seen. Risk factor analysis (Table 2) showed that most patients received cytosine arabinoside-based chemotherapy [19] and had profound neutropenia (80%) for a median of 5 days before the day of blood culture. Eight patients (31%) received stem cell transplantations.

In total, 27 VS isolates were obtained from the 26 episodes of bloodstream infection, as 2 different spp. of VS — *Streptococcus oralis* and *Streptococcus salivarius* — were simultaneously isolated from the same febrile

Table 1. General characteristics of pediatric hemato-oncology patients (n = 25) with viridans streptococci (VS) bacteremia

Variable	No. of patients
Age	
<2 years	4
2-10 years	10
>10 years	11
Gender	
Male	13
Female	12
Underlying disease	
Acute lymphocytic leukemia	3
Acute myeloid leukemia	11
Lymphoma	4
Solid tumor	5
Others	2[b]
Clinical foci (no. [%])[a]	
Isolated bacteremia	17 (63)[c]
Pneumonia	6 (22)[d]
Others	4 (15)[e]

[a]A 17-year-old girl with acute myeloid (M3) leukemia had *Streptococcus mitis* pneumonia and endocarditis. A 1-year-10-month-old boy with acute myeloid (M5) leukemia had two episodes of VS sepsis caused by *Streptococcus oralis* and *Streptococcus uberis*, respectively during the study period.
[b]Severe aplastic anemia (1), juvenile myelomonocytic leukemia (1).
[c]Sepsis (2/17).
[d]Acute respiratory distress syndrome (1/6).
[e]Meningoencephalitis (1), endocarditis (1), mastoiditis (1), and necrotizing fasciitis (1).

episode of a 1-year, 7-month-old girl with hepatoblastoma. *Streptococcus mitis* was the most common bloodstream isolate (48%), followed by *S. oralis* (29%) [Table 3]. Penicillin susceptibility tests showed that 12 of the 27 isolates (44%) were susceptible, 4 (14%) intermediately susceptible, and 11 (42%) resistant to penicillin. Only 1 of the 15 penicillin non-susceptible isolates was susceptible to third-generation cephalosporins (cefotaxime Etest). However, although empirical antibiotic treatments were not effective in half of the episodes (13 susceptible cases vs 13 non-susceptible cases), the outcomes were not different from those who had received appropriate initial therapy (mortality: 3/13 cases each in the susceptible and non-susceptible groups; survived: 10/13 cases in each group, respectively; chi-squared test by Yate's correction, p=0.642).

Table 2. Predisposing risk factors of viridans streptococci bacteremia

Risk factor	No. of episodes (%) (n = 26)
Profound neutropenia[a]	21 (80)
Chemotherapy	21 (80)
High-dose cytosine arabinoside therapy[b]	11 (42)
Trimethoprim-sulfamethoxazole prophylaxis	12 (46)
Use of antacids or H_2 antagonist	5 (19)
Intravenous hyperalimentation	3 (11)
Stem cell transplantation	8 (31)

[a]Defined as total neutrophils <500/μL.
[b]Defined as either cytosine arabinoside 100 mg/m^2/dose for 7 doses or 1 g/m^2/dose for 8 doses according to the Taiwan Pediatric Oncology Group-AML-97A protocol [19].

Despite treatment with susceptible antibiotics, all patients had fever for a median duration of 9.5 days. Nevertheless, over half of the patients (57%) responded to antibiotic therapy and became afebrile before the resolution of neutropenia. Intensive care was warranted in 35% of the episodes (Table 4), and the median intensive care unit (ICU) stay was 8 days. About one-third (31%) of these children developed hypotension and required vasopressor therapy. Eight of the 26 episodes (31%) required mechanical ventilation. *S. mitis* was the most likely pathogen (90%) in the presence of obvious clinical foci (Table 5). Patients who developed pneumonia were more prone to respiratory failure requiring mechanical ventilation (5/6 had complications of respiratory failure, 83%) and hypotension (5/6, 83%). Acute respiratory failure and hypotension made clinical courses more complicated, as shown by higher rates of ICU admissions (83%) and a higher mortality (50%) among patients with pneumonia. There were 6 deaths in this study — 2 cases developed late complications of *Enterobacter cloacae* sepsis, 2 cases showed intracranial hemorrhage with acute hydrocephalus on image studies, and the other 2 deaths due to pulmonary hemorrhage were thought to have resulted from VS sepsis. The overall mortality was 23%.

Discussion

VS bacteremia has become a common problem in neutropenic adults with malignancies, and children are more prone to it than adults [2,7]. A retrospective study conducted at NTUH in 1999 had shown that VS bacteremia was responsible for 6.5% of all bacteremic episodes in hospitalized neutropenic children [17], which was lower than previously reported rates [20,21]. The median age of children in our study was 8.6 years (103 months), which was also older than the 50 and 88 months, respectively, that 2 other studies reported [22,23]. AML was the most common malignancy (11/25 patients). However, although the incidence of VS bacteremia during intensive chemotherapy for AML in children aged less than 10 years has been

Table 3. Penicillin susceptibility patterns among 27 bloodstream isolates of viridans streptococci

Streptococcus spp.	No. of isolates (%)	No. of fully resistant isolates	No. of intermediately resistant isolates
Streptococcus mitis	13 (48)	5	3
Streptococcus oralis	8 (29)	5	1
Streptococcus salivarius	3 (11)	0	0
Streptococcus sanguis	1 (4)	0	0
Streptococcus intermedius	1 (4)	0	0
Streptococcus uberis	1 (4)	1	0

Table 4. Clinical presentation of 26 bloodstream viridans streptococci infections

Clinical presentation	No. of episodes (%)	Median duration (days)
Fever	26 (100)	0-21 (9.5)
Antibiotic treatment	26 (100)	7-115 (16.5)
Hospitalization	26 (100)	11-115 (32.0)
Intensive care unit admission	9 (35)	1-68 (8.0)
Hypotension requiring vasopressor treatment	8 (31)	1-32 (3.0)
Oxygen treatment	12 (46)	1-115 (3.5)
Mechanical ventilation	8 (31)	1-115 (3.5)
Death	6 (23)	

reported to be as high as 71.8% [21], only 56% of the total patients in this study — including both patients with AML and non-AML hemato-oncological diseases — were aged less than 10 years old (6/11 AML and 8/14 non-AML patients).

Disruption of the mucosal barrier following chemotherapy is a significant risk factor for VS bloodstream infection, but it was hard to evaluate the severity of mucositis since this was a retrospective study conducted by chart review. All patients had indwelling central venous catheters, and 80% of them had chemotherapy-associated neutropenia for a median duration of 5 days. Other important risk factors, such as allogenic bone marrow transplantation, use of antacid or H_2 receptor antagonists, and prophylaxis with trimethoprim-sulfamethoxazole, were identified in 31%, 19%, and 46% of VS bloodstream infection episodes, respectively.

S. mitis and *S. oralis* comprised of 48% and 29% of the isolated VS spp., respectively. Moreover, *S. mitis* was found to be particularly associated with complicated courses. The resistance of VS to the various antimicrobial agents is also becoming a matter of growing concern [10-12,14,24]. Children are more likely to be colonized by penicillin-resistant VS than adults [25,26], and reports have indicated a significant association between repeated exposures to systemic antibiotics and the incidence of β-lactam-resistant bloodstream VS isolates [27,28]. It is hypothesized that children with cancer who require more frequent systemic antibiotics are more likely to be colonized and further infected by penicillin-resistant VS.

Penicillin susceptibility testing revealed that 12 (44%) of the 27 bloodstream VS isolates were susceptible, 11 (41%) were intermediate, and 4 (15%) were resistant. Only one of the 11 penicillin-intermediate VS spp. was susceptible to cefotaxime, although the VS isolates were still uniformly susceptible to vancomycin. The need for empirical vancomycin treatment in patients with febrile neutropenia has been widely disputed. In a retrospective review [29], mortality was found to be significantly higher when vancomycin was not included in the empirical antibiotic regimen while treating cancer patients with neutropenic bacteremia. Although as high as 50% of the bloodstream VS isolates in this study were not susceptible to empirical antibiotics, the overall mortality was not affected by the appropriateness of the initial empiric antimicrobial therapy. Nevertheless, this

Table 5. Manifestations of viridans streptococci infection by clinical foci

Variable/event	Isolated bacteremia (n = 17) No. (%)	Pneumonia (n = 6) No. (%)
Streptococcus mitis	7 (41)	5 (83)
Duration of fever (days [median])	0-12 (2)	1-3 (2)
Intensive care unit admission	3 (18)	5 (83)
Hypotension	2 (12)	5 (83)
Mechanical ventilation	2 (12)	5 (83)[a]
Mortality	2 (12)	3 (50)

[a]One patient developed acute respiratory distress syndrome that was treated with high-frequency oscillatory ventilation.

deduction is speculative and a well-designed, prospective study will be needed to better address this issue.

Previous studies showed that VS bloodstream infections incurred a complication rate in the range of 0-26% [2,7,24]. However, we found a much higher rate of complications (10/27, 37%). Pneumonia (6/10, 60%) was the leading complication, and adult respiratory distress syndrome, which was considered a characteristic complication of VS bacteremia, occurred in only one of the 6 pneumonia cases. Meningoencephalitis, endocarditis, mastoiditis, and necrotizing fasciitis, although rarely reported earlier, were recognized as complications in this series.

Nine children (35%) were admitted to the ICU due to hypotension, respiratory failure, or status epilepticus and pneumonia represented the major diagnosis in these, as hypotension (5/8, 63%) and respiratory failure warranting mechanical ventilation (5/8, 63%) occurred more frequently in such complicated VS bacteremia. Mortality was also higher in patients who developed pneumonia (50%). It is clear that even clinically stable patients with VS sepsis should be monitored for respiratory symptoms meticulously. Central nervous system complications of VS sepsis are rarely found in neutropenic patients [30]. Although acute neurological symptoms occurred concurrently in 4 cases with VS bloodstream infections, only 1 of them had VS-positive cerebrospinal fluid. The other 3 patients excluded from analysis for VS meningoencephalitis included 1 patient with concurrent herpes simplex virus type 1 central nervous system infection and 2 with intracranial hemorrhages.

In conclusion, VS are generally considered pathogens of low virulence, but can cause bloodstream infections in hemato-oncologic children with neutropenia. *S. mitis* infections and the development of pneumonia are associated with complicated clinical courses and higher mortalities. Penicillin non-susceptible VS strains are an emerging threat, and susceptible empirical antibiotic treatments did not reduce overall mortality.

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