Nosocomial bloodstream infections due to viridans streptococci in haematological and non-haematological patients: species distribution and antimicrobial resistance

Outi Lyytikäinen1*, Merja Rautio2,3, Petteri Carlson3,4, Veli-Jukka Anttila4, Risto Vuento5, Hannu Sarkkinen6, Anja Kostiala1, Marja-Liisa Väisänen2, Arja Kanervo2 and Petri Ruutu1 on behalf of the Hospital Infection Surveillance Team†

Departments of 1Infectious Disease Epidemiology and 2Microbiology, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki; 3Jorvi Hospital, Espoo; 4Helsinki University Central Hospital, Helsinki; 5Tampere University Hospital, Tampere; 6Päijät-Häme Central Hospital, Lahti, Finland

Received 9 December 2003; returned 13 January 2004; revised 2 February 2004; accepted 2 February 2004

Objectives: We studied the species distribution and antimicrobial susceptibility of viridans streptococci (VS) isolates causing nosocomial bloodstream infections (BSIs) in Finnish hospitals.

Patients and methods: Patients with nosocomial BSIs due to VS were identified through a hospital-wide prospective laboratory-based surveillance in two university and two regional hospitals during September 1998–August 2001. Isolates of VS were sent to the reference laboratory for species confirmation and antimicrobial susceptibility testing.

Results: A total of 2038 nosocomial BSIs were identified; 108 (5%) of the BSIs were caused by VS. Of the VS BSIs, 66% were in patients with a haematological malignancy, 14% in patients with a solid tumour and 18% in patients who had undergone surgery preceding the infection. The most common species group identified was Streptococcus mitis (82%). High-level penicillin resistance (≥4mg/L) and cefotaxime resistance (≥4mg/L) were present in 5% and 4% of isolates, respectively; both were detected only in haematological patients. However, in non-haematological patients, resistance to erythromycin (17%), and reduced susceptibility to levofloxacin (14%) and penicillin (19%) were common.

Conclusions: The resistance problems in VS are not limited to haematological patients. These findings may have significant clinical implications in the choice of both empirical antibiotic and antimicrobial prophylaxis regimens.

Keywords: epidemiology, surveillance, antibiotic resistance

Introduction

Viridans streptococci (VS) are prevalent in the normal flora of the upper respiratory tract, the female genital tract and all sections of the gastrointestinal tract.1 Nosocomial bloodstream infections (BSIs) caused by VS represent an increasingly important problem, particularly among patients with haematological malignancies.2 In the past, VS were considered to be uniformly susceptible to β-lactam antimicrobial agents, macrolides and tetracyclines. However, the emergence of strains resistant to β-lactams and other antibiotics is a cause of concern and could compromise currently used prophylactic and therapeutic antibiotic regimens.3,8 In addition, penicillin-resistant oral streptococci constitute the genetic reservoir for β-lactam resistance in Streptococcus pneumoniae.9,10

In the present study, we examined the species distribution and antimicrobial susceptibility of VS isolates obtained from patients with nosocomial BSIs identified through hospital-wide surveillance in four Finnish hospitals during September 1998–August 2001.
Methods

Hospitals

Four Finnish hospitals participated in the prospective hospital-wide laboratory-based surveillance on nosocomial BSIs: two university hospitals (both 1600 beds), one central hospital (600 beds) and one district hospital (450 beds).

Microbiological methods

Each participating laboratory detected growth in blood cultures, identified organisms and performed susceptibility testing according to the modified NCCLS methods standardized by the Finnish Study Group for Antibiotic Resistance. Blood isolates were stored in skimmed milk at −70 °C until further use.

Surveillance methods

Infection-control nurses in each hospital regularly reviewed the laboratory database for positive blood culture results. The CDC definition for nosocomial BSI was used.11 Multiple blood cultures yielding the same organism within one week were considered a single episode of BSI. Clinical information and microbiological data were recorded on a standardized case record form and sent monthly to the National Public Health Institute (KTL).

Case identification and bacterial isolates

All nosocomial BSI cases resulting from VS reported during September 1998–August 2001 were included in the study. All blood isolates of VS obtained from these cases were sent to the Department of Microbiology at the KTL for further testing.

Bacterial identification

Species and species groups of VS were identified by phenotypic characterization.1,12,13 In addition, the commercial test kit API Strep (BioMérieux, Marcy l’Étoile, France) was used.

Antimicrobial susceptibility

MICs were determined by an agar dilution technique, as recommended by the NCCLS, using Mueller–Hinton agar supplemented with 5% (v/v) sheep blood for penicillin, cefotaxime, erythromycin, clindamycin, vancomycin, levofloxacin and telithromycin.14 Plates were incubated in a 5% CO₂ atmosphere for 20–24 h at 35 °C.

Statistical analysis

Univariate analysis of categorical variables was conducted with the χ² test with Yates’ correction or Fisher’s exact test, as appropriate.

Results

A total of 2038 nosocomial BSIs were identified; 108 (5%) of the BSIs were caused by VS. The median age of the patients was 50 years (range, 0–87), and 61 (57%) were male. Predisposing factors included haematological malignancy (66%), surgery (18%), solid tumour (14%), intensive care (8%), haemodialysis (5%), newborn status (5%), delivery (2%) and organ transplantation (1%).

VS isolates were further identified to species groups: mitis group (n = 89), anginosus group (n = 10), and salivarius group (n = 9). Mitis-group isolates were more likely to be found in haematological patients than in non-haematological patients (90% versus 68%, P < 0.01), whereas anginosus-group isolates were seen more frequently in non-haematological patients (24% versus 1%, P < 0.01). Salivarius-group isolates were equally common in haematological and non-haematological patients (9% versus 8%).

The activities of the various antimicrobial agents are summarized in Table 1. High-level penicillin resistance (MIC of ≥4mg/L) was found in five isolates (5%); all belonged to the mitis group. Intermediate penicillin resistance was noted in 26 isolates (24%; mitis group, n = 21; salivarius group, n = 5). A high level of cefotaxime resistance (MIC of ≥4mg/L) was found in four isolates (4%); all belonged to the mitis group. Intermediate cefotaxime resistance was noted in four isolates (4%; mitis group, n = 4). Of the 31 strains, which were intermediate or fully resistant to penicillin, 68% were also resistant to at least one other antimicrobial (13% resistant to cefotaxime, 52% resistant to erythromycin, 6% to both cefotaxime and erythromycin and 6% resistant to clindamycin). The isolates with reduced susceptibility to levofloxacin were mostly found among isolates susceptible to β-lactam agents (82%, 14/17). Of the 29 erythromycin-resistant strains, two (7%) were resistant to clindamycin, five (17%) had telithromycin MIC values of ≥0.5 mg/L and six (21%) had reduced susceptibility to levofloxacin. Among the five strains in the salivarius group with reduced susceptibility to penicillin, one strain was resistant.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (mg/L)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>MIC range (mg/L)</th>
<th>% Resistant (breakpoint)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0.06</td>
<td>1</td>
<td>&lt;0.03–4</td>
<td>5 (≥4)</td>
<td>71</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.125</td>
<td>1</td>
<td>&lt;0.03–4</td>
<td>4 (≥4)</td>
<td>93</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.125</td>
<td>8</td>
<td>&lt;0.03–32</td>
<td>27 (≥1)</td>
<td>73</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.06</td>
<td>0.125</td>
<td>&lt;0.03–32</td>
<td>2 (≥1)</td>
<td>98</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.5</td>
<td>0.5</td>
<td>&lt;0.03–1</td>
<td>0 (&gt;1)</td>
<td>100</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2</td>
<td>4</td>
<td>&lt;0.5–4</td>
<td>0 (≥8)</td>
<td>84</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>&lt;0.03</td>
<td>0.25</td>
<td>&lt;0.03–2</td>
<td>No breakpoint available</td>
<td>No breakpoint available</td>
</tr>
</tbody>
</table>

<sup>a</sup>MIC breakpoints for resistance are those defined by the NCCLS in 2002 for susceptibility testing of VS to all agents except those for which no breakpoints have been established.

Table 1. In vitro activities of selected antimicrobial agents against VS isolated from patients with 108 nosocomial bloodstream infections resulting from VS
to erythromycin and clindamycin. All 10 strains in the angiosus group were susceptible to all antimicrobial agents tested.

Overall, the antibiotic resistance was detected mostly in haematological patients (Table 2). However, resistance to erythromycin, and reduced susceptibility to penicillin and levofloxacin were also common in non-haematological patients.

### Discussion

Our results indicate that resistance to β-lactam agents among our haematological patients was higher than that reported in neutropenic cancer patients in Germany, but lower than in Spain and the USA. The results on resistance to erythromycin are similar to those reported previously from Europe and the USA. Among strains with intermediate and high-level resistance to penicillin, resistance to other antimicrobial agents, especially erythromycin, was common, as in the USA. Even though we did not observe strains resistant to levofloxacin, reduced susceptibility to levofloxacin was common, particularly in strains susceptible to β-lactam agents. We also noted a higher prevalence of resistance among Streptococcus mitis group isolates than among the other species of VS examined, as reported previously.

In a nationwide German multicentre study (1996–1999), Reinert et al. evaluated 156 episodes of bacteraemic streptococcal infections in neutropenic patients. No resistance to penicillin was observed among 14 strains of S. mitis, or among 41 strains of Streptococcus oralis. Resistance to erythromycin varied between 21%–29% by species. Carratala et al. studied 23 episodes of BSIs caused by VS in neutropenic cancer patients in one Spanish hospital during 1987–1992. Thirteen of 23 episodes (57%) were caused by penicillin-resistant VS strains (MIC range, 0.25–8 mg/L) and 10 of the penicillin-resistant strains were highly resistant to penicillin (43%). Rates of resistance to cephalosporins varied between 14%–53%. In the most recent study from Spain by Alcaide et al., among 77 strains of VS isolated from blood samples of neutropenic patients with cancer, 40% were resistant to penicillin and 35% to erythromycin.

Among 352 blood-culture isolates of VS from 43 USA medical centres during 1993–1994, 13% exhibited high-level penicillin resistance and 43% had intermediate resistance to penicillin; high-level penicillin resistance was more common among strains of S. mitis (16%) and Streptococcus salivarius (17%) than among Streptococcus milleri strains (2%). Furthermore, 20% of strains were resistant to cefuroxime, 17% were resistant to ceftriaxone and >33% were resistant to erythromycin. During 1994–1996, Pfaller et al. examined the species distribution and antimicrobial susceptibility profile of 295 streptococcal nosocomial bloodstream isolates at more than 30 USA medical centres. These authors reported 9% of VS to be resistant to penicillin. The most commonly identified species were S. mitis and Streptococcus sanguis. Importantly, 69% of the penicillin-intermediate and -resistant strains of VS were also resistant to at least one additional agent (31% resistant to ceftriaxone, 51% resistant to erythromycin and 15% resistant to both ceftriaxone and erythromycin). The results are in line with our findings as well as those reported previously by Doern et al. Diekema et al. examined the in vitro activity of 62 bloodstream and other sterile site isolates of VS from 10 cancer treatment hospitals in the USA. Resistance to penicillin and levofloxacin was 11% and 3.2%, respectively.

β-Lactam-resistant strains of VS are particularly prevalent in countries with a high incidence of penicillin-resistant pneumococci, such as Spain. Southern European countries have higher proportions of penicillin-non-susceptible S. pneumoniae than in Northern Europe, and resistance to penicillin correlated with outpatient sales of β-lactams and macrolides. In Finland, the incidence of penicillin-resistant pneumococci is still low, but increasing resistance to macrolides in pneumococci is of concern. Compared with other European countries, antibiotic use in Finland is not low, but moderate, and the use of macrolides and quinolones is higher than in other Northern European countries [H. Goossens, University of Antwerp, Belgium, personal communication; European Surveillance on Antimicrobial Consumption (ESAC), http://www.uu.ac.be/ESAC]. In a recent Finnish study on antimicrobial susceptibility patterns of VS from normal oral flora of elderly persons, no high-level penicillin resistance was found. However, reduced susceptibility to penicillin was 17%, and resistance to erythromycin and levofloxacin was 22% and 2%, respectively.

The results of the current investigation suggest that emergence of resistance in VS is taking place in Finland, which is in general considered to be a country with a low prevalence of antimicrobial resistance. Our findings also show that the choices for both antimicrobial prophylaxis and empirical antibiotic regimens are becoming limited. Critical use of antibiotics is essential in controlling the increasing resistance of microorganisms, including VS.

### Acknowledgements


The idea for the current study came from Professor Hannele Jousimies-Somer who died during the implementation of the study, and is therefore not a named author.
References


6. Diekema, D. J., Jones, R. N. & Rolston, K. V. I. (1999). Antimicrobial activity of gatifloxacin compared to seven other compounds tested against gram-positive organisms isolated at 10 cancer-treatment centers. Diagnostic Microbiology and Infectious Disease 34, 37–43.


