PERGAMON

European Journal of Cancer 39 (2003) 1284–1289

European Journal of Cancer

www.ejconline.com

Viridans streptococci bacteraemia in children with fever and neutropenia: a case–control study of predisposing factors

H. Paganini[a,*], V Staffolani[a], P. Zubizarreta[b], L. Casimir[c], H. Lopardo[c], V. Luppino[a]

[a]*Department of Infectious Diseases, Hospital de Pediatría Profesor Dr. Juan P. Garrahan, Buenos Aires, Argentina*
[b]*Department of Hemato-oncology, Hospital de Pediatría Profesor Dr. Juan P. Garrahan, Buenos Aires, Argentina*
[c]*Department of Microbiology, Hospital de Pediatría Profesor Dr. Juan P. Garrahan, Buenos Aires, Argentina*

Received 15 July 2002; received in revised form 2 January 2003; accepted 14 March 2003

Abstract

Viridans streptococci (VS) are an increasing cause of bacteraemia in neutropenic patients with cancer. Case–control studies of predisposing factors for acquisition of this infection in children are not published. Between January 1989 and December 1999, 168 episodes of bacteraemia in 161 children with fever and neutropenia of haemato-oncology origin were analysed. 15 cases (9%) in 15 patients were caused by VS. Each case patient was compared with 6 matched control patients; 2 with other Gram-positive cocci (group 2), 2 with gram-negative bacilli bacteraemia (group 3) and two children with fever and neutropenia without bacteraemia (group 4). The median age of patients was 4.1 years (range: 2–15 years). 87% of children had acute leukaemia or lymphomas. Pneumonia was the predominant clinical focus (70%). Shock was observed in 13% of patients. ARDS was observed in one child who died of this complication. Multivariate analysis of risk factors for the development of VS bacteraemia showed that two factors were independent predictors: high doses of cytosine-arabinoside (ARA-C) as part of the chemotherapy treatment (Odds Ratio (OR): 9.3; Confidence Interval (CI) 1.56–55.5) ($P < 0.014$) and the presence of pneumonia (OR: 1.36: CI 2.27–81.9) ($P < 0.0043$). We propose that further studies are warranted to confirm these results.

Keywords: *Viridans streptococci*; Bacteraemia; Children; Cancer; Predisposing factors

1. Introduction

The *Viridans streptococci* (VS) species encompass a heterogeneous group of atypical streptococci and are part of the physiological flora of the oropharyngeal and genital regions [1].

Most infections caused by these microorganisms have been associated with a low morbidity [2]. However, endocarditis in patients with valvular abnormalities and bacteraemia in children with cancer are associated with a high mortality rate [2–4].

VS species are an increasing cause of bacteraemia in neutropenic patients with cancer and following bone marrow transplantation [5,6]. Several predisposing risk factors of bacteraemia have been observed. Severe neutropenia, prophylactic antibiotic treatment with co-trimoxazole or quinolones, chemotherapy involving high doses of cytosine-arabinoside (ARA-C), the presence of oropharyngeal mucositis and strong colonisation of patients were the most frequent risk factors observed [5–11]. Previous studies have included adult patients. Studies including paediatric patients are scarce and there are no studies with a case–control design methodology [4,12–15].

We report the results of a retrospective case–control study identifying factors that predispose febrile neutropenic children with cancer to VS species bacteraemia.

2. Patients and methods

We reviewed the episodes of VS bacteraemia that occurred in febrile neutropenic children with cancer from January 1989 to December 1999, who were hospitalised at the Hospital de Pediatría 'Profesor Dr. Juan P. Garrahan' in Buenos Aires, Argentina. This hospital

* Corresponding author at: Mariano Moreno 2080, (1636) Olivos, Buenos Aires, Argentina. Fax: +54-11-308-5325.
E-mail address: hpaganini@intramed.net.ar (H. Paganini).

0959-8049/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0959-8049(03)00272-7

is a 550-bed tertiary care paediatric centre, with special assistance for onco-haematology patients and solid-organ recipients, as well as children undergoing cardiac surgery or neurosurgery.

A case of VS bacteraemia was defined when a culture of the same VS species was obtained from two or more samples of blood taken within a 48-h period or when one positive blood culture was obtained together with clinical signs of sepsis. Children aged less than 18 years old with neutropenia after chemotherapy for malignant disease and an absolute neutrophil count (ANC) <500 10^6 cells/l or <1000 10^6 cells/l, with a predicted decline to $\leqslant 500$ 10^6 cells/l, plus one episode of fever with a temperature of more than 38.5 °C taken axillary or two records higher than 38 °C within 24 h were included. Severe neutropenia was defined as less than 100 neutrophils$\times 10^6$ cells/l of blood. Cases with polymicrobial bacteraemia, defined as the presence of more than one organism in the blood culture, were excluded.

For each case patient (group 1), 6 control patients were selected. These controls were selected randomly from a group of children who developed bacteraemia during the study period. Data were collected from a pre-existing database. Controls were randomly selected to achieve equivalent and comparable samples. The selection of three control groups was decided upon as different factors favour bacteraemia according to the microorganism involved. Bacteraemias caused by Gram-negative microorganisms are associated with different predisposing factors from those caused by Gram-positive bacteria. Cases without bacteraemia served as comparisons with the other groups of bacteraemic patients. Two children (per case) with bacteraemia involving other aerobic Gram-positive bacteria, except coagulase-negative staphylococcal bacteraemia, were entered into group 2. These patients were excluded because most of these infections were expected to be related to central venous catheters. 2 patients with bacteraemia caused by Gram-negative bacilli (per case) were entered into group 3 and two children with febrile neutropenia without bacteraemia (per case) were entered into group 4. Children who had undergone a bone marrow transplantation were excluded from the analysis.

All isolated organisms were identified according to standard methods described in Ref. [16] and their susceptibility was assessed by disk diffusion according to the criteria of the National Committee for Clinical Laboratory Standards (NCCLS) [17].

Adult respiratory distress syndrome (ARDS) was defined as the occurrence of tachypnoea (respiratory rate >60/min), arterial hypoxoemia (arterial oxygen pressure <60 mm Hg), and bilateral pulmonary infiltrates. Pneumonia was defined as an acute illness associated with $\geqslant 1$ of the following respiratory signs and symptoms: new cough with or without sputum production, pleuritic chest pain, dyspnoea, fever or hypothermia, abnormal breath sounds on auscultation, and the presence of a new infiltrate on a chest radiograph. Shock was defined as a systolic pressure lower than the 5th percentile and oliguria. Sinusitis was defined by clinical and radiographic signs. Diarrhoea was defined as several daily loose stools that persisted for more than 3 consecutive days. Oral mucositis was defined as generalised inflammation plus ulceration of the oropharyngeal mucosa persisting for more than 3 consecutive days. Catheter-related infections were defined based on Guidelines for the management of intravascular catheter-related infections [18]. No children received fluoroquinolones or cotrimoxazole prophylaxis during the study period. High doses of ARA-C ranged between 100 mg/m^2 every 12 h for 8 days and 2 g/m^2 every 12 h for 2 days. Use of haemopoietic growth factors was decided upon after 1992 by the attending oncologist and after 1994 according to the guidelines of the American Society of Clinical Oncology (ASCO) [19].

Peripheral blood and urine cultures, as well as a chest X-ray were taken for all patients at admission. Blood samples from port-catheters and from the peripheral veins for quantitative differential cultures were also taken in all cases. When skin and soft tissue infections, diarrhoea, pharyngitis or any infection was suspected, cultures of the involved source were obtained. The following investigations were done for each case of pneumonia: (1) Blood cultures, (2) direct immunofluorescence in respiratory secretions for respiratory syncytial virus (RSV), influenza virus, para-influenza virus and adenovirus, enzyme-linked immunosorbent assay (ELISA) in respiratory secretions for *Mycoplasma pneumoniae*. Whenever a bronchoalveolar lavage (BAL) or a tracheal aspiration sample was available, *Pneumocystis carinii* was ruled out by histopathological-specific stains.

All children under study were managed as inpatients of the hospital.

Between 1989 and 1991, the initial empirical antibiotic therapy for children with febrile neutropenia was piperacillin and amikacin. Between 1992 and 1995, the therapy was changed to ceftazidime and amikacin. After 1995, patients were categorised by risk. Low-risk patients received ceftriaxone and amikacin, and high-risk children received ceftazidime and then imipenem or meropenem together with amikacin.

The risk factors analysed in this study were gender, age, haemato-oncological underlying disease, type and dose of chemotherapy, previous antibiotic treatment, previous use of granulocyte-colony stimulating factor (G-CSF) and histamine type 2 antagonists, long duration of catheter use, duration of neutropenia, presence of mucositis and type of clinical foci.

Statistical analysis was performed using multivariate and multivariable methods. Risk was expressed as relative risk, and statistical significance was established using P values and 95% Confidence Intervals (CI). Chi-square

and Fisher tests were used for nominal variables, and Student's *t*-test for numerical variables. Significance level was set at 0.05. Multivariate analysis was performed using logistic regression (forward stepwise method). The software used was Complete Statistical System (CSS)/Statistica, 5.1 (Startsoft Corp., Tulsa, OK, USA).

3. Results

Between January 1989 and December 1999, 168 episodes of bacteraemia in 161 children with fever and neutropenia after chemotherapy were analysed. *Staphylococcus aureus* (26), Coagulase-negative staphylococci (24), *Escherichia coli* (20), Gram-negative bacilli of unknown type (15), *Klebsiella pneumoniae* (12) and *Pseudomonas aeruginosa* (12) were the most frequently isolated pathogens. Fifteen episodes in 15 patients (9%) were caused by VS. All of the isolates were speciated. The most common *S. viridans* was *Streptococcus mitis* (70%). 35% of all isolated *S. viridans* were resistant to penicillin.

Characteristics of patients with VS bacteraemia are given in Table 1. The median age was 4.1 years (range: 2–15 years). 87% of children had acute leukaemia or lymphomas. Nine children received high doses (HD) of ARA-C as part of their chemotherapy treatment. 9 cases (60%) had bone marrow disease involvement. Eleven episodes occurred in children treated for acute myeloblastic leukaemia or acute lymphoblastic leukaemia. Eight (53%) episodes resulted in more than 10 days of neutropenia, and 10 (67%) had severe mucositis. One child had a maculo-papular rash and 3 patients (20%) had diarrhoea. Shock was observed in two children and ARDS in one patient. Pneumonia was the predominant clinical focus (70%). Only one child had sinusitis. The median duration of fever and neutropenia in children with VS bacteraemia were 4 and 8 days, respectively. One child died (7%). The cause of death was ARDS.

Table 1
General characteristics of neutropenic children with cancer who experienced fever and bacteraemia due to *Viridans streptococci* (VS)

Variable	Value
Median age in years (range)	4.1 (2–15)
<2 years	2
2–10 years	12
>10 years	1
Gender (male/female)	7/8
Acute lymphoblastic leukemia	6
Acute myeloblastic leukemia	5
Lymphomas	2
Solid tumors	2
Clinical foci n (%)[a]	10 (67)
• Pneumonia	7
• Cellulites	2
• Sinusitis	1
• Catheter-related bacteraemia	1
Median duration of fever in days (range)	4 (1–11)
Median duration of neutropenia in days (range)	8 (2–25)
Deaths *n* (%)	1 (7)

[a] One child had two clinical foci.

The characteristics of the VS cases (group 1) versus children with other Gram-positive cocci bacteraemia (group 2) are given in Table 2. The proportion of case patients with acute leukemia or lymphomas was higher than that of control patients ($P<0.05$). Case patients presented more episodes of pneumonia ($P=0.056$). In addition, case patients had more severe mucositis and received high doses of ARA-C and histamine type 2 antagonists more often than the controls patients did ($P<0.05$).

When the comparison was made between cases and children with Gram-negative bacilli bacteraemia (group 3), only the presence of pneumonia and severe mucositis were statistically significant predisposing risk factors for developing bacteraemia ($P<0.05$) (Table 3).

Table 4 shows the comparison between cases and patients without bacteraemia (group 4). Children with VS bacteraemia had a higher proportion of patients aged less than 2 years, with acute leukaemia or lymphoma and ANC $<100\ 10^6$ cells/l than controls ($P<0.05$). The cases received high doses of ARA-C more often than the control patients ($P<0.05$). The presence of pneumonia, long duration of catheter use, use of granulocyte colony-stimulating factor (G-CSF) and G-CSF and broad spectrum ATB were also significantly higher among the cases ($P<0.05$).

No statistical differences in the duration of neutropenia between cases (group 1, median: 8 days) and controls (groups 2 and 3) were observed (medians in days: 7 and 8.5, respectively) ($P>0.05$). Conversely, statistically significant differences were observed between cases (median: 8 days) and children without bacteraemia (median: 4.5 days) ($P<0.05$).

Multivariate analysis of risk factors showed that two factors were independent predictors for the development of VS bacteraemia: high doses of ARA-C as part of the chemotherapy treatment (odds ratio (OR): 9.3; CI 1.56–55.5) ($P<0.014$) and the presence of pneumonia (OR: 1.36; CI 2.27–81.9) ($P<0.0043$).

4. Discussion

VS bacteraemia has become a common problem in neutropenic adults with cancer with an incidence rate ranging from 14 to 30% [6,9,11], and a mortality rate of 10–15% [5,7,8]. In our institution, VS was responsible for 9% of all bacteraemic episodes in neutropenic children hospitalised from 1989 to 1999. This rate was lower than those reported by Weisman and colleagues and by

Table 2
Univariate analysis of predisposing factors for bacteraemia between cases with *Viridans streptococci* and controls with other Gram-positive cocci in their blood cultures

Variable	Cases	Controls	RR	(95% CI)	*P* value
	Group 1 *S. viridans* ($n=15$)	Group 2 Gram (+) cocci ($n=30$)			
Median age in years	4.1	4.2			NS
Age less than 2 years n (%)	2 (13)	5 (17)	0.84	(0.24–2.92)	NS
Male gender *n* (%)	7 (47)	15 (50)	0.84	(0.40–2.1)	NS
Acute leukemia/lymphoma *n* (%)	13 (87)	15 (50)	3.95	(1.01–15.3)	0.017
ANC $<100\ 10^6$ cells/l	6 (40)	8 (27)	0.83	(0.36–1.9)	NS
High doses of ARA-C *n* (%)	10 (67)	4 (13)	4.15	(1.75–9.8)	0.001
Previous broad spectrum ATB treatment *n* (%)	8 (53)	9 (30)	1.88	(0.83–4.26)	NS
Histamine type H2 antagonists *n* (%)	5 (33)	1 (3)	3.25	(1.71–6.17)	0.012
Pneumonia *n* (%)	7 (47)	6 (20)	2.87	(0.92–8.93)	0.056
Severe mucositis *n* (%)	10 (67)	9 (30)	2.74	(1.12–6.7)	0.019
Long-duration of catheter use *n* (%)	9 (60)	12 (40)	1.72	(0.73–4.02)	NS
G-CSF *n* (%)	2 (13)	6 (20)	0.71	(0.2–2.55)	NS
Median duration of neutropenia in days	8	7			0.48

ANC, absolute neutrophil count; ARA-C, cytosine-arabinoside; ATB, antibiotic; G-CSF, granulocyte-colony stimulating factor; RR,relative risk; 95% CI, 95% Confidence Interval; NS, non-significant.

Table 3
Univariate analysis of predisposing factors for bacteraemia between cases with *Viridans streptococci* and controls with Gram-negative bacilli positive in their blood cultures

Variable	Cases	Controls	RR	95% CI	*P* value
	Group 1 *S. viridans* ($n=15$)	Group 3 *Gram (−) bacilli* ($n=30$)			
Median age in years	4.1	4.6			NS
Age less than 2 years *n* (%)	2 (13)	6 (20)	0.71	(0.19–2.5)	NS
Male gender *n* (%)	7 (47)	13 (43)	1.09	(0.48–2.5)	NS
Acute leukaemia/lymphoma *n* (%)	13 (87)	22 (73)	1.86	(0.5–6.9)	NS
ANC $<100\ 10^6$ cells/l	6 (40)	8 (27)	0.91	(0.39–2.1)	NS
High doses of ARA-C *n* (%)	10 (67)	11 (37)	2.19	(0.89–5.38)	NS
Histamine type 2 antagonists *n* (%)	5 (33)	8 (27)	1.23	(0.52–2.91)	NS
Previous broad spectrum ATB treatment *n* (%)	8 (53)	12 (40)	1.43	(0.63–3.27)	NS
Pneumonia *n* (%)	7 (47)	2 (7)	4.4	(1.49–12.9)	0.005
Severe mucositis *n* (%)	10 (67)	8 (27)	3	(1.23–7.30)	0.01
Long-duration of catheter use *n* (%)	9 (60)	22 (73)	0.68	(0.30–1.53)	NS
G-CSF *n* (%)	2 (13)	3 (10)	1.23	(0.39–3.94)	NS
Median duration of neutropenia in days	8	8.5			0.90

ANC, absolute neutrophil count; ARA-C, cytosine-arabinoside; ATB, antibiotic; G-CSF, granulocyte-colony stimulating factor.

Table 4
Univariate analysis of predisposing factors for bacteraemia between cases with *Viridans streptococi* and controls without bacteraemia

Variable	Cases	Controls	RR	(95% CI)	*P* value
	Group 1 *S. viridans* ($n=15$)	Group 4 *No bacteraemia* ($n=30$)			
Median age in years	4.1	5.5			NS
Age less than 2 years *n* (%)	2 (13)	0	3.3	(2.1–5.2)	0.01
Male gender *n* (%)	7 (47)	11 (77)	1.31	(0.58–2.99)	NS
Acute leukaemia/lymphoma *n* (%)	13 (87)	12 (40)	5.2	(1.33–20.4)	0.003
ANC $<100\ 10^6$ cels/l	6 (40)	7 (23)	4.1	(1.87–9.09)	0.001
High doses of ARA-C *n* (%)	10 (67)	6 (20)	3.5	(1.45–8.47)	0.003
Histamine type 2 antagonists *n* (%)	5 (33)	13 (43)	0.75	(0.31–1.83)	NS
Previous broad spectrum ATB treatment *n* (%)	8 (53)	2 (7)	4	(1.92–8.33)	0.001
Pneumonia *n* (%)	7 (47)	2 (7)	5.18	(1.73–15.6)	0.002
Severe mucositis *n* (%)	10 (67)	15 (50)	1.6	(0.65–3.92)	NS
Long-duration of catheter use *n* (%)	9 (60)	9 (30)	2.25	(0.97–5.24)	0.05
G-CSF *n* (%)	2 (13)	17 (57)	0.21	(0.05–0.8)	0.006
Median duration of neutropenia in days	8	4.5			0.01

ANC, absolute neutrophil count; ARA-C, cytosine-arabinoside; ATB, antibiotic; G-CSF, granulocyte-colony stimulating factor.

Valteau and colleagues in children who had undergone bone marrow transplantation procedures [14,15].

The median age of children in our study was 50 months, which was less than the 88 months published by Valteau and colleagues in Ref. [14]. Conversely, Gamis and colleagues recently reported a high incidence of VS bacteraemia in children aged less than 2 years old during intensive treatment for acute myeloid leukaemia [12]. Only 13% of our patients were aged less than 2 years. In our series, 13 and 7% of children had shock and ARDS, respectively, a rate similar to that reported in adults and children [4,5].

The mortality rate of VS bacteraemia in adults and children with cancer patients ranges from 6 to 30% [4,5,9,14]. It has been associated with the presence of respiratory complications and shock. In our study, one child died of ARDS.

Several series of VS bacteraemia observed in neutropenic children with cancer were the subject of publications described in Refs. [3,4,14,15,20], but none of these studies included a case–control study design. Case–control studies of predisposing factors for VS bacteraemia have been carried out in adult patients [6,7] comparing patients with VS bacteraemia with patients without bacteraemia gram-positive cocci different from VS. Only one study has compared VS bacteraemia patients with Gram-negative bacilli bacteraemia [21].

Severe neutropenia, the presence of oropharyngeal mucositis, prophylactic antibiotic treatment with co-trimoxazole or quinolones, histamine type 2 antagonists, chemotherapy involving high doses of ARA-C, and strong colonisation of patients were the most frequent predisposing risk factors observed from studies in the literature [5–11].

Elting and colleagues demonstrated that in VS bacteraemia severe neutropenia occurred in 87% of adult cases versus 20% of controls [7]. This was confirmed by other studies [5,14]. However, other published series established that bacteraemia can occur in patients whose neutropenia is less severe, similar to the results in our series.

Several authors have suggested that oral mucositis is the most likely portal of VS entry [6–8,11]. In 1995, Richard and colleagues, using genotypic methods, showed that VS colonising the oral cavity of neutropenic patients with oral mucositis were indistinguishable from those isolated from blood cultures [22]. Mucositis may be a consequence of chemotherapeutic treatments including ARA-C. Oral mucositis breaks down the natural defence of the epithelium, helping to expose the patient to infection. In our series, oropharyngeal lesions were significantly more frequent in cases than in children with Gram-positive cocci infections or those without bacteraemia.

Antibiotic prophylaxis is also thought to play a role in the development of VS bacteraemia. Co-trimoxazole and fluoroquinolones are the most frequent antibiotics administered [5,21]. However, our patients received no antibiotic prophylaxis.

Elting and colleagues demonstrated an increasing incidence of VS septicaemia in their centre paralleling the increasing use of histamine type 2 antagonists [7]. The use of these drugs decreases gastric acidity, which is a natural barrier against bacteria. In our series, children with VS received histamine type 2 antagonists more often than patients with Gram-positive cocci bacteraemia.

Although VS are often isolated from respiratory tract specimens, they are rarely ascribed clinical significance. Marrie and colleagues described bacteraemia VS pneumonia associated with predisposing host factors (i.e. older patients, alcoholism, lung carcinoma and diabetes mellitus) [23]. Sotiropoulos and colleagues reported pneumonia in 20% of children with leukaemia and with alpha-streptococcal septicaemia [4]. The causes of respiratory complications in febrile neutropenic patients with VS bacteraemia have not been clearly elucidated. The pulmonary toxicity of ARA-C and the polymorphonuclear leucocytes have been evoked [24]. ARDS is produced by a neutrophil-mediated mechanism, whereas pneumonia is due to a direct bacterial invasion of lung tissue by VS. In our multivariate analysis, the presence of pneumonia was one of the most important risk factors for the development of VS bacteraemia.

Children with VS bacteraemia received high doses of ARA-C significantly more often in the multivariate analysis. This confirmed the results of previous studies [4,25,26]. This finding suggests that high doses of ARA-C may play a role in the development of VS bacteraemia. High-dose ARA-C regimens are used in the treatment of leukaemias and lymphomas and are highly myelotoxic, inducing prolonged and severe neutropenia. Our patients were predominantly treated with high doses of ARA-C in the context of induction therapy for acute leukaemia which further enhances the duration of neutropenia due to bone marrow invasion and favours the development of concomitant severe mucositis after the associated administration of anthracyclines. We tested high dose ARA-C as a risk factor for VS bacteraemia following the evidence reported in Ref. [26]. However, perhaps the real underlying risk factor for VS bacteraemia is severe mucositis in the context of prolonged episodes of neutropenia.

The need for initial vancomycin and teicoplanin in the empirical treatment of fever and neutropenia has been widely debated [27]. Recently, Bruckner and co-workers [20] analysed 38 VS isolates in 33 children with cancer and revealed only 21% of strains were penicillin-susceptible and highly resistant to third generation cephalosporins. These data were confirmed by others [28]. Based on our data, where the VS resistance rate reached 35%, vancomycin or teicoplanin should be considered

as the empirical primary treatment in children with fever and neutropenia, who are seriously ill or who are suspected of having a VS bacteraemia (high doses of ARA-C and pneumonia). To confirm this recommendation, further studies are warranted.

In conclusion, our study has identified the use of high doses of ARA-C and the presence of pneumonia as risk factors for the development of VS bacteraemia in children with fever and neutropenia undergoing therapy for cancer.

References

1. Frandsen EV, Pedrazzoli V, Kilian M. Ecology of viridans streptococci in the oral cavity and pharynx. *Oral Microbiol Immunol* 1991, **6**, 129–133.
2. Facklam RR. Physiological differentiation of viridans streptococci. *J Clin Microbiol* 1977, **5**, 184–201.
3. Pizzo PA, Ladish S, Witebsky FG. Alpha-hemolytic streptococci: clinical significance in the cancer patient. *Med Pediatr Oncol* 1978, **4**, 367–370.
4. Sotiropoulos SV, Jackson MA, Woods GM, Hicks RA, Cullen J, Freeman AI. Alpha-streptococcal septicemia in leukemic children treated with continuous or large dosage intermittent cytosine arabinoside. *Pediatr Infect Dis J* 1989, **8**, 755–758.
5. Bochud PY, Calandra T, Francioli P. Bacteremia due to viridans streptococci in neutropenic patiets: a review. *Am J Med* 1994, **97**, 256–264.
6. Bochud PY, Eggiman P, Calandra T, Van Melle G, Saghafi L, Francioli P. Bacteremia due to viridans streptococcus in neutropenic patients with cancer: clinical sprectrum and risk factors. *Clin Infect Dis* 1994, **18**, 25–31.
7. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis* 1992, **14**, 1201–1207.
8. Cohen J, Donnely JP, Worsley AM, Catovsky D, Goldman JM, Galton DA. Septicemia caused by viridans streptococci in neutropenic patients with leukemia. *Lancet* 1983, **2**, 1452–1454.
9. Menichetti F, Del Favero A, Guerciolini R, *et al*. Viridans streptococci septicemia in cancer patients: a clinical study. *Eur J Epidemiol* 1987, **3**, 316–318.
10. Villablanca JG, Steiner M, Kersey J, *et al*. The clinical spectrum of infections with viridans streptococci in bone marrow transplant patients. *Bone Marrow Transplant* 1990, **5**, 387–393.
11. Burden AD, Oppenheim BA, Crowther D, *et al*. Viridans streptococcal bacteraemia in patients with haematological and solid malignancy. *Eur J Cancer* 1991, **27**, 409–411.
12. Gamis AS, Howells WB, DeSwarte-Wallace J, Feusner JH, Buckley JD, Woods WG. Alpha hemolytic streptococcal infection during intensive treatment for acute myeloid leukemia: a report from the children's cancer group study CCG-2891l. *J Clin Oncol* 2000, **18**, 1845–1855 1845-1855.
13. Henslee J, Bostrom B, Weisdorf D, Ramsay N, McGlave P, Kersey J. Streptococcal sepsis in bone marrow transplant patient [letter]. *Lancet* 1984, **1**, 393.
14. Valteau D, Hartmann O, Brugières L, *et al*. Streptococcal septicemia following autologous bone marrow transplantation in children treated with high-dose chemotherapy. *Bone Marrow Transplant* 1991, **7**, 415–419.
15. Weisman SJ, Scoopo FJ, Johnson GM, Altman AJ, Quinn JJ. Septicemia in pediatric oncology patients: the significance of viridans streptococcal infections. *J Clin Oncol* 1990, **8**, 453–459.
16. Facklam RR, Washington II JA. Streptococcus and related catalase-negative gram-positive cocci. In Balows A, Hausler Jr WJ, Herrmann KL, Isenberg HD, Shadomy HJ, eds. *Manual of Clinical Microbiology,* 5th edn. Washington, DC, American Society for Microbiology, 1991, 238–257.
17. Barry AL, Thornsberry C. Susceptibility tests: diffusion test procedures. In Ballows A, Hausler Jr WJ, Herrman KL, Isenberg HD, Shadomy HJ, eds. *Manual of Clinical Microbiology,* 5th edn. Washington, DC, American Society for Microbiology, 1991, 1117–1125.
18. Mermel LA, Farr BM, Sherertz RJ, *et al*. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001, **32**, 1249–1272.
19. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 1994, **12**, 2471–2508.
20. Bruckner LB, Korones DN, Karnauchow T, Hardy DJ, Cigliotti F. High incidence or penicillin resistance among α-hemolytic streptococci isolated from the blood of children with cancer. *J Pediatr* 2002, **140**, 20–26.
21. Kern W, Kurrle E, Schmeiser T. Streptococcal bacteraemia in adult patients with leukemia undergoing aggressive chemotherapy. A review of 55 cases. *Infection* 1990, **18**, 138–145.
22. Richard P, Amador del Valle G, Moreau P, *et al*. Viridans streptococcal bacteraemia in patients with neutopnia. *Lancet* 1995, **345**, 1607–1609.
23. Marrie TJ. Bacteremic community-acquired pneumonia due to viridans group streptococci. *Clin Invest Med* 1993, **16**, 38–44.
24. Tham RT, Peters WG, De Bruine FT, WIllemze R. Pulmonary complications of cytosine-arabinoside therapy: radiographic findings. *Am J Roentgenol* 1987, **149**, 23–27.
25. Andersson BS, Cogan BM, Keating MJ, Estey EH, McCredie KB, Freireich EJ. Subacute pulmonary failure complicating therapy with high-dose Ara-C in acute leukemia. *Cancer* 1985, **56**, 2181–2184.
26. Wolff SN, Marion J, Stein RS, *et al*. High-dose cytosine arabinoside and daunorrubicin as consolidation therapy for acute nonlymphocytic leukemia in first remission: a pilot study. *Blood* 1985, **65**, 1407–1411.
27. Pizzo PA. Drug therapy: management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med* 1993, **328**, 1323–1332.
28. Carratalá J, Alcaide F, Fernandez-Sevilla A, Corbella X, Linares J, Gudiol F. Bacteremia due to viridans streptococci that are highly resistant to penicillin: increase among neutropenic patients with cancer. *Clin Infect Dis* 1994, **20**, 1169–1173.