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Papers

Viridans Streptococcal Bacteraemia in Patients with Haematological and Solid Malignancies

A. David Burden, Beryl A. Oppenheim, Derek Crowther, Anthony Howell, Godfrey R. Morgenstern, J. Howard Scarffe and Nicholas Thatcher

Thirty-three episodes of septicaemia caused by viridans streptococci are reported in 32 adults under treatment for malignant diseases. The underlying diseases were acute leukaemia (17), lymphoma (4), myeloma (1), small cell carcinoma of the bronchus (6), carcinoma of the breast (2) and carcinoma of the stomach (2). Important predisposing factors included severe neutropenia and oral mucositis due to intensive chemotherapeutic regimens. There was a poor response to standard empirical antibiotics and a mortality of 12%. A role for prophylactic penicillin in high risk groups is suggested.
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INTRODUCTION

VIRIDANS STREPTOCOCCI were first recognised as a cause of septicaemia in cancer patients in 1978 [1, 2] and have subsequently become an increasing problem, especially in those receiving intensive chemotherapy [3]. Oral mucosal lesions have been suggested as the portal of entry [4]. The ensuing clinical course is variable but includes a rapidly fatal form with features of shock and adult respiratory distress syndrome [5].

Most cases have been described among children undergoing treatment for haematological malignancies [6]. We have noticed an increasing incidence among adult patients with both haematological and solid tumours and this prompted a review of all bacteraemias in cancer patients involving viridans streptococci over a 28 month period.

PATIENTS AND METHODS

All patients treated in the departments of Haematology and Medical Oncology at the Christie Hospital between January 1988 and May 1990 were included. Episodes of viridans streptococcal bacteraemia were identified from the microbiology records and data from the relevant case notes analysed. Leukaemia patients and those undergoing bone marrow transplantation had been treated in a purpose-built unit with isolation facilities whereas those with solid tumours were treated on an open ward. Blood for culture had been obtained from peripheral vein and central line (where present) in any patient with a temperature of greater than 38° C and intravenous antibiotics started empirically. Cultures were incubated at 37° C and examined at intervals for 14 days using the BACTEC radiometric system. Isolates were identified as viridans streptococci by standard criteria and further characterised using the API Strep system.

Correspondence to B.A. Oppenheim, Microbiology Department, Withington Hospital, West Didsbury, Manchester M20 8LR, U.K.
A.D. Burden, D. Crowther, A. Howell, J.H. Scarffe and N. Thatcher are at the Department of Medical Oncology; B.A. Oppenheim is at the Department of Microbiology; and G.R. Morgenstern is at the Department of Haematology, Christie Hospital and Holt Radium Institute Manchester, U.K.
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RESULTS

Patient characteristics

During the study period of 28 months, 233 bacteraemic episodes were documented of which 33 (14.2%) involved viridans streptococci. Of the 32 patients concerned (1 patient had two episodes of viridans streptococcal bacteraemia during different neutropenic periods), 21 (65.6%) were male and 11 (34.4%) female, the age range being 16 to 76 years (median 54). The underlying malignancies are recorded in Table 1. Patients with solid tumours made up 31% of cases. All patients were receiving or recovering from chemotherapy and 88% had received previous courses of chemotherapy.

The patients with small cell carcinoma of the bronchus were receiving intensive chemotherapy with carboplatin, ifosfamide, etoposide and vincristine, with concurrent thoracic and cranial radiotherapy. Those with carcinoma of the breast had been treated with an experimental regimen of doxorubicin and cyclophosphamide, supported by haemopoietic colony stimulating factor. Those with gastric carcinoma were receiving moderately intensive therapy with cisplatin, doxorubicin and etoposide. The leukaemias, lymphomas and multiple myeloma were all

Table 1. Underlying malignancy

Acute lymphoblastic leukaemia (2 BMT)	9(28%)
Acute myeloid leukaemia (1 BMT)	8(25%)
Non-Hodgkin lymphoma	3(9%)
Hodgkin's lymphoma	1(3%)
Multiple myeloma	1(3%)
Small cell carcinoma of bronchus	6(20%)
Carcinoma of the breast	2(6%)
Carcinoma of the stomach	2(6%)

BMT = bone marrow transplantation.

Table 2. Response to empiric antibiotics

Initial antibiotic regimen	No. treated	No. responding
Netilmicin, piperacillin	21	6 (29%)
Netilmicin, piperacillin, metronidazole	5	5 (100%)
Ceftazidime	3	1 (33%)
Ciprofloxacin	2	0
Netilmicin, piperacillin, vancomycin	1	0
Erythromycin	1	1 (100%)
Total	33	13 (39%)

being treated with intensive chemotherapy and 2 patients with acute lymphoblastic leukaemia and 1 with acute myeloid leukaemia had undergone bone marrow transplantation, following a conditioning regimen of total body irradiation and cyclophosphamide. Thirty-two of the 33 episodes occurred in neutropenic patients (granulocyte count $<0.5 \times 10^9$) and at the time of infection neutropenia had been present between 0 and 19 days (median of 2 days).

10 patients were on antibiotic prophylaxis at the time of onset of infection (all with cotrimoxazole) and 8 were on acyclovir. 21 patients had received previous courses of antibiotics.

Clinical features

The commonest abnormalities detected clinically related to the oropharynx. "Mucositis", represented by a sore throat, oral ulceration, candidal or herpetic lesions, was present in 25 patients (78%) of whom 7 also had diarrhoea. A further 5 patients (16%) had diarrhoea alone leaving only 3 patients with neither oral mucositis nor diarrhoea. Of these, 2 had pleural effusions. 4 patients (12%) developed significant hypotension with fatal outcome.

Empiric antibiotic therapy varied over the period of study, but most patients were treated with piperacillin and an aminoglycoside. In 5 cases metronidazole was included in the initial treatment (Table 2). Only 13 (39%) of the 33 episodes responded without alterations to the initial therapy and although the numbers involved are small the only empirical regimen which was universally successful was piperacillin with netilmicin and metronidazole. The single patient treated with erythromycin was not neutropenic at the time of infection although chemotherapy had been started, and clinically appeared to have a chest infection.

Microbiology

The details of the infecting organisms are presented in Table 3. In 55% of episodes the infection was mixed. The most common coinfecting organisms were coagulase negative staphylococci and coliforms, and in only one case was an anaerobe (*Fusobacterium nucleatum*) isolated. There were no significant differences between pure and mixed infections in terms of clinical features, severity and duration of neutropenia or response to empiric antibiotics.

Mortality

4 patients (2 acute lympocytic leukaemia, 1 carcinoma of the bronchus and 1 carcinoma of the stomach) died of the infection giving a case fatality of 12.1%. Fatal cases were characterised by shock early in the clinical course and in addition all 4 cases had oral lesions. The species of streptococcus involved were *Streptococcus mitis* in 2 cases, *S. sanguis* in 1 and mixed *S. sanguis* and *Pseudomonas maltophilia* in the fourth. All fatal cases had been treated empirically with piperacillin and an aminoglycoside but none had received metronidazole in the initial regimen. 3 of the 4 had had modifications in their antibiotic therapy, with vancomycin added in all 3, ceftazidime in 2, and benzyl penicillin and metronidazole in 1 case. Necropsy was performed on 3 of the patients and it is notable that the appearances of the adult respiratory distress syndrome were present in 2 cases and pulmonary consolidation in a third. Additional features were severe intestinal ulceration and subarachnoid haemorrhage in one case. No abnormalities were detected in the hearts.

DISCUSSION

This study confirms the clinical importance of viridans streptococci as a cause of sepsis in neutropenic cancer patients. Of 233 microbiologically documented septicaemias, viridans streptococci were involved in 14% of cases with a mortality of 12%.

These organisms are normal inhabitants of the mouth, oropharynx and intestinal tract. This correlates with the very high incidence of oral inflammation or ulceration (78%) and to a lesser extent diarrhoea (37%) found in this series. Mucositis probably presents a portal of entry and neutropenia allows persistence of infection and septicaemia. Thus both myeloid and non-myeloid toxicity of the chemotherapeutic regimens seem to be important and the use of intensive regimens would account for the increasing incidence of viridans streptococcal septicaemia in leukaemic patients. Equally, as more intensive regimens are applied to solid tumours, viridans streptococcal septicaemia has emerged in this group of patients.

The poor clinical response to piperacillin and an aminoglycoside was unexpected as these organisms are likely to be sensitive to this combination *in vitro* [7]. This raises the question of an undetected coinfecting organism which, in view of the response obtained with metronidazole, may be a fastidious oral anaerobe. The mortality for this form of infection (12%) appears higher than for other bacterial causes in our hands [8]. At least half of the deaths were associated with the adult respiratory distress syndrome as previously described although the mechanism remains unclear in neutropenic patients [9].

Prevention is clearly important. Scrupulous attention to oral hygiene and the use of cytotoxic regimens with the least non-myeloid toxicity make sense. If a group at particular risk of

Table 3. Infecting organisms

	No.	Mixed	Coinfecting organisms	
S. sanguis	17	8	Coagulase negative staphylococci	3
			E. coli	2
			Fusobacterium nucleatum	1
			Ps. maltophilia	1
			S. mitis	1
S. mitis	13	8	Coagulase negative staphyloccoci	3
			E. coli	4
			Aeromonas hydrophila	1
			Enterobacter cloacae	1
S. salivarius	1	1	*Ps. aeruginosa*	1
Unidentified streptococcus	2	0		

mucositis in conjunction with neutropenia can be identified, prophylactic oral penicillin or benzylpenicillin introduced early in the course of the fever may be of benefit. This needs to be assessed prospectively in a randomised control trial.

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Expression of HLA-D Subloci DR and DQ by Breast Carcinomas is Correlated with Distinct Parameters of Favourable Prognosis

Christina A. Brunner, Josef M. Gokel, Gert Riethmüller and Judith P. Johnson

The expression of HLA-D region products HLA-DR, DQ and DP by primary breast carcinomas was examined for its relationship to standard prognostic parameters. A positive correlation was found between the expression of HLA-DR and the differentiation state of the tumour ($P = 0.02$) and the expression of progesterone receptors ($P = 0.002$), two parameters which are associated with good prognosis and with each other. No correlation was seen between these parameters and the expression of HLA-DQ or HLA-DP. In contrast, tumour diameter was inversely correlated with the expression of HLA-DQ ($P = 0.0004$) although no association was observed between this parameter and HLA-DR expression. Essentially all HLA-DQ positive tumours had a diameter of less than 2 cm although these represented only 50% of the tumours of this size examined. These data show that in breast carcinomas HLA class II expression is correlated with several distinct parameters of good prognosis and suggest that HLA-DQ expression may define a subtype of T1 tumours.
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INTRODUCTION

THE HLA-D class II antigens of the major histocompatibility complex (MHC) are highly polymorphic cell surface molecules which control immune recognition through the presentation of foreign antigens to regulatory T cells [1–3]. While constitutive expression of HLA-class II molecules is restricted to B cells, myelomonocytic cells and their precursors, these molecules can be induced on many other cell types by lymphokines [4]. Class II molecules are also found on some types of malignant tumours where their expression has often been shown to be of prognostic relevance. Depending on the type of tumour, the expression of HLA class II antigens can be associated with either good or poor prognosis. Thus, expression of HLA-D region molecules by cutaneous melanoma increases in freqeuncy with tumour progression and is associated with the early occurrence of metastases [5, 6]. In contrast, HLA-class II expression on larynx carcinomas is associated with highly differentiated tumours which have a good prognosis [7]. In some solid tumours, such as colorectal carcinomas, the expression of class II molecules does not appear to have any prognostic significance [8].

Although previous investigations have shown that HLA-D region products are expressed by breast carcinomas, no conclusions could be drawn on the relationship of this to tumour stage or prognostic parameters [9–13]. Given the fact that 20–30% of women with stage I disease develop metastases, it is important to try to establish additional prognostic markers. In the study presented here, the expression of the HLA-D region molecules HLA-DR, HLA-DQ and HLA-DP on primary breast carcinomas has been examined for its correlation with histopathological G-grading, hormone receptor expression, tumour size and lymph-node status, parameters important for predicting disease free interval and overall survival.

Correspondence to J.P. Johnson.
C.A. Brunner, G. Riethmuller and J.P. Johnson are at the Institute for Immunology and J.M. Gokel is at the Institute of Pathology, University of Munich, Goethestrasse 31, 8000 Munich 2, Germany.
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