Journal of Infection (1989) **18**, 231–248

Invasive streptococcal infections in the era before the acquired immune deficiency syndrome: a 10 years' compilation of patients with streptococcal bacteraemia in North Yorkshire

M. Barnham

Departments of Microbiology, Harrogate General Hospital, Harrogate, North Yorkshire HG2 7ND and Friarage Hospital, Northallerton, North Yorkshire DL6 1JG, U.K.

Accepted for publication 19 *December* 1988

Summary

Significant streptococcal (non-pneumococcal, non-enterococcal) bacteraemia was detected in 100 patients in two Health Districts of North Yorkshire in the decade 1978–1988. Patients with these infections accounted for 11% of the total 902 patients in the districts in whom bacteraemia was diagnosed during the period. Infection was most often seen with β-haemolytic streptococci (52 patients) comprising Lancefield group A (*Streptococcus pyogenes*) (20 patients), group B (13), group C (5), group G (9), haemolytic *Streptococcus milleri* and non-groupable streptococci (5). The wide variety of serious infections included cellulitis, abscess, septicaemia, pneumonia, septic arthritis, necrotising fasciitis, acute endocarditis and mycotic aneurysm. Of these 52 patients, 21 (40%) died. α-Haemolytic streptococcal bacteraemia was diagnosed in 38 patients of whom 24 (63%) suffered from endocarditis and three (8%) died. Three of ten patients with non-haemolytic or anaerobic streptococcal bacteraemia died also. Six of the 100 patients with streptococcal bacteraemia had concomitant acute virus infections. Of the total 56 patients with infective endocarditis diagnosed in the districts during the period, streptococci were responsible in 30 (54%) of them. The predisposing factors, clinical features and outcome of the infections are described and discussed.

Introduction

A general decline in serious β-haemolytic streptococcal infections has taken place during this century in many developed countries. It is thought to be due largely to improvements in hygiene, housing and nutrition, hastened by the development and widespread use of antibiotics in the later years. Nonetheless, sporadic severe infections continue to occur, sometimes with a rapid course that makes successful diagnosis and treatment difficult to achieve.[1–3] The pattern of infection with Lancefield group A (*Streptococcus pyogenes*) in the U.K. in recent years has changed with an apparent increase in aggressive M-type 1 infections.[4,5] Infection with Lancefield group B streptococci has received special attention in the last 25 years and the number of serious infections, particularly in young babies, appears to have increased.[6] Outbreaks of severe systemic infection with Lancefield group C streptococci have also been described in recent years.[7,8]

Viridans streptococci remain an important cause of infective endocarditis, a disease undergoing marked changes in its epidemiology.[9] These organisms are

0163-4453/89/030249+18 $02.00/0

also being increasingly recognised as a cause of significant systemic infection in children with underlying anatomical and physiological problems[10] as well as in neutropenic and cancer patients.[11–13] Recent years have seen a steady increase in reports to the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) of α- and β-haemolytic streptococcal bacteraemia, thought to be due mainly to improvements in diagnostic procedures and reporting.[14]

This review gives details of all the patients with streptococcal bacteraemia detected in the two Health Districts of Harrogate and Northallerton in the decade 1978–1988. The aim has been to describe current problems of invasive streptococcal infection and to determine the relative frequencies of the various groups and species of streptococci causing them. The recent arrival of human immunodeficiency virus (HIV) infection and the acquired immune deficiency syndrome (AIDS) in the population may influence the prevalence and patterns of streptococcal disease. If so, the present findings may provide useful data for future comparison.

Patients, materials and methods

The Harrogate and Northallerton Health District microbiology laboratories currently receive about 105 000 specimens a year from a catchment population of about 260 000. The community is partly urban and partly rural. The local hospitals provide a full range of modern general medical and surgical services but are without specialised units. Indications for blood culture are decided by doctors according to the clinical condition of their patients. Almost all blood cultures sent to the laboratories come from hospitals, very few being submitted by general practitioners from patients at home.

During the last ten years, testing techniques in the laboratories have been modified but the general arrangements for blood culture have been as follows. Each blood culture kit has contained two bottles, one of Fastidious Anaerobe Broth (Lab M) and one of biphasic Vacuneda medium (Medical Wire & Equipment Co. Ltd) or laboratory-prepared tryptone soya broth containing Liquoid (0·05 %) and gelatin (1·0 %) with or without 0·1 % agar and 0·5 % glucose. Blood (10 ml) was collected cleanly from each patient and injected equally into the two culture bottles. These were then returned quickly to the laboratory and incubated at 37 °C for at least 5 days. Aerobic and anaerobic subcultures were made on 6 % horse blood agar medium at 18 h and after 5 days or whenever bacterial growth otherwise became manifest in the bottles.

Organisms were identified by generally approved bacteriological techniques[15] that included Lancefield grouping by means of commercially available test kits (Streptex: Wellcome Diagnostics, Phadebact Streptococcus Test: Pharmacia Diagnostics; Streptococcal Grouping Kit: Oxoid Ltd). In the earlier years of study, significant systemic isolates of viridans streptococci were sent for identification to the Streptococcus Reference Unit, Division of Hospital Infection, Central Public Health Laboratory, Colindale, London but since 1983 they have been identified in our own laboratories by use of the API-20STREP test (API Products Ltd). β-Haemolytic streptococci were typed in the Streptococcus Reference Unit according to generally approved techniques

Table I *Determination of species and type* of 52 isolates of β-haemolytic streptococci from blood cultures*

Lancefield group	No. of isolates	Species/types (No. of isolates of each)
A	20	M – type 1 (4), M 3 (1), M 4 (1), M 6 (2), M 9 (1), M 12 (2), T 28 R 28 (2); not typed (7)
B	13	Types Ia, b, c, a/c, b/c, one each; III (1), III R (2); non-typable (2); not typed (3)
C	5	*Strep. equisimilis*: T202 (1), T 305 (1), not typed (1); species not determined (2)
F	2	*Strep. milleri*
G	9	T 16 (1), T 202 (1), T 7/302 (2), T7/305/306 (1); non-typable (1); not typed (3)
Not groups A–G	3	*Strep. milleri* (2); species not determined (1)

* Typing done in the Streptococcus Reference Unit, Division of Hospital Infection, Central Public Health Laboratory, Colindale, London. *Strep. milleri* is likely to be known as *Strep. anginosus* in the future.[39]

and, since 1983, by means of a newly developed T-antigen typing system for groups C and G.[16]

All positive blood cultures were brought to the attention of the consultant microbiologist and their clinical significance decided after discussion with the doctors concerned and often after visiting the patient. In each case, further discussions usually took place on the patient's progress and response to treatment. Details of all significant isolates and the clinical course of infection in each case have been saved in Harrogate since April 1978 and in Northallerton from July 1979. For purposes of this study, the records were compiled of patients with α-, β-, non-haemolytic and anaerobic streptococcal bacteraemia up to the end of June 1988, a period of 10 years and 3 months for the larger Harrogate district and of 9 years for the Northallerton district. When the outcome of the illness was unclear the patient's case notes were reviewed. Patients with pneumococcal and enterococcal infections were excluded from this review.

Results

In the decade of the study, 100 patients with clinically significant streptococcal bacteraemia (non-pneumococcal, non-enterococcal) were detected. β-Haemolytic streptococci were the most often found, comprising 52 % of the total. Of these, group A were the commonest (20 patients) followed by group B (13 patients), group G (9 patients), group C (5 patients), haemolytic *Streptococcus milleri* (4 patients) and a streptococcus not of groups A–G (1 patient). The typing results of these organisms are shown in Table I. Most of the group A streptococci were of 'low number' M-types and the group B streptococci of types I and III; various T-types of group C and group G streptococci were encountered. α-Haemolytic streptococci made up 38 % of the total, comprising

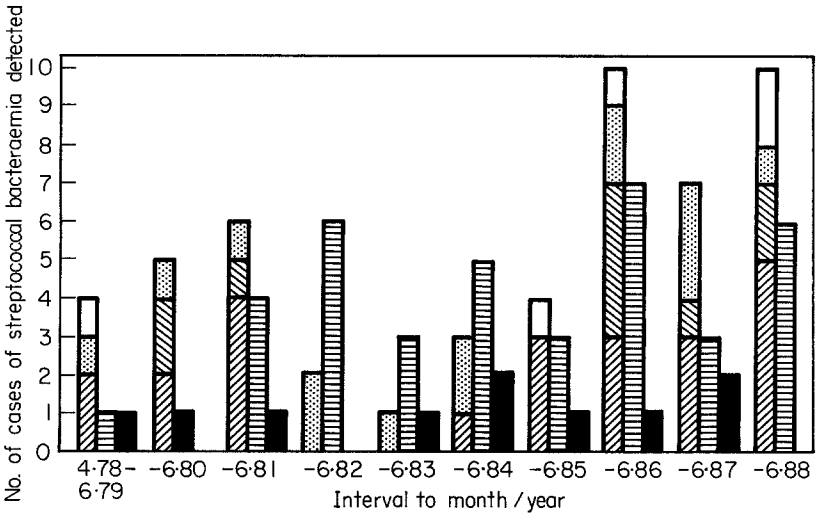

Fig. 1. Number of patients with streptococcal bacteraemia detected in two districts of North Yorkshire shown in yearly intervals. β-Haemolytic streptococci: ▨, group A (total 20); ▧, group B, (total 13); ⊠, group C (total 5) plus group G (total 9); □, *Strep. milleri* and streptococci not grouped A–G (total 5); ▤, α-haemolytic streptococci (total 38); ■, non-haemolytic (total 7) and anaerobic streptococci (total 3).

Streptococcus sanguis (14), *Streptococcus milleri* (6), *Streptococcus mitior* (*oralis*) (6), *Streptococcus mitis* (5), *Streptococcus salivarius* (2), *Streptococcus bovis* (1), *Streptococcus bovis/equinus* (1) and species not determined (3). Non-haemolytic streptococci accounted for 7% of the total, including one isolate identified as *Streptococcus mutans*; anaerobic steptococci made up only 3% of the total isolates.

The 100 patients with streptococcal infection accounted for 11% of the total 902 patients in the districts diagnosed as having significant bacteraemia with any organism during the period. By comparison, blood cultures from 83 of the 902 patients (9·2%) yielded pneumococci and 27 (3·0%) yielded enterococci. The streptococci made up 10·5% of the 951 significant bacterial isolates from these patients. In 92 of the 100 patients, the culture was purely of streptococci. In eight, a second organism was present at the start or during the course of the illness: *Staphylococcus aureus* in four (patients nos. 2, 30, 56, 96), *Escherichia coli* in two (nos. 54, 89), *Staphylococcus epidermidis* in one (a 58-year-old man with *Strep. mitior* endocarditis) and *Bacteroides fragilis* in one (no 100).

The annual numbers of patients who yielded streptococci from the blood are shown in Fig. 1. All groups and species of streptococci increased during the study period; between 1980–82 and 1986–88 there was a 60% increase in detection of α-haemolytic streptococci and 100% increase in that of β-haemolytic streptococci. Factors probably responsible for this change included the general increase in all specimens received in the laboratories during the period (45% increase) and increased use of blood culture as a diagnostic technique (numbers received doubled during the last 4 years of the study, with a growing tendency to sample each patient more than once). The total number of significant bacterial isolates of all species from the blood doubled during the

Table II *Clinical features of 20 patients with* Streptococcus pyogenes *bacteraemia*

Patient No.	Sex, age	Predisposing factors	Clinical features	Outcome
1	M 4 days	Prematurity, prolonged rupture of the membranes	Jaundice, septicaemia	Recovered
2	M 1 year	—	Infected eczema, fever	Recovered
3	F 2 years	—	Tonsillitis, fever, convulsions	Recovered
4	F 5 years	—	Tonsillo-pharyngitis, otitis media, septic polyarthritis	Recovered
5	M 8 years	—	Dental abscess, septicaemia	Recovered
6	F 9 years	Chicken pox	Infected rash, fever	Recovered
7	M 11 years	—	Pharyngitis, osteomyelitis of os calcis	Recovered
8	F 28 years	Influenza A	Post-influenzal pneumonia	Recovered
9	M 39 years	—	Necrotising fasciitis, septicaemia	Died
10	F 55 years	Paraplegia	Pneumonia	Died
11	M 60 years	Carcinomatosis	Pneumonia, septicaemia	Recovered
12	F 69 years	Diabetes	Septicaemia	Died
13	F 70 years	Aplastic anaemia, steroid therapy	Septic arthritis of hip, septicaemia	Died
14	F 73 years	Head injury	Cellulitis of face	Recovered
15	F 77 years	—	Cellulitis of leg, septicaemia	Died
16	M 78 years	Carcinoma of lung	Pneumonia	Died
17	M 80 years	Carcinoma of stomach	Collapse after laparotomy	Died
18	F 82 years	—	Pneumonia	Recovered
19	F 91 years	Peripheral vascular disease, gangrenous toe	Cellulitis of leg	Recovered
20	F 92 years	—	Pneumonia	Recovered

period of 10 years, streptococci forming a more-or-less constant proportion throughout.

The clinical features of infection with *Strep. pyogenes* are shown in Table II, listed in order by ages of the patients. Further details of certain patients are available elsewhere (patients no. 3 and 4,[17] 10 and 20[18]). Seven systemic infections (35%) were in children under the age of 12 years. These arose mainly from oro-pharyngeal and skin infections; all the patients survived. Two otherwise healthy young adults (patients 8 and 9) suffered from very serious infections with *Strep. pyogenes* M-type 1. One had necrotising fasciitis of the leg which proved fatal, the other had post-influenzal pneumonia followed by extensive desquamation of the skin. Of the 11 remaining patients, 55 years of age or more, five suffered from pneumonia due to *Strep. pyogenes* and three from spreading streptococcal cellulitis; seven (64%) had serious underlying medical disorders and six died (55%). The overall mortality rate for *Strep. pyogenes* bacteraemia was 35%.

Table III *Clinical features of 13 patients with group B streptococcal bacteraemia*

Patient no.	Sex, age	Predisposing factors	Clinical features	Outcome
21	F 1 day	Prematurity	Neonatal varicella, fever	Recovered
22	M 1 day	Prematurity	Septicaemia	Died
23	M 1 day	—	Respiratory distress, septicaemia	Recovered
24	M 3 months	Prematurity	Apnoea after laparotomy and small bowel resection	Recovered
25	M 3 months	—	Cot death; septicaemia, early meningitis (also cytomegalovirus interstitial pneumonitis)	Died
26	F 8 months	—	Cot death: septicaemia	Died
27	F 22 years	Pregnancy	Puerperal septicaemia	Recovered
28	M 25 years	—	Pneumonia, acute endocarditis	Died
29	M 59 years	Urethral stricture	Fever	Recovered
30	F 76 years	Peripheral vascular disease, ulceration of foot	Cellulitis of leg, fever	Recovered
31	F 82 years	—	Acute endocarditis	Died
32	M 84 years	—	Septic arthritis of knee	Recovered
33	F 86 years	—	Fever	Recovered

The features of patients with group B streptococcal infection are listed according to age in Table III (further details are available as follows: patients 25 and 26[3], 28[2]) Six systemic infections (46 % of the total) arose in the first year of life, three on the first day. Clinical features included respiratory distress and septicaemia. The mortality rate in these patients was 50 %. Puerperal septicaemia and rapidly fatal pneumonia with endocarditis affected two previously healthy young adults. Five infections (38 %) were in patients $\geqslant$ 59 years of age. Clinical features included cellulitis, septic arthritis and non-specific febrile illnesses. Only the one patient with acute endocarditis died of the infection. The overall mortality for group B streptococcal bacteraemia was 38 %.

Features of the five patients with group C streptococcal bacteraemia are shown in Table IV. Upper or lower respiratory tract infection arose in three of these patients. The three over 60 years of age had conditions predisposing to infection; two of them died. Overall mortality in this small series was 60 %. The patients with group G streptococcal bacteraemia are also listed in Table IV (further details are available as follows: patient 39;[2] 40, 42, 46, 47[19]). All of these patients were over the age of 55 years and four (44 %) died of the infection. Features included spreading cellulitis of the leg in four, pneumonia in two, as well as septicaemia and septic arthritis. Predisposing factors were commonly present.

Table IV *Clinical features of 14 patients with Lancefield group C or G streptococcal bacteraemia*

Lancefield group	Patient no.	Sex, age	Predisposing factors	Clinical features	Outcome
C	34	F 11 years	—	Pharyngitis, septicaemia	Recovered
C	35	M 32 years	—	Acute epiglottitis	Died
C	36	M 61 years	Carcinomatosis, hepatic failure	Pneumonia	Died
C	37	F 77 years	Femoral embolectomy	Post-operative mycotic aneurysm	Recovered
C	38	F 85 years	Cardiac failure	Cellulitis of legs, septicaemia	Died
G	39	M 56 years	—	Pneumonia, acute endocarditis	Died
G	40	F 58 years	Prolymphocytic leukaemia	Pneumonia, septicaemia	Recovered
G	41	M 69 years	Painful inguinal hernia	Septicaemia	Recovered
G	42	F 71 years	—	Cellulitis of leg, septicaemia	Died
G	43	F 72 years	—	Cellulitis of ankle, septicaemia, acute renal failure	Recovered
G	44	M 75 years	Pancytopenia	Septic polyarthritis, septicaemia	Died
G	45	F 83 years	Anaemia, probable leukaemia	Septicaemia cellulitis of leg	Died
G	46	F 87 years	—	Cellulitis of leg, fever	Recovered
G	47	M 89 years	Sacral sore	Fever	Recovered

In patients 35, 37, 38, the organism was identified as *Streptococcus equisimilis*.

Table V *Clinical features of bacteraemic patients yielding non-groupable β-haemolytic streptococci or* Streptococcus milleri

Lancefield group species, haemolysis	Patient no.	Sex, age	Predisposing factors	Clinical features	Outcome
Not grouped A–G	48	M 34 years	—	Acute, non-perforating duodenal ulcer, fever	Recovered
Strep. milleri					
β-Haemolytic, not grouped A–G	49	M 3 years	—	Abscess under tongue, fever	Recovered
α-Haemolytic	50	M 20 years	—	Pig farmer with septicaemia after laceration to hand	Recovered
α-Haemolytic	51	M 43 years	Polyposis coli, ileostomy	Multiple liver abscesses	Recovered
α-Haemolytic	52	M 47 years	Ventricular septal defect	Endocarditis after dental treatment	Recovered
α-Haemolytic	53	M 52 years	Mitral valve disease	Endocarditis	Recovered
β-Haemolytic, not grouped A–G	54	M 53 years	Rheumatoid disease, Gold treatment	Cellulitis of ankle	Recovered
α-Haemolytic	55	F 58 years	Acute hepatitis B	Dental abscess, fever	Recovered
α-Haemolytic	56	M 61 years	Mitral valve disease	Endocarditis	Died with *Staph. aureus* superinfection
β-Haemolytic, Group F	57	M 76 years	—	Acute cholangitis, septicaemia	Died
β-Haemolytic, Group F	58	F 88 years	Carcinoma of the colon	Pelvic abscess	Died

Table V lists the clinical features of patients infected with non-groupable β-haemolytic streptococci and *Strep. milleri* (further details are available for patients 48[20], and 50[21]). The organism from patient 48 was unfortunately not identified as to species. Experience indicates, however, that most β-haemolytic streptococci not of groups A–G isolated from clinical specimens are *Strep. milleri* (unpublished observations). Four of the ten isolates of *Strep. milleri* were β-haemolytic and two of these were of Lancefield group F; the remaining six were α-haemolytic. Four patients suffered from abscesses, two in the mouth and two in the abdomen; three had endocarditis with α-haemolytic strains. Predisposing factors were commonly present. The three oldest patients (30% of all with the organism) died, one with a *Staph. aureus* superinfection that appeared during the course of treatment for endocarditis.

Table VI lists the clinical features of 32 patients yielding α-haemolytic streptococci other than *Strep. milleri*. Endocarditis was the presenting feature in 21 patients (66%). The condition in one of the two who died, a 60-year-old man, was first diagnosed *post mortem*. Infection was found on ventricular septal defects in patients aged 12, 25 and 50 years, on a prosthetic valve in a man of 33 years and on a bicuspid aortic valve in a man of 62 years; four other patients were known to have had pre-existing valvular disease. Eleven patients showed other patterns of infection with α-haemolytic streptococci but none died. Two children suffered from serious lower respiratory tract infections (patients 80 and 83); two patients developed febrile bacteraemic infection arising from a focus in the mouth (patients 81 and 85) and two from the biliary tract (patients 89, 90). Aggressive infection with *Strep. sanguis* was seen in a young child who developed septicaemia, purpura and disseminated intravascular coaggulation but recovered on appropriate antibiotic therapy; also in a man who developed extensive cellulitis and abscesses in the hand and arm after an injury while chopping wood.

The clinical features of patients with non-haemolytic and anaerobic streptococcal bacteraemia are given in Table VII. Of those patients infected with non-haemolytic streptococci, endocarditis or endarteritis was a feature in four and the respiratory tract a source of infection in at least two others. In two of the three patients with anaerobic streptococcal bacteraemia, the teeth were a source of infection and one died. One patient developed mixed *Bacteroides fragilis* and anaerobic streptococcal bacteraemia from an infected sacral sore.

A review of infective endocarditis during the decade under study revealed a total of 56 bacteriologically proven cases in the two districts, four with two different infecting organisms present in the course of the illness. Streptococci, as described above, were responsible for infection in 30 (54%) of these patients of whom six (20%) died. Three of these deaths came very rapidly in patients with acute β-haemolytic streptococcal endocarditis (patients 28, 31, 39). Other organisms causing infective endocarditis in the districts included *Staph. aureus* in 19 patients (34% of the total) of whom eight died (42%), three with *Staph. epidermidis* and one each with *Enterococcus faecalis*, *Haemophilus parainfluenzae*, *Coxiella burnetii* and mixed *Pseudomonas aeruginosa* and *Bacillus cereus*.

Concomitant virus infection and streptococcal bacteraemia were seen in six (6%) of the 100 patients in this series. Varicella-zoster virus infected two

Table VI *Clinical features of 32 bacteraemic patients yielding viridans streptococci other than* Strep. milleri

Organism	Patient no.	Sex, age	Predisposing factors	Clinical features	Outcome
Viridans streptococci*	59–70	M (10) F (11) (range 12–89 years)		Endocarditis	Two died
Strep. mitis	80	M 2 months		Bronchiolitis, pneumonia	Recovered
Strep. oralis	81	F 11 months	Hand, foot and mouth disease, oral ulceration	Fever	Recovered
Strep. sanguis	82	M 1 year		Septicaemia, DIC, purpura	Recovered
Viridans streptococcus (species not determined)	83	M 4 years		Bronchopneumonia	Recovered
Strep. mitis	84	F 21 years	Spina bifida, pregnant	Infected Spitz–Holter valve	Recovered
Viridans streptococcus (species not determined)	85	F 24 years	Psoriatic arthritis, erupting wisdom teeth	Fever	Recovered
Strep. sanguis	86	M 63 years	Splinter of wood injury	Abscess and cellulitis of hand and arm	Recovered
Strep. mitis	87	M 69 years	Rheumatoid disease, steroid treatment	Septic arthritis of wrist	Recovered
Strep. sanguis	88	F 73 years	Alcoholism, hepato-renal failure, ascites	Fever, jaundice	Recovered
Strep. sanguis	89	M 78 years	Carcinoma of bile duct	Post-operative fever	Recovered
Strep. salivarius	90	M 78 years	Gall stones	Acute pancreatitis and cholangitis	Recovered

* Species of streptococcus in the 21 patients with endocarditis: *Strep. sanguis* (10); *Strep. mitior* (5); *Strep. mitis* (2); *Strep. bovis* (1); *Strep. bovis II/equinus* (1); *Strep. salivarius* (1); viridans, species not determined (1).

DIC = disseminated intravascular coagulation.

Table VII *Clinical features of bacteraemic patients yielding non-haemolytic or anaerobic streptococci*

Organism	Patient no.	Age, sex	Predisposing factors	Clinical features	Outcome
Non-haemolytic streptococci	91	F 9 years		Acute epiglottitis, intubated, fever	Recovered
Non-haemolytic streptococci	92	M 54 years		Endocarditis	Recovered
Non-haemolytic streptococci	93	F 54 years	Aortic valvular disease	Endocarditis	Recovered
Non-haemolytic streptococci	94	M 59 years	Aortic aneurysm	Endarteritis	Died
Non-haemolytic streptococci	95	M 66 years	Chronic myeloid leukaemia	Fever, rigors	Recovered
Non-haemolytic streptococci	96	F 74 years	Rheumatoid arthritis, anaemia	Pneumonia	Died
Non-haemolytic streptococci	97	F 79 years		Endocarditis	Recovered
Anaerobic streptococci	98	F 34 years	Dental clearance	Septicaemia, acute renal failure	Died
Anaerobic streptococci	99	M 54 years		Dental abscess, fever	Recovered
Anaerobic streptococci	100	M 72 years	Rheumatoid arthritis, active sacral ulceration	Fever	Recovered

The non-haemolytic streptococcus in patient no. 97 was identified as *Strep. mutans*.

patients; a neonate with congenital infection and group B streptococcal bacteraemia (patient 21) as well as a 9-year-old girl with secondarily infected chickenpox vesicles and who developed a clinically mild *Strep. pyogenes* bacteraemia (patient 6). Patient 8 suffered severe *Strep. pyogenes* pneumonia and septicaemia in association with influenza virus A infection. A 3 months' old baby who died of a 'cot death' had systemic group B streptococcal infection while cytomegalovirus was found in the lungs which showed the histological changes of interstitial pneumonitis[3] (patient 25). Patient 55 developed a dental abscess with *Strep. milleri* bacteraemia during the course of acute hepatitis B infection. An 11-month-old child developed *Strep. oralis* bacteraemia with high fever during an attack of hand, foot and mouth disease with inflamed oral ulceration (patient 81).

The overall mortality in this series of 100 patients with streptococcal bacteraemia was 26%, 21 of 52 patients with β-haemolytic streptococcal infection died (40%) as did three of 38 with α-haemolytic streptococcal infection (8%) and three of ten yielding non-haemolytic or anaerobic streptococci (30%).

Discussion

Streptococci were responsible for infection in 11% of all bacteraemic patients detected in this study. Other serious localised infections with β-haemolytic streptococci were seen in the districts either without bacteraemia, without being tested for it or tested only after antibiotics had been given; these are not included in this report. Clearly, streptococci continue to pose a formidable clinical problem with high rates of morbidity and mortality among the patients concerned.

The results of the study were broadly similar to those described by others. Young[14] reviewed details of 45205 reports of bacteraemia sent to the PHLS Communicable Disease Surveillance Centre (CDSC) and found 5% due to β- and 6% due to α- and non-haemolytic streptococci. Reports of bacteraemia more than doubled during that 6-year study. They accounted for a steadily increasing proportion of the total reports of all infections received, the increase being thought to be due largely to improvements in national reporting and to more vigorous clinical investigation of patients. During the present study, the number of cases of streptococcal bacteraemia recognised in our laboratories doubled but this was in proportion to increases in isolation of other organisms. Also, there was evidence that blood culture was becoming a more popular diagnostic test in the districts. Increases in bacteraemia reported from other centres[22] may, in part, be similarly explained. Subtle changes may also be taking place in the local incidence of streptococcal diseases, such as an increase in *Strep. pyogenes* M type 1 infections which may be very aggressive,[4,5] and changes in the epidemiology and aetiology of infective endocarditis in an increasingly elderly population.[9] The number of isolates in the survey was too small to allow clear conclusions to be drawn on these points.

Infection with β-haemolytic streptococci was the most common, found in 52% of the patients with streptococcal bacteraemia. The order of frequency of Lancefield groups among these streptococci was group A followed by groups B,

G and C, an order similar to that seen in the national reports to CDSC[17] and in organisms referred to the Division of Hospital Infection at Colindale.[23]

Strep. pyogenes bacteraemia, mainly with 'low number' M-types, was found in patients of all ages but with the highest mortality in the elderly. In children, *Strep. pyogenes* bacteraemia was most commonly found as a complication of oro-pharyngeal and skin infections, in healthy young adults as a rapidly evolving severe infection with the portal of entry not always being known, and in older patients as a variety of serious infections often associated with underlying medical disorders. Similar patterns of illness and mortality with *Strep. pyogenes* have been reported by others.[24–28]

Nearly half the group B streptococcal infections arose within the first year of life. They featured respiratory distress, septicaemia and high mortality rate. In adults the infection was usually less severe, presenting with cellulitis, septic arthritis, puerperal fever and non-specific febrile illnesses. Severe neonatal infection with these organisms appears to have become more common in this country over recent decades. It accounts for about half the strains of group B streptococci isolated from blood cultures and referred to the Division of Hospital Infection for typing.[6, 23, 29] Infection in infants beyond the neonatal period and in others is seen much less often but in this study there were three such patients. Two presented as 'cot deaths'[3] while another was a similar rapidly fatal infection in a young man found dead in bed (patient 28).[2] The incidence of diagnosed bacteraemic group B streptococcal infection in the first year of life in this study was one case per 4800 live births in the districts, 50% being within the neonatal period. Group B streptococcal bacteraemia in adults is usually less severe than it is in the very young, following childbirth or being seen in patients with serious predisposing conditions such as cancer.[30, 31] Type II group B streptococci have been found less often than type I or III in invasive infections in the U.K.;[6] none was identified in the present series.

Group C streptococcal bacteraemia is uncommon and in this series was found in only five patients. In the three in whom the organism was identified, it was *Strep. equisimilis*, a species quite commonly carried in the respiratory tract but rarely causing aggressive disease.[32] In a study of the species of β-haemolytic group C streptococci in all specimens submitted in a year to the Harrogate and Northallerton laboratories, 85% were *Strep. equisimilis*, 13·5% *Strep. milleri* and 1·5% *Strep zooepidemicus*.[33] This latter species, generally acquired from animals, can cause severe invasive disease in human beings.[8] Although it was not detected or recognised in the blood culture study, it did cause serious infection here during the period, in particular causing septic arthritis of the knee.[34]

Group G streptococcal bacteraemia was found only in patients over 55 years of age. Serious predisposing factors were commonly present and the mortality rate was high. Similar patterns of severe systemic infection have been reported by others.[35, 36] The general clinical features of this infection were recently reviewed.[37]

Ten patients in this study suffered serious infection with *Strep. milleri* including four with abscesses and three with endocarditis. The haemolytic properties and Lancefield groupability of the organisms varied from case to case. These illnesses and laboratory features are typical of those previously

described with the organism.[23, 29] Although the naming of this streptococcus has been controversial,[38] it is likely that it will be known as *Streptococcus anginosus* in the future.[39]

Viridans streptococci have been more commonly found as a cause of infective endocarditis than of other systemic diseases.[23, 29] This was the principal clinical feature in two thirds of the patients in the present series. *Strep. sanguis* was the commonest isolate in our patients with endocarditis followed by *Strep. mitior*. Sussman *et al.*[40] found no significant correlation between streptococcal species and clinical outcome in this disease. Eleven patients suffered from other varieties of viridans streptococcal bacteraemia complicating local infections in the mouth, lungs, biliary tract and elsewhere. Some of these patients were already compromised by serious disease such as cancer, rheumatoid disease and alcoholic cirrhosis. Oral ulceration caused by cytotoxic therapy has been considered to be the portal of entry for viridans streptococci in patients with neutropenia and neoplastic disease. Such patients show a high incidence of systemic infection with these organisms.[11–13] The oral ulceration produced by hand, foot and mouth disease may have been the portal of entry for one patient in this study (no. 81). Dajani[10] described invasive viridans streptococcal infections including pneumonia, septicaemia, endocarditis and meningitis in children with underlying medical problems. Others have also reported serious infections in neonates.[41] In the present series two children developed pneumonia and bacteraemia with these organisms. The two patients with *Strep. bovis* infection had no evidence of intestinal disease such as has been described in some cases.[42, 43]

Patients with non-haemolytic and anaerobic streptococcal bacteraemia made up only 10% of the present series and included four patients with endocarditis or endarteritis. The teeth and respiratory tract were considered the portals of entry in four patients and an infected sacral sore in one. These organisms may be difficult to identify to the level of species[23] but in the one tested here the organism was found to be *Strep. mutans*.

The local review of infective endocarditis showed streptococci responsible for 54% of the cases. The three patients with acute β-haemolytic streptococcal endocarditis died but only three of those with α- or non-haemolytic streptococcal endocarditis died (11%). Infection with *Staph. aureus* had a high mortality rate of 42%. These figures are similar to those of a recent prospective 10-year study of infective endocarditis at St Thomas' Hospital, London.[44]

The age of the patient has been considered to be important in streptococcal disease.[45] Age relates to the various periods of vulnerability and immunity in a human lifetime, to the relevant sites of carriage and exposure to streptococci and to their propensity to cause disease. Age-related patterns may be seen in the series described here. In particular should be noted the striking difference in mortality between young and old with *Strep. pyogenes* infections; the contrasting patterns of group B infection in the very young and group G infection only in the older patients; the underlying congenital heart defects commonly present in the younger patients with infective endocarditis and the metabolic, neoplastic and degenerative diseases underlying infection in many of the older patients. The exact relationship between general predisposing

factors and streptococcal infection in the patient is usually unclear. Parker suggested that local tissue damage associated with systemic diseases or the treatment given for them was often the most important element in this.[29]

Concomitant acute virus infections were present in at least six patients in the series. They may have been more common than this but were not looked for routinely. Viruses may predispose to bacterial infection by the immunosuppression they may cause[46] and by the production of local tissue damage which provides a portal of entry or suitable conditions locally for bacterial growth.[47] The infections may be mutually synergistic such as in influenza plus *Staph. aureus* pneumonia when bacterial enzymes enhance activity of the virus by cleavage of surface precursor haemagglutinins.[48] Freeman and Gould found evidence of recent virus infection in 30% patients with invasive *Staph. aureus* infection leading to endocarditis.[49] Also, a viral prodrome has been noted in patients with bacterial peritonitis during continuous ambulatory peritoneal dialysis[50] and in patients developing 'spontaneous' streptococcal myositis.[51] Acute varicella and enterovirus infections have been described in association with serious group A and B streptococcal infections.[52,53] Dagan, Hall and Menegus reported that the combined bacterial and viral infections may produce misleading arrays of clinical symptoms and signs.[54] Acute virus infections are common and studies with carefully matched controls are needed to establish firmly their possible role in the aetiology of invasive streptococcal infections.

From the first diagnosis in 1985 up to the end of the study period only 13 patients in the two districts were known to be infected with HIV, mainly haemophiliacs. Two patients died with AIDS. Streptococcal infection was not diagnosed in any of these patients. The population studied was therefore believed to be generally free of HIV during the period of the study. The problems of streptococcal disease described were therefore likely to have been those of a 'virgin' community with respect to this virus. The position is likely to change, however, in the near future and the opportunity for such a study as this may not come again.

Little information is yet available on the epidemiological interplay between HIV and streptococcal infections. The most common invasive bacterial infections in patients with AIDS are with mycobacteria, salmonellae and capsulated bacteria such as pneumococci and *Haemophilus influenzae*.[55,56] Serious α- and β-haemolytic streptococcal infections have been described in these patients, particularly in paediatric practice.[57–59] Moreover, immune stimulation by common streptococcal infections may possibly provoke the progression of HIV infection.

The immunological disturbances caused by HIV infection are far-reaching and involve antibody as well as cell-mediated responses.[60,61] Deficiencies of particular immunoglobulin subclasses may underlie the patterns of bacterial superinfection seen in these patients. Examples include IgG2 deficiency and infection with organisms bearing polysaccharide and teichoic acid capsules.[62,63] The treatment of HIV-infected patients may also play a part in the appearance in them of bacterial infections. Patients with AIDS and receiving interleukin-2 have been found to suffer more often than expected from invasive infections with *Staph. aureus* and Gram-negative bacilli.[64] The impact

HIV infection may have on the epidemiology of streptococcal diseases remains to be seen. It is to be hoped that the findings of this study in a population hardly yet exposed to the virus may prove useful for future comparisons.

(I thank the staff of the Division of Hospital Infection, Central Public Health Laboratory Colindale, London for their kind help in identifying and typing strains of streptococci and for helpful advice given in the course of this work.)

References

1. Ispahani P, Donald FE, Aveline AJD. *Streptococcus pyogenes* bacteræmia: an old enemy subdued, but not defeated. *J Infect* 1988; **16**: 37–46.
2. Barnham M. Rapidly fatal group B and G streptococcal infections in adults. *J Infect* 1980; **2**: 279–281.
3. Barnham M, Henderson DC. Group B streptococcal infection presenting as sudden death in infancy. *Arch Dis Child* 1987; **62**: 419–420.
4. Gaworzewska E, Colman G. Changes in the pattern of infection caused by *Streptococcus pyogenes*. *Epidemiol Infect* 1988; **100**: 257–269.
5. Colman G, Efstratiou A, Gaworzewska E. The pyogenic streptococci. *PHLS Microbiol Dig* 1988; **5**: 5–7.
6. Parker MT. Infections with group-B streptococci. *J Antimicrob Chemother* 1979; **5** (Suppl A): 27–37.
7. Group C streptococcal infections associated with eating homemade cheese. *MMWR* 1983; **32**: 510–516.
8. Barnham M, Edwards AT. *Streptococcus zooepidemicus* infections in England 1979–1986. In: *Proceedings of the Xth Lancefield International Symposium on Streptococci and Streptococcal Diseases*, Cologne 1987. (in press).
9. Hayward GW. Infective endocarditis: a changing disease. *Br Med J* 1973; **2**: 706–709: 764–766.
10. Dajani AS. Biologic significance of non-group D alpha-hemolytic streptococci from blood and csf. In: *Proceedings of the Xth Lancefield International Symposium of Streptococci and Streptococcal Diseases*, Cologne 1987. (in press).
11. Cohen J, Worsley AM, Goldman JM, Donnelly JP, Catovsky D, Galton DAG. Septicaemia caused by viridans streptococci in neutropenic patients with leukaemia. *Lancet* 1983; **ii**: 1452–1454.
12. Viscoli C, Van der Auwera P, Meunier F. Gram-positive infections in granulocytopenic patients: an important issue? *J Antimicrob Chemother* 1988; **21** (Suppl C): 149–156.
13. Del Favero A, Menichetti F, Bucaneve G, Minotti V, Pauluzzi S. Septicaemia due to gram-positive cocci in cancer patients. *J Antimicrob Chemother* 1988; **21** (Suppl C): 157–162.
14. Young SEJ. Bacteraemia 1975–1980: a survey of cases reported to the PHLS Communicable Disease Surveillance Centre. *J Infect* 1982; **5**: 19–26.
15. Cowan ST, Steel KJ. *Manual for the identification of medical bacteria*. London: Cambridge University Press, 1974.
16. Efstratiou A. The serotyping of hospital strains of streptococci belonging to Lancefield group C and group G. *J Hyg (Camb)* 1983; **90**: 71–80.
17. Barnham M. Bacteraemia in streptococcal infections of the throat. *J Infect* 1983; **7**: 203–209.
18. Barnham M, Kerby J. *Streptococcus pyogenes* pneumonia in residential homes: probable spread of infection from the staff. *J Hosp Infect* 1981; **2**: 255–257.
19. Barnham M. Group G streptococcal septicemia. *J Infect* 1985; **11**: 83–84.
20. Barnham M. The gut as a source of the haemolytic streptococci causing infection in surgery of the intestinal and biliary tracts. *J Infect* 1983; **6**: 129–139.
21. Barnham M. Pig bite injuries and infection: report of seven human cases. *Epidemiol Infect* 1988; **101**: 641–645.
22. Spencer RC. Blood cultures: where do we stand? *J Clin Pathol* 1988; **41**: 668–670.

23. Parker MT, Ball LC. Streptococci and aerococci associated with systemic infection in man. *J Med Microbiol* 1976; **9**: 275–302.
24. Keefer CS, Ingelfinger FJ, Spink WW. Significance of hemolytic streptococcic bacteraemia. *Arch Intern Med* 1937; **60**: 1084–1097.
25. Cruikshank JG, Hart RJC, George M, Feest TG. Fatal streptococcal septicaemia. *Br Med J* 1981; **282**: 1944–1945.
26. Warren RE. Difficult streptococci. *J Hosp Infect* 1988; **11** (Suppl A): 352–357.
27. Bibler MR, Rouan GW. Cryptogenic group A streptococcal bacteraemia: experience at an urban general hospital and review of the literature. *Rev Infect Dis* 1986; **8**: 941–951.
28. Henkel JS, Armstrong D, Blevins A, Moody MD. Group A beta-hemolytic streptococcus bacteraemia in a cancer hospital. *JAMA* 1970; **211**: 983–986.
29. Parker MT. The pattern of streptococcal disease in man. In: Skinner FA, Quesnel LB, Eds. *Streptococci*. London: Academic Press. 1978; 71–106.
30. Verghese A, Mireault K, Arbeit RD. Group B streptococcal bacteraemia in men. *Rev Infect Dis* 1986; **8**: 912–917.
31. Armstrong D, Blevins A, Louria DB, Henkel JS, Moody MD, Sukany M. Groups B, C and G streptococcal infections in a cancer hospital. *Ann NY Acad Sci* 1970; **1974**: 511–522.
32. Kuski MR. Group C streptococcal infections. *Pediatr Infect Dis J* 1987; **6**: 856–859.
33. Barnham M. In pursuit of the 'new nephritogenic streptococcus'. *Darlington Postgrad J* 1987; **6**: 54–61.
34. Barnham M, Ljunggren A, McIntyre M. Human infection with *Streptococcus zooepidemicus* (Lancefield group C): three case reports. *Epidemiol Infect* 1987; **98**: 183–190.
35. Finch RG, Aveline A. Group G streptococcal septicaemia: clinical observations and laboratory studies. *J Infect* 1984; **9**: 126–133.
36. Smyth EG, Pallett AP, Davidson RN. Group G streptococcal endocarditis: two case reports, review of the literature and recommendations for treatment. *J Infect* 1988; **16**: 169–176.
37. Gaunt PN, Seal DV. Group G streptococcal infections. *J Infect* 1987; **15**: 5–20.
38. Facklam RR. The major differences in the American and British streptococcal taxonomy schemes with special reference to *Streptococcus milleri*. *Eur J Clin Microbiol* 1984; **3**: 91–93.
39. Ruoff KL. *Streptococcus anginosus* ("*Streptococcus milleri*"): the unrecognized pathogen. *Clin Microbiol Rev* 1988; **1**: 102–108.
40. Sussman JI, Baron EJ, Tenenbaum MJ, Kaplan MH, Greenspan J, Facklam RR, Tyburski MB, Goldman MA, Kanxer BF, Pizzarello RA. Viridans streptococcal endocarditis: clinical, microbiological and endocardiographic correlations. *J Infect Dis* 1986; **154**: 597–603.
41. Haffar AAM, Fuselier PA, Baker CJ. Species distribution of non-group D alpha-hemolytic streptococci in maternal genital and neonatal blood cultures. *J Clin Microbiol* 1983; **18**: 101–103.
42. Honberg PZ, Gutschik E. *Streptococcus bovis* bacteraemia and its association with alimentary-tract neoplasm. *Lancet* 1987; **i**: 163–164.
43. Leport C, Bure A, Leport J, Vilde JL. Incidence of colonic lesions in *Streptococcus bovis* and enterococcal endocarditis. *Lancet* 1987; **i**: 748.
44. Monsdale MT, Eykyn SJ, Phillips I. Infective endocarditis 1970–1979: a study of culture-positive cases in St. Thomas' Hospital. *Q J Med* 1980; new series XLIX *no. 195*: 315–328.
45. Powers GF, Boisvert PL. Age as a factor in streptococcosis. *J Pediatr* 1944; **25**: 481–504.
46. Rouse BT, Horohov DW. Immunosuppression in viral infections. *Rev Infect Dis* 1986; **8**: 850–873.
47. Degre M. Interaction between viral and bacterial infections in the respiratory tract. *Scand J Infect Dis* 1986; *Suppl 49*: 140–145.
48. Tashiro M, Ciborowski P, Klewk H-D, Pulverer G, Rott R. Role of staphylococcus protease in the development of influenza pneumonia. *Nature* 1987; **325**: 536–537.
49. Freeman R, Gould FK. Factors affecting development of peritonitis in continuous ambulatory peritoneal dialysis. *Br Med J* 1985; **290**: 318–319.
50. Goodship THJ, Heaton A, Rodger RSC, Ward MK, Wilkinson R, Kerr DNS. Factors affecting development of peritonitis in continuous ambulatory peritoneal dialysis. *Br Med J* 1984; **289**: 1485–1486.

51. Yoder EL, Mendez J, Khatib R. Spontaneous gangrenous myositis induced by *Streptococcus pyogenes*: case report and review of the literature. *Rev Infect Dis* 1987; **9**: 382–385.
52. Fischbacher CM, Green ST. Varicella and life-threatening streptococcal infection. *Scand J Infect Dis* 1987; **19**: 519–520.
53. Sferra TJ, Pacini DL. Simultaneous recovery of bacterial and viral pathogens from cerebrospinal fluid. *Pediatr Infect Dis J* 1988; **7**: 552–556.
54. Dagan R, Hall CB, Menegus MA. Atypical bacterial infections explained by a concomitant virus infection. *Pediatrics* 1985; **76**: 411–414.
55. Adler MW. ABC of AIDS: range and natural history of infection. *Br Med J* 1987; **294**: 1145–1147.
56. Young LS. Treatable aspects of infection due to human immunodeficiency virus. *Lancet* 1987; **ii**: 1503–1506.
57. Hewitt WD, Farrar WE. Bacteraemia and ecthyma caused by *Streptococcus pyogenes* in a patient with acquired immunodeficiency syndrome. *Am J Med Sci* 1988; **295**: 52–54.
58. Ho DD, Murata GH. Streptococcal lymphadenitis in homosexual men with chronic lymphadenopathy. *Am J Med* 1984; **77**: 151–153.
59. Krasinsky K, Borkowsky W, Bonk S, Lawrence R, Chandwani S. Bacterial infections in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 1988; **7**: 323–328.
60. Melbye M. The natural history of human T lymphotropic virus – III infection – the cause of AIDS. *Br Med J* 1986; **292**: 5–12.
61. Beverley P, Sattentan Q. ABC of AIDS: immunology of AIDS. *Br Med J* 1987; **294**: 1536–1538.
62. Hanson L, Soderstrom R, Aranzini A, Bengtsson U, Bjorkander J, Soderstrom T. Immunoglobulin subclass deficiency. *Pediatr Infect Dis J* 1988; **7**: S17–S21.
63. Aucouturier P, Couderc LJ, Gouet D, Danon F, Gombert J, Matheron S, Saimot AG, Clauvel JP, Preud'homme JL. Serum immunoglobulin G subclass dysbalances in the lymphadenopathy syndrome and acquired immune deficiency syndrome. *Clin Exp Immunol* 1986; **63**: 234–240.
64. Murphy, PM, Lane HC, Gallin JI, Fauci AS. Marked disparity in incidence of bacterial infections in patients with the acquired immunodeficiency syndrome receiving interleukin-2 or interferon-gamma. *Ann Intern Med* 1988; **108**: 36–41.