Group C Streptococcal Bacteremia: Analysis of 88 Cases

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Eighty-eight cases of group C streptococcal bacteremia were reviewed retrospectively. Most patients had underlying diseases (72.7%), predominantly cardiovascular disease (20.5%) or malignancy (20.5%). The infection originated most often from the upper respiratory tract (20.5%), the gastrointestinal tract (18.2%), or the skin (17.1%). Prior exposure to animals or animal products was reported in 23.9% of cases. The most common clinical manifestations of group C streptococcal bacteremia were endocarditis (27.3%), primary bacteremia (22.7%), and meningitis (10.2%). Of streptococcal isolates, 61.4% were not speciated, 19.3% were *Streptococcus equisimilis*, 17.1% were *Streptococcus zooepidemicus*, and two (2.3%) were *Streptococcus equi*. The isolates were sensitive to most antibiotics, and most patients were treated with β-lactam agents. Mortality was high (25.0%), especially among older patients and patients with endocarditis, meningitis, and disseminated infection. Group C streptococcal bacteremia does not differ from bloodstream infection caused by other β-hemolytic streptococci with regard to clinical presentation, treatment, or outcome.

Group C streptococci are common pathogens in animals and also cause infections in humans. *Streptococcus equisimilis*, *Streptococcus zooepidemicus*, and *Streptococcus equi* have been implicated as causes of bacteremia in humans [1–3]. Multiple manifestations of group C streptococcal infection associated with bacteremia have been reported, including pharyngitis [3], epiglottitis [4], sinusitis [5], and meningitis [6]; infections of soft tissue [3], bone [7], and joints [8]; intraabdominal abscesses [3]; pneumonitis [9]; intravascular infections [10]; pericarditis [11]; and endocarditis [12]. Primary bacteremia has been reported as well [2].

While recent reviews have looked at the different manifestations of group C streptococcal infection [2, 3], the ramifications of bacteremia with this organism have not been extensively explored. It has been assumed that optimal treatment for group C streptococcal bacteremia is similar to that for bloodstream infection with streptococci of Lancefield group A or B. However, some reports suggest that group C streptococcal bacteremia may be more malignant and, like serious group G streptococcal infection [13], may require special vigilance with regard to antibiotic tolerance and susceptibility patterns.

In this article we present three new cases of group C streptococcal bacteremia and review 85 cases reported in the literature. We have analyzed risk factors, presentations, manifestations, treatments, and outcomes in these cases to gain further insight into this uncommon infection.

Methods

The English-language literature was extensively reviewed for cases of group C streptococcal bacteremia; both computer-generated listings and cross-referencing of published articles were used. A case was considered evaluable if sufficient demographic information was available for the clear identification of an individual patient. In addition, the patient was required to have documented evidence of bacteremia, with at least one blood culture positive for group C streptococci. The requirement for an illness compatible with streptococcal bacteremia minimized the inclusion of patients with contaminated blood cultures.

All cases were assessed (when data were available) for age, gender, duration of illness before admission, clinical presentation, underlying diseases, source of infection, treatment modalities, antibiotic sensitivities of the pathogen, duration of therapy, outcome, recurrence, and sequelae. Data were assessed by Student's t test and χ^2 analysis.

Case Reports

Case 1. A 48-year-old woman who had received chemotherapy 10 days earlier for metastatic breast cancer presented to her local hospital with a 3- to 4-day history of fever, anorexia, mucositis, and hematochezia. She was neutropenic and was treated with ceftazidime before transfer to the University of Michigan Medical Center on that same day.

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The patient was an ill-appearing woman with a temperature of 37.6°C, a pulse of 100/min, a blood pressure of 130/82 mm Hg, and respirations of 20/min. On physical examination she had oral thrush; severe mucositis; petechiae over her arms and trunk; tender, swollen left knee and ankle joints; and multiple erythematous, tender, macular lesions measuring up to 3 cm by 7 cm on the left elbow, left knee, right posterior arm, and right buttock. Funduscopic, pulmonary, cardiac, and abdominal examinations were normal. Except for disorientation to time and place, the patient's neurologic examination was normal.

Laboratory studies revealed 800 white blood cells (WBCs)/μL (40% neutrophils, 16% band forms, and 44% lymphocytes), a hemoglobin level of 9.4 g/dL, a hematocrit of 28.4%, and a platelet count of 204,000/μL. Renal function and the level of serum electrolytes were normal. Tests of hepatic function gave elevated values, with an aspartate aminotransferase level of 51 U/L and an alanine aminotransferase level of 48 U/L. Hematuria with a few leukocytes was noted on urinalysis. A chest roentgenogram, echocardiogram, and lumbar puncture were normal.

Because of swelling and tenderness, arthrocenteses of the left tibiotalar and subtalar joints were done. Turbid yellow fluid was aspirated from each joint. The tibiotalar aspirate contained 250 WBCs/μL and 360,000 red blood cells (RBCs)/μL. The subtalar aspirate had 345 WBCs/μL (73% neutrophils, 26% histiocytes, and 1% eosinophils) with 3,305 RBCs/μL. Gram staining and culture of both fluids yielded negative results.

Six blood cultures were positive for group C streptococci (*S. equisimilis*). The isolate was uniformly sensitive to all classes of penicillins, cephalosporins, and macrolides, with MICs of $\leq$0.2 μg/mL. The MIC of vancomycin, gentamicin, and ciprofloxacin was 0.4 μg/mL. No antibiotic tolerance was evident; i.e., the MICs equaled the MBCs of all antibiotics.

Because of a penicillin allergy, the patient was given a 4-week course of vancomycin and tobramycin for septic arthritis and possible endocarditis. Her condition improved quickly, with resolution of neutropenia and clearance of skin lesions.

Case 2. A 58-year-old man with a history of alcohol abuse and laryngeal carcinoma was admitted to Evanston Hospital following a grand mal seizure. One week before admission he had developed nausea, vomiting, diarrhea, and low-grade fever, and 2 days before admission he had become short of breath. He had a blood pressure of 60/0 mm Hg, a pulse of 140/min, respirations of 30/min, and a temperature of 38.3°C. Rhonchi were heard on pulmonary examination; no murmur was heard. Examination of the eyes, abdomen, and skin was normal except for a 6-cm erythematous, tender, warm area on the left medial thigh.

Laboratory evaluation revealed hyponatremia (sodium, 124 mEq/L), hypokalemia (potassium, 3.4 mEq/L), and metabolic acidosis (anion gap, 27). Evidence of disseminated intravascular coagulation was present, with a platelet count of 69,000/μL, elevated prothrombin and partial thromboplastin times, and the presence of fibrin split products. The patient had leukocytosis (13,200 WBCs/μL, with 63% neutrophils, 21% band forms, 8% lymphocytes, and 8% monocytes), hepatic dysfunction (aspartate aminotransferase, 645 U/L; alanine aminotransferase, 131 U/L; and lactate dehydrogenase, 719 U/L), microscopic hematuria, and a creatine phosphokinase level of 11,000 U/L.

Despite vigorous resuscitation with fluids, the patient became unresponsive, apneic, and bradycardic and required mechanical ventilation and support with pressors. Antibiotic therapy with ceftazidime and vancomycin was initiated. Twelve hours after admission, two sets of blood cultures yielded group C streptococci (*S. equisimilis*). The organism was sensitive to all penicillins, cephalosporins, and macrolides but resistant to sulfonamides as assessed by Kirby-Bauer disk susceptibility testing. The antibiotic regimen was changed to 12 million units of benzylpenicillin daily.

Bacteremia cleared after 24 hours, and the patient became afebrile. A systolic murmur was heard on the third day, and an echocardiogram revealed a vegetation on the noncoronary cusp of the aortic valve. The results of computed tomography of the head and lumbar puncture were normal. Four days after admission fever again developed. *Staphylococcus epidermidis* was cultured from an arterial catheter and blood. Antibiotic therapy was changed to vancomycin for 10 days, and the patient then completed a 4-week course of therapy with penicillin G without further complications.

Case 3. A 49-year-old woman presented to Evanston Hospital with a 1-day history of bloody diarrhea. She had noted a change in her bowel habits over the previous 2 months but reported that she had not had fever, weight loss, or anorexia. She had previously been well.

Physical examination revealed an obese woman in no distress who had a temperature of 37.8°C. A mass was felt on rectal examination, and the stool was positive for blood. Laboratory examination showed a WBC count of 16,000/μL, with 76% neutrophils, 12% band forms, 4% lymphocytes, 5% monocytes, and 3% eosinophils; a hemoglobin level of 10.4 g/dL; a hematocrit of 32.5%; and a platelet count of 634,000/μL.

On the night of admission, the patient's temperature rose to 39°C. Cultures of blood drawn that night yielded group C streptococci (*S. equisimilis*) sensitive to all penicillins, cephalosporins, and sulfonamides. Therapy with cefoxitin was begun and continued for 2 weeks. A biopsy revealed adenocarcinoma of the colon. The patient had no complications from her streptococcal sepsis.

Results

Demographics. A total of 88 cases of group C streptococcal bacteremia were reviewed [1–43]. Fifty-nine patients (67%)

were male and 29 (33%) were female. Seventeen patients (19.3%) were <18 years of age. The mean age of all patients (± SEM) was 45 ± 2.6 years (range, 1 month to 93 years), that for males was 47 ± 3.3 years, and that for females was 41 ± 4.4 years.

Underlying diseases. Many of the 88 patients had serious underlying illnesses, including cardiovascular disease (20.5%), malignancy (20.5%), and immunosuppression (14.8%) (table 1). Twenty-three patients (26.1%) had no underlying disease noted.

Microbiology. Seventeen isolates (19.3%) were *S. equisimilis* ([2–4, 7, 13–22] and our three cases), 15 (17.1%) were *S. zooepidemicus* [6, 9, 23, 24, 42], and two (2.3%) were *S. equi* [25, 43]; 54 isolates (61.4%) were not speciated. No case of *Streptococcus dysgalactiae* bacteremia was found. Eight patients (9.1%) had polymicrobial bacteremia: three with aerobic gram-negative bacilli, three with anaerobic gram-negative bacilli, and two with gram-positive cocci [3, 26].

Exposure to animals. Twenty-one patients (23.9%) had a history of exposure to animals or animal products [6, 9, 10, 14, 23, 24, 26–28, 43]. Fourteen (66.7%) of the 21 infections (including a cluster of 10 cases of bacteremia traced to the consumption of unpasteurized cow's milk in England [6]) were due to *S. zooepidemicus* [6, 9, 23, 24], one was due to *S. equisimilis* [14], one was due to *S. equi* [43], and five isolates were not speciated [10, 26–28]. Four patients were farmers [10, 23, 24, 26], one was a butcher [27], and several had had contact with dogs, cows, or horses, some of which had been ill [9, 14, 28, 43].

Table 1. Underlying conditions in patients with group C streptococcal bacteremia.

Condition	No. of patients (%)*
Cardiovascular disease	18 (20.5)
Valvular disease	9
Coronary artery disease	7
Peripheral vascular disease	2
Malignancy	18 (20.5)
Leukemia/aplasia	10
Solid tumors	7
Lymphoma	1
Immunosuppression	13 (14.8)
Chemotherapy	9
Other†	4
Substance abuse	8 (9.1)
Alcohol	6
Intravenous drug	2
Chronic wounds or stasis	7 (8.0)
Diabetes mellitus	7 (8.0)
Chronic renal failure	6 (6.8)
Miscellaneous conditions‡	19 (21.6)
None	23 (26.1)

* Many patients had more than one underlying condition. In 19 cases underlying conditions were not mentioned.
† Radiation therapy, splenectomy, glucocorticoids, and hypogammaglobulinemia.
‡ Arthritis, gastrointestinal disease, neurologic disease, hypertension, chronic obstructive pulmonary disease.

Source of infection. The source of group C streptococcal bacteremia was not clearly identified in many cases; no specific portal of entry for infection was found in 34 cases (38.6%) (table 2). An upper respiratory tract source was noted in all patients with pneumonia and sinusitis [3, 5, 9, 19] and in many neutropenic patients with bacteremia ([3, 14, 26] and our case 1). The gastrointestinal tract was believed to be the source of bacteremia in 16 patients, including 10 whose illness was traced directly to the ingestion of contaminated milk ([3, 6] and our case 3). Cutaneous sources included wounds, ulcerations, and bacteremia associated with intravenous drug use ([1, 3, 8, 26, 27, 29–32] and our case 2). All of the infections from genitourinary sources occurred in women during the peripartum period [3, 22, 33, 34].

Signs and symptoms. Systemic symptoms were common (table 3); fever, chills, and fatigue were noted most often. For the 50 patients whose body temperature was recorded at admission, the mean temperature was 39.1°C ± 0.1°C (range, 35.2°C–40.8°C). Four patients were afebrile.

Focal symptoms included gastrointestinal symptoms in 43 (61.4%) of the 70 evaluable cases; most common were vomiting (13 cases), nausea (nine), and diarrhea (seven). The neurologic symptoms in 27 cases (38.6%) included a change in mental status in 15 instances and headache in nine. Respiratory symptoms, including dyspnea, chest pain, and coryza, were recorded in 19 cases (27.1%) and bone and joint pain

Table 2. Probable source of infection with group C streptococci.

Source	No. of patients (%)
Upper respiratory	18 (20.5)
Gastrointestinal	16 (18.2)
Food-borne	10 (11.4)
Other	6 (6.8)
Cutaneous	15 (17.1)
Genitourinary	5 (5.7)
Not known	34 (38.6)

Table 3. Signs and symptoms in patients with group C streptococcal bacteremia.

Sign/symptom	No. of patients (%)*
Systemic	
Fever	47 (67.1)
Chills	21 (30.0)
Fatigue	16 (22.9)
Myalgia	8 (11.4)
Anorexia	7 (10.0)
Night sweats	4 (5.7)
Focal	
Gastrointestinal	43 (61.4)
CNS	27 (38.6)
Respiratory	19 (27.1)
Bone/joint	8 (11.4)

* Most patients had more than one sign or symptom. The analysis was based on the 70 patients whose symptoms were evaluable.

in eight (11.4%). The mean duration of symptoms before admission (evaluable in 61 cases) was 14 ± 2.7 days (range, 0.5–150 days).

The clinical syndromes associated with group C streptococcal bacteremia are listed in table 4. Endocarditis, the most frequently reported manifestation, was present in 24 cases (27.3%) ([3, 6, 12, 13, 16, 18, 23, 26, 27, 30, 32, 34–39] and case 2). Primary bacteremia was reported in 20 cases (22.7%) ([1–3, 6, 7, 9, 14, 25, 26, 28, 29, 31, 40] and case 3), meningitis in nine (10.2%) [6, 22, 24, 28, 40–42], cutaneous and subcutaneous infections in eight (9.1%) [3, 26, 29, 43], and disseminated infection in five (5.7%) ([17, 20, 21, 33] and case 1). The remaining 22 patients had a variety of syndromes associated with group C streptococcal bacteremia [3, 4, 8–11, 15, 19, 40]. The number of patients in each of these categories was too small to serve as a basis for meaningful conclusions.

Endocarditis. The most common syndrome seen with group C streptococcal bacteremia was endocarditis, occurring in 24 cases. Thirteen patients had definite endocarditis [3, 6, 16, 26, 27, 30, 32, 34, 36, 37] and 11 had probable endocarditis ([3, 6, 12, 13, 18, 23, 35, 36, 38, 39] and case 2), according to the criteria of Von Reyn et al. [44]. The mean age of patients with endocarditis (± SEM) was 53.2 ± 4.2 years; two patients were children [18, 38]. Five cases of endocarditis were due to *S. zooepidemicus* [6, 32], four to *S. equisimilis* ([13, 16, 18] and case 2), and the rest to unspeciated isolates. In only eight cases was a possible source of infection identified (skin lesions in four, dental pathology in two, septic abortion and intravenous drug use in one each), but another four cases were preceded by exposure to animals. Known underlying cardiac valvular disease was present in only seven cases [3, 12, 18, 23, 26, 32, 38], but in 12 cases not enough detail was given to evaluate this parameter (table 5). As expected, the most commonly involved valves were the aortic (eight of 20 cases) and the mitral (seven of 20). Four other patients each had two valves infected (the aortic and mitral in three and the aortic and tricuspid in one); one patient had tricuspid endocarditis, and in four cases the valve involved was not stated.

The mean duration of symptoms (± SEM) was 17.4 ± 2.8 days; most patients had subacute endocarditis. Symptoms were described in 19 of 24 cases, and signs were noted in 18. Nonspecific symptoms (chills, fever, fatigue, anorexia) predominated. Nine patients had dyspnea; seven had nausea, vomiting, or abdominal pain; and six had CNS manifestations (confusion, ataxia, hemiparesis). Murmurs were noted at the time of admission in all but three cases and fever in all but three. Embolic phenomena (petechiae, Roth's spots, Janeway lesions, Osler's nodes) were present in only eight cases, and splenomegaly was found in four.

Twenty-three patients were treated with antibiotics, most commonly either penicillin G or ampicillin combined with streptomycin (six patients) [3, 16, 23, 32, 35, 39] or gentamicin (two patients) [12, 27] or penicillin G alone (eight patients) ([13, 18, 26, 30, 36, 38] and case 2). Four patients received a penicillin and cefotaxime [6], two received sulfonamides [34, 36], one received no antibiotics (because endocarditis was not diagnosed before death [3]), and one received unspecified antibiotics [37]. Four patients required surgical replacement of the affected heart valve because of severe congestive heart failure [26, 27, 36, 37], and two required a permanent pacemaker for complete heart block [26, 27].

Complications of group C streptococcal endocarditis were common, including refractory heart failure in nine cases; major embolic events involving the brain, the eye, the lung, or an extremity in 10; and renal failure in three. In six cases the size of the vegetation was mentioned at the time of surgery or necropsy; four of the six patients had large vegetations [3,

Table 4. Clinical syndromes associated with group C streptococcal bacteremia.

Syndrome	No. of patients (%)
Endocarditis	24 (27.3)
Primary bacteremia	20 (22.7)
Neutropenia	8
Meningitis	9 (10.2)
Cutaneous infection	8 (9.1)
Abscess	5
Cellulitis	3
Disseminated infection	5 (5.7)
Intraabdominal infection	5 (5.7)
Peritonitis	2
Abscess	3
Pneumonia	4 (4.6)
Head/neck infection	4 (4.6)
Sinusitis	2
Pharyngitis/epiglottitis	2
Bone/joint infection	3 (3.4)
Arthritis	2
Osteomyelitis	1
Vascular infection	3 (3.4)
Mycotic aneurysm	2
Fistula infection	1
Genitourinary infection	2 (2.3)
Pericarditis	1 (1.1)

Table 5. Underlying cardiac valvular disease in patients with group C streptococcal endocarditis.

Valvular disease	No. of patients*
Bicuspid aortic valve disease	3
Ventriculoseptal defect	2
Preexisting murmur, etiology not defined	2
Rheumatic valvular disease	1
Asymmetric septal hypertrophy	1
Normal valves†	5
Unknown or not stated	12

* Two patients had more than one lesion.
† Proved at necropsy or surgery.

16, 27, 34]. Eight patients (33.3%) died of endocarditis [3, 6, 13, 16, 32, 34, 36]. Three who died had received either sulfonamides or no antibiotics [3, 34, 36]. One patient died within 2 days of diagnosis [16]. The mean age of those dying was 64.8 ± 5.5 years.

Primary bacteremia. Twenty patients, eight of whom were neutropenic, had bacteremia alone. The mean age of the neutropenic patients (± SEM) was 34.5 ± 10.3 years; four were children. Seven of these patients had recently received chemotherapy for acute leukemia [2, 3, 14, 25, 26], and one was chronically neutropenic secondary to aplastic anemia [31]. Symptoms were nonfocal and included fever in seven instances and skin lesions in two. Group C streptococci were isolated from the throat of two patients and the nares of two, although clinical signs of pharyngitis or upper respiratory infection were not present. Only one isolate was speciated (*S. equisimilis*) [14]. There were three episodes of polymicrobial bacteremia—two in one patient and one in a second patient; two of these episodes involved *Escherichia coli* [3. 26], and one involved *Klebsiella pneumoniae* [3]. Two patients relapsed with streptococcal bacteremia, presumably from urinary and pharyngeal sources [3]. Most patients were initially treated with broad-spectrum antibiotics and then switched to more specific therapy with penicillin or cephalothin once group C streptococci were identified. Only one of these patients died, and he was in leukemic relapse [26]. Other patients responded rapidly to 10–14 days of antibiotic treatment and had no sequelae.

The 12 nonneutropenic patients with primary bacteremia tended to be older (mean age, 56.7 ± 6.4 years); only one of these patients was a child. Four patients were healthy [7, 9, 28, 40], while no history was given for three patients [6]. Underlying illnesses included mycosis fungoides [29], carcinoma of the vulva [1], carcinoma of the colon (case 3, present report), rheumatic heart disease [28], and—in a single patient—diabetes mellitus, congestive heart failure, and chronic renal failure [3]. Of four infections with *S. zooepidemicus* [6, 9], three were due to the ingestion of milk and one to contact with an infected horse. Two patients had primary bacteremia due to *S. equisimilis* ([7] and case 3), and six isolates were not speciated. Patients presented with fever [7], gastrointestinal symptoms [6], myalgias [3], and headache [2]. Ten patients were treated with a penicillin. The only patient who died received no antibiotics [3]. One patient relapsed with acute cholecystitis and bacteremia, presumably after seeding of the gallbladder [28]; another patient developed cervical spine osteomyelitis as a late complication [7].

Meningitis. Meningitis due to group C streptococci occurred mostly at the extremes of age. Five of six adult patients were elderly (mean age, 63.7 ± 6.8 years) [6, 24, 28, 42], and three patients were infants (two neonates and one 4 months of age) [22, 40, 41]; all had previously been healthy. Three elderly patients had consumed contaminated milk [6], and the other two had exposure to animals as a possible source of infection [24, 28]. Meningitis was due to *S. zooepidemicus* in four elderly patients, *S. equisimilis* caused disease in a 2-day-old infant [22], and nonspeciated strains were responsible for the remaining four cases. The illness was acute in all cases but especially in infants, who were ill for only 1 day before diagnosis. The primary symptom in the elderly was confusion. Results of CSF analysis (given for five patients) were typical of acute bacterial meningitis: numerous leukocytes (290–5,300 cells/μL), with a predominance of neutrophils; low glucose levels (22–29 mg/dL); and elevated protein concentrations (157–740 mg/dL). All patients were treated with penicillin G. The children all lived, although one had serious sequelae [41]; two of the five elderly patients died [6].

Cutaneous and subcutaneous infection. Eight patients had cutaneous or subcutaneous infection; three had cellulitis [3, 26] and five had abscesses [3, 29, 43]. These patients were elderly (mean age, 62 ± 7.3 years), and five of the eight had serious underlying illnesses. Two patients with diabetes mellitus, peripheral vascular disease, and venous stasis ulcers developed lower extremity cellulitis [3]; two patients with malignancy had abscesses and another had cellulitis [3, 26, 29]. All responded quickly to therapy with penicillins or cephalosporins, although one patient with Hodgkin's disease and a breast abscess relapsed twice [3]. Three patients had incision and drainage of the abscess in addition to antibiotic therapy.

Disseminated infection. Five patients had bacteremia and involvement of multiple organ systems without specific criteria for endocarditis. These patients tended to be young (31.6 ± 5.2 years; range 19–48 years) and female (four of five). Three patients had been healthy [17, 21, 33], one was neutropenic secondary to chemotherapy for breast carcinoma (case 1, present report), and the last had congenital heart disease and chronic renal failure [20]. All were acutely ill, presenting within 3–6 days of the onset of symptoms. No exposures to animals were mentioned. All five patients had fever, four had gastrointestinal symptoms, and three had bone and joint pain. Three patients had septic arthritis or osteomyelitis, three had pneumonia, two had skin abscesses, two had pharyngitis/mucositis, two had hematuria or pyuria, and one had meningitis and brain abscess. Three patients had bacteremia due to *S. equisimilis* [17, 20, 21], and two isolates were not speciated. Three patients were treated with penicillin or a cephalosporin. The patient given vancomycin and tobramycin was allergic to penicillin. One patient in the preantibiotic era survived after prolonged hospitalization and multiple surgical procedures [33]. The two patients who died had previously been healthy [17, 21].

Laboratory findings. The mean WBC count was 15,544 ± 1,316/μL in the 36 patients for whom these data were reported. Little information on other laboratory tests was given. Although such findings were mentioned in only 13 cases, 10 patients had elevated transaminase and/or serum bilirubin levels and five were noted to be jaundiced. Titers

of antistreptolysin O were elevated in four of six cases tested [4, 7, 18, 20, 27, 39], and three of these four patients had *S. equisimilis* bacteremia. The streptozyme test was positive in one other case [38].

Treatment. Sixty-eight patients were treated with antibiotics alone, 17 underwent a surgical procedure (generally valve replacement in those with endocarditis and incision and drainage in those with abscesses) as well as antibiotic treatment, one in the preantibiotic era was treated with surgery alone, and two died before treatment could be given. Antibiotic treatment of group C streptococcal bacteremia was difficult to assess because patients received multiple antibiotics—with varying doses, routes, and durations—during hospitalization. The mean duration of therapy for all patients was 22.4 ± 2.4 days (range, 0–128 days). Patients with endocarditis generally received longer courses of therapy (usually 4–6 weeks). Most patients received a penicillin alone (38.8%), a penicillin with an aminoglycoside (22.4%), or a cephalosporin alone or combined with an aminoglycoside or penicillin (24.7%). Small numbers of patients received other antibiotics—vancomycin, erythromycin, clindamycin, or sulfonamides.

Antibiotic susceptibilities. Antibiotic susceptibilities were determined for only 32 isolates of group C streptococci. These isolates were uniformly sensitive to penicillin, ampicillin, cephalothin, chloramphenicol, clindamycin, and erythromycin. One of four isolates was resistant to tetracycline and seven of nine to aminoglycosides. Although four isolates were sensitive to trimethoprim-sulfamethoxazole, three isolates were resistant to sulfonamides alone.

MBCs were evaluated in only 10 instances ([13, 15, 18, 19, 21, 22, 32, 39, 43] and case 1). Tolerance (defined as an MBC ≥32-fold higher than the MIC) to penicillin or gentamicin was found in only one isolate [13]. The combination of penicillin and an aminoglycoside was synergistic in one isolate [13] but not in another [18]. Synergy was not mentioned in most cases.

Complications. Six patients had recurrent group C streptococcal bacteremia [3, 28, 29]; three had one relapse and three had two. All but one of these patients had underlying hematologic disorders, including neutropenia in two instances [3] and hypogammaglobulinemia in one [3]. All patients with relapses responded to repeated courses of antibiotics; in two cases drainage or removal of the source of recurrent infection was also required.

Eight patients had significant sequelae, including vertebral osteomyelitis [7], acute cholecystitis [28], and epidural abscess due to group C streptococci [3]. In addition, permanent functional disability followed endocarditis in three cases (stroke, blindness, and limb ischemia, respectively [6, 35, 36]) and meningitis in two cases (deafness and mental retardation, respectively [41, 42]). One patient developed candida endocarditis as he finished therapy for group C streptococcal endocarditis [30].

Eight patients (9.3%) had evidence of coagulopathy: three had disseminated intravascular coagulation ([9, 20] and case 2), three had pulmonary emboli [3, 6], and one each had deep venous thrombosis without mention of pulmonary emboli [28] and multiple septic thrombi noted in many viscera at necropsy [17]. Whether the pulmonary emboli and deep venous thrombosis represented complications of streptococcal bacteremia or were secondary to prolonged debilitating illness in these patients is not known.

Only one patient was documented to have glomerulonephritis with subendothelial antigen-antibody complexes [9]. This complication occurred during bacteremia; no patient had poststreptococcal glomerulonephritis.

Mortality. Twenty-two patients died (25.0%). The difference in mortality between male and female patients was not significant. The patients who died were significantly older than those who survived (57 ± 4 years vs. 41.0 ± 3.1 years; $P = .008$). Only one child died. Six (40%) of 15 patients with *S. zooepidemicus* infection and three (17.6%) of 17 patients with *S. equisimilis* infection died (difference not significant). Mortality was highest among patients who had endocarditis, meningitis, and disseminated infection with multiple-organ involvement. The duration of symptoms in patients who lived did not differ significantly from that in patients who died (12.8 ± 3.4 days vs. 18.1 ± 3.7 days). Patients who died received significantly fewer days of therapy than patients who survived (13.2 ± 3.8 days vs. 25.5 ± 2.7 days; $P = .018$).

Discussion

Streptococci belonging to Lancefield group C have been recognized as a cause of infections in humans with increasing frequency in recent years. This increase may reflect the advent of rapid specific tests for the typing of streptococci in clinical microbiology laboratories [45]. In the past the use of a bacitracin disk, to which group C streptococci may be susceptible, led to the identification of some of these organisms as group A streptococci [35, 45]; moreover, many laboratories did not speciate β-hemolytic streptococci that were not group A.

Group C streptococci may be found as normal flora in the pharynx, the gastrointestinal and genitourinary tracts, and the skin [46–48]. The pharynx is a common reservoir, with 2%–8% of healthy individuals harboring group C streptococci [46]. Forrer and Ellner found group C streptococci as often as group A streptococci in patients with upper respiratory complaints [48]; however, only half of the patients with group C streptococci in the pharynx had clinical evidence of pharyngitis.

The four species of group C streptococci—*S. equisimilis*, *S. zooepidemicus*, *S. equi*, and *S. dysgalactiae*—are differentiated by biochemical and other characteristics [49]. Most strains produce β hemolysis on sheep blood agar, but all types of hemolysis have been noted [49]. All four species are com-

mon pathogens in domestic animals, birds, rabbits, and guinea pigs [50].

S. dysgalactiae is an uncommon human pathogen that has not been noted to cause bacteremia [51]. This organism, which does cause mastitis in cows, generally produces α hemolysis or no hemolysis, ferments trehalose, and produces a soluble hemolysin that is not streptolysin O or S [49, 50].

S. equisimilis is considered the most common group C streptococcal species to colonize and cause infection in humans [52–54]. However, in our review of the cases of bacteremia in which the organism was speciated, *S. equisimilis* was only slightly more common than *S. zooepidemicus*. *S. equisimilis* ferments trehalose but not sorbitol and produces streptokinase and streptolysin O but not streptolysin S [49, 52]. Domestic animals (horses, cattle, pigs, and chickens) may be infected with *S. equisimilis*; pneumonia, septic arthritis, septicemia, and abscesses have been noted [50, 55, 56].

S. zooepidemicus, reported by many authors to be a common animal pathogen and an uncommon human pathogen [50, 57, 58], was almost as common as *S. equisimilis* in our review of bacteremia. *S. zooepidemicus* ferments sorbitol but not trehalose, produces a novel hemolysin but not streptolysin O or S, does not produce streptokinase, and is not considered part of the normal flora in humans [49, 50, 52, 53]. Significant, often epidemic infection occurs in domestic animals (horses, cattle, sheep, and pigs) [50, 56–58]. Pneumonitis, septicemia, and abscesses are common manifestations of infection in animals.

S. equi is primarily a pathogen of horses [57]. The organism ferments neither trehalose nor sorbitol, produces a soluble hemolysin but not streptolysin O or S, and does not produce streptokinase [49]. *S. equi* causes strangles, a serious and highly contagious respiratory illness in young horses [57]. We found only two cases of *S. equi* bacteremia [25, 43], one of them in a horse caretaker [43].

Group C streptococci often are associated with exposure to animals; almost one-quarter of the cases of bacteremia we reviewed were preceded by exposure to animals. In some cases direct exposure to ill animals preceded group C streptococcal bacteremia, while in others exposure to animal products occurred as part of a job and no discrete exposure to an ill animal was documented. Most cases of human infection with *S. zooepidemicus* can be traced back to an animal source [6, 9, 23, 24, 58–60], and some cases of infection with *S. equisimilis* can also be linked to animal exposure [55]. Group C streptococci appear to be unique among the common β-hemolytic streptococci (groups A, B, C, F, and G) in terms of the relationship between exposure to animals and transmission of infection. Although group A streptococci have caused outbreaks of infection in meat packers, the meat most likely served as a vehicle for spread of the organism from person to person rather than as a source of the organism [61].

Food-borne spread of infection with β-hemolytic streptococci, notably groups A and C, has been reported [58, 62]. A milk-borne outbreak of *S. zooepidemicus* infection in Halifax, Yorkshire, England, is a dramatic example of the spread of group C streptococci from animals to humans; in that instance unpasteurized milk from cows colonized with *S. zooepidemicus* was consumed [6]. Other food-borne outbreaks involving group C streptococci include an outbreak in New Mexico in which cheese made from unpasteurized cow's milk was the source of infection [63].

β-Hemolytic streptococci are an unusual cause of bacteremia, found in only 2%–3% of cases in one large study from the Mayo Clinic [64]. In that investigation group C streptococci represented ~5% of all β-hemolytic streptococcal isolates from bacteremia and accounted for only 0.1% of all positive blood cultures. More frequently isolated β-hemolytic streptococci included those of group A (0.8% of all cultures), group B (0.6%), and group G (0.2%) [64]. In certain institutions these frequencies may vary; for instance, in women's hospitals group B streptococcal bacteremia is more common [65], and in hospitals that serve a large number of intravenous drug users group A streptococcal bacteremia may be more frequent [66].

The majority of infections due to group C streptococci are community acquired. In our series 88.2% of cases were community acquired and only 11.8% were clearly acquired in the hospital. Likewise, the majority of bacteremic group A and group G streptococcal infections are community acquired [64, 67–71], whereas group B streptococcal bacteremia in adults is often hospital acquired [65, 72–74]; i.e., 46%–70% of nonparturient adults with group B streptococcal bacteremia acquire the infection in the hospital [72, 73].

We found that underlying diseases were commonly associated with the development of group C streptococcal bacteremia. Approximately 75% of patients for whom data on underlying conditions were available had significant underlying diseases, including cardiovascular disease, malignancy, and immunosuppression. This figure is similar to those for groups A, B, F, and G streptococcal bacteremia, in which malignancies, cardiovascular diseases, diabetes mellitus, immunosuppression, and chronic renal or hepatic disease are noted frequently [64, 67–71, 75]. Perhaps group G streptococci have a stronger association with malignancy than do other β-hemolytic streptococci [64, 67, 69, 71], and group A streptococci have an increased association with intravenous drug use [66]. If parturient women and neonates are excluded from the group analyzed, patients with group B streptococcal bacteremia have underlying diseases similar to those noted for patients infected with the other β-hemolytic streptococci [72, 73, 76].

The portal of entry for the majority of bacteremic streptococcal infections is the skin. Particularly in group A and group G streptococcal infections, the upper respiratory and gastrointestinal tracts are uncommon sources of bacteremia [64, 69, 70]. We found that only 17.1% of cases of group C streptococcal bacteremia had a well-described cutaneous

source; upper respiratory and gastrointestinal tract sources were slightly more common. The reasons for the differences in source between infections due to group C streptococci and those due to other β-hemolytic streptococci may be related to the high proportion of patients with group C streptococcal infection related to animal exposure.

The most common presentation of bacteremic group C streptococcal infection was that of an acute illness with fever, chills, and prostration. In this regard, group C infections were similar to those caused by other β-hemolytic streptococci [1, 64, 68–73]. The exception to this pattern of acute presentation was endocarditis. Most patients with group C streptococcal endocarditis had a subacute illness.

Gastrointestinal symptoms were common among patients with group C streptococcal bacteremia, even though actual infection of the gastrointestinal tract was uncommon. A preponderance of gastrointestinal problems has also been noted in cases of bacteremia due to other β-hemolytic streptococci, especially those of group A [66, 70].

Group C streptococci did not differ from streptococci of groups A, B, F, and G in the ability to cause protean disease manifestations. Bacteremic group C streptococcal infections ranged from local skin and subcutaneous infections to deep-seated suppurative infections in almost every organ system to primary bacteremia with no obvious source or metastatic focus in both neutropenic and nonneutropenic hosts. This spectrum of disease manifestations is similar to those noted in studies from Cleveland [3, 71, 75, 76] and at the Mayo Clinic [64, 77]; the authors of these studies reviewed and compared group-specific β-hemolytic streptococcal infections in their patients. It appears that group F streptococci are more likely to cause abscesses and suppurative complications [75, 77] and that group G streptococci are more likely to cause primary bacteremia [71]. Endocarditis appears to be more common with group C and group G streptococci than with organisms of groups A and B, even though the latter more often cause bacteremia [1, 64].

Endocarditis was the most common manifestation of group C streptococcal bacteremia. Most often the presentation of group C streptococcal endocarditis was subacute, whereas endocarditis due to streptococci of groups A, B, and G is usually acute in presentation [66, 67, 78–83]. β-Hemolytic streptococci can produce large valvular vegetations, and the course of infection is often aggressive, with valvular destruction and major emboli noted frequently [67, 78, 79, 81, 83]. Group C streptococci appeared to be similar in this regard; major emboli to the CNS, limbs, and lungs developed in 37.5% of patients in this series.

Mortality was high (33.3%) among patients with group C streptococcal endocarditis. Group G streptococcal endocarditis has been associated with mortality of 43%–67% [67, 79] and group B streptococcal endocarditis with mortality of 20%–85% in several small series [78, 81–83] and an overall mortality of 43.5% in a review of 62 cases [81]. The lower overall mortality reported for group A streptococcal endocarditis (14%–18%) probably reflects the resurgence of this infection in intravenous drug users and the predominance of tricuspid valve involvement in this population [66, 80].

Group A streptococci are responsible for almost all of the nonsuppurative complications of glomerulonephritis and rheumatic fever. Non-group A β-hemolytic streptococci have never been reported to cause rheumatic fever and rarely cause glomerulonephritis. Both group C and group G have occasionally been associated with glomerulonephritis [9, 84–87]. It is interesting that all of our patients whose group C streptococcal infection resulted in acute glomerulonephritis were infected with *S. zooepidemicus*. Barnham and associates have postulated that endostreptosin, a cytoplasmic polypeptide found in some strains of *S. zooepidemicus* as well as in group A streptococci, might be involved in the pathogenesis of glomerulonephritis [9, 85].

Group C streptococci are exquisitely sensitive to penicillin G, although Barnham et al. have found that *S. zooepidemicus* is killed by penicillin more slowly than is *S. equisimilis* [88]. Group C streptococci resemble those of groups A and G, with penicillin MICs of <0.1 μg/mL for most strains [89, 90]. Streptococci of groups B and F are often more resistant to penicillin [89]. Although penicillin G is the most active antibiotic, group C streptococci are susceptible to all penicillins, cephalosporins, and vancomycin [89, 90]. Tetracycline sensitivity is variable [58, 89], and organisms resistant to erythromycin have been reported recently [88, 91]. Resistance to sulfonamides is common, although more isolates appear to be susceptible to trimethoprim-sulfamethoxazole [17, 23, 28]. In a patient with a serious penicillin allergy, vancomycin should be used to treat group C streptococcal bacteremia.

The question of tolerance to penicillin and other antibiotics in group C and other streptococci has been raised by several authors [3, 13, 68, 92, 93]. We found little documentation of penicillin tolerance in the cases of group C streptococcal bacteremia we reviewed [13, 15, 18, 19, 21, 22, 32, 39]. Although Portnoy et al. [92] have described tolerance as a common finding in clinical (but not necessarily bacteremic) isolates of group C streptococci, Rolston et al. [93] did not find tolerance to be common. Similarly, conflicting results have been noted in studies of tolerance in group G streptococci [71]. In fact, whether the in vitro phenomenon of tolerance has relevance for the in vivo clinical response to an antibiotic is not clear [94].

Another controversial aspect of antibiotic treatment of group C streptococcal infections, especially endocarditis, centers around the questions of whether synergy is common with penicillins and aminoglycosides and whether combination therapy with these agents should be used to effect more rapid killing of the organism [3, 12, 13, 39]. Data are insufficient for a clear recommendation, although Stein and Panwalker noted that morbidity (severe congestive heart failure with a need for cardiac valve replacement) was less frequent among

patients with group C streptococcal endocarditis who received combination therapy than among those who received penicillin alone [12]. Similar controversy surrounds the use of combination antibiotic therapy vs. single antibiotic therapy in patients with group G streptococcal bacteremia [67, 71, 79]. Overall, we found no clear-cut evidence for the benefit of combination aminoglycoside-penicillin therapy in group C streptococcal bacteremia.

Mortality among patients with group C streptococcal bacteremia was 25%, not unlike the figure noted for bacteremia involving groups A, B, F, and G [64, 67-70, 72, 73, 77]. Infection with *S. zooepidemicus* appeared to be more virulent than that due to *S. equisimilis*; for example, mortality was more than twice as high with *S. zooepidemicus* infection. Barnham et al. noted increased recovery of *S. zooepidemicus* from sites of invasive infection in humans; these authors also found evidence of greater pathogenicity and lower antibiotic susceptibility of *S. zooepidemicus* than of *S. equisimilis* [88].

Mortality from group C streptococcal bacteremia was significantly higher among older patients. The association of increasing mortality with increasing age has been noted in patients with bloodstream infection due to streptococci of group B [72] and group F [75] but not in several large series of patients with other β-hemolytic streptococci in the blood [1, 64, 67, 69]. The presence of serious underlying diseases was a more common predictor of death from β-hemolytic streptococcal bacteremia than was age in many large series [64, 68, 69, 71]. As expected, mortality was highest among patients with the most serious manifestations of group C streptococcal infection (endocarditis, meningitis, and disseminated infection with multiple-organ involvement); this finding was in accord with those in studies of bloodstream infection with other β-hemolytic streptococci [69, 71, 75, 76].

Group C streptococcal bacteremia causes a wide variety of clinical syndromes, some associated with high mortality. However, neither its clinical presentation nor its mortality differs clearly from that of non-group C β-hemolytic streptococcal bacteremia. Group C streptococcal infection is often a zoonosis and should be suspected in clinically bacteremic patients who have had direct or indirect contact with animals.

References

1. Duma RJ, Weinberg AN, Medrek TF, Kunz LJ. Streptococcal infections: a bacteriologic and clinical study of streptococcal bacteremia. Medicine (Baltimore) **1969**;48:87-127
2. Arditi M, Shulman ST, Davis AT, Yogev R. Group C β-hemolytic streptococcal infections in children: nine pediatric cases and review. Rev Infect Dis **1989**;11:34-45
3. Salata RA, Lerner PI, Shlaes DM, Gopalakrishna KV, Wolinsky E. Infections due to Lancefield group C streptococci. Medicine (Baltimore) **1989**;68:225-39
4. Schwartz RH, Knerr RJ, Hermansen K, Wientzen RL. Acute epiglottitis caused by β-hemolytic group C streptococci. Am J Dis Child **1982**;136:558-9
5. Layon J, McCulley D. Subdural empyema and group C *Streptococcus*. South Med J **1985**;78:64-6
6. Edwards AT, Roulson M, Ironside MJ. A milk-borne outbreak of serious infection due to *Streptococcus zooepidemicus* (Lancefield group C). Epidemiol Infect **1988**;101:43-51
7. Asplin CM, Beeching NJ, Slack MPE. Osteomyelitis due to *Streptococcus equisimilis* (group C). BMJ **1979**;1:89-90
8. Hamilton ME, Gibson RS. Group C streptococcal arthritis. NY State J Med **1980**;80:1746-7
9. Barnham M, Ljunggren A, McIntyre M.Human infection with *Streptococcus zooepidemicus* (Lancefield group C): three case reports. Epidemiol Infect **1987**;98:183-90
10. Perkins DE Jr, McRae RP. An arteriosclerotic aneurysm of the abdominal aorta secondarily infected with group C, beta-hemolytic streptococci: report of a case. Am J Clin Pathol **1974**;62:646-8
11. Marsa RJ, Blomquist IK, Bansal RC, Boucek FC, Elperin LS. Acute pericarditis due to group C *Streptococcus*: report of a medically treated case. Am J Med **1989**;86:474-6
12. Stein DS, Panwalker AP. Group C streptococcal endocarditis: case report and review of the literature. Infection **1985**;13:282-5
13. Portnoy D, Wink I, Richards GK, Blanc MZ. Bacterial endocarditis due to a penicillin-tolerant group C streptococcus. Can Med Assoc J **1980**;122:69-75
14. Appelbaum PC, Shaikh BS, Gordon RA, Hallgren EJ. Septicemia due to *Streptococcus equisimilis* in a child with acute lymphoblastic leukemia. Cancer **1979**;44:1226-7
15. Barson WJ. Group C streptococcal osteomyelitis. J Pediatr Orthop **1986**;6:346-8
16. Bullock JD, Cruz MG, Rabin ER, Sonnenwirth AC. A fatal case of group C streptococcal endocarditis. Case report. Mo Med **1970**;67:595-8
17. Chung SJ. Meningitis caused by *Streptococcus equisimilis* (group C). South Med J **1982**;75:769
18. Goldberg P, Shulman ST, Yogev R. Group C streptococcal endocarditis. Pediatrics **1985**;75:114-6
19. Noble JT, McGowan K. Group C streptococcal pneumonia in an adolescent. Am J Dis Child **1983**;137:1023
20. Rizkallah MF, Hoffler E, Ayoub EM. Serological confirmation of group C streptococcal pneumonia. J Infect Dis **1988**;158:1092-4
21. Stamm AM, Cobbs CG. Group C streptococcal pneumonia: report of a fatal case and review of the literature. Rev Infect Dis **1980**;2:889-98
22. Hervas JA, Labay MV, Rul-lan G, Aguilar L, Gil J, Alomar P. Neonatal sepsis and meningitis due to *Streptococcus equisimilis*. Pediatr Infect Dis J **1985**;4:694-5
23. Martinez-Luengas F, Inclan GM, Pastor A, Montejo M, Barron J, Baroja A, Aguirre C. Endocarditis due to *Streptococcus zooepidemicus* [letter]. Can Med Assoc J **1982**;127:13
24. Mohr DN, Feist DJ, Washington JA 2nd, Hermans PE. Meningitis due to group C streptococci in an adult. Mayo Clin Proc **1978**;53:529-32
25. Braunstein H, Tucker E, Gibson BC. Infections caused by unusual beta hemolytic streptococci. Am J Clin Pathol **1971**;55:424-30
26. Mohr DN, Feist DJ, Washington JA 2nd, Hermans PE. Infections due to group C streptococci in man. Am J Med **1979**;66:450-6
27. Davies MK, Ireland MA, Clarke DB. Infective endocarditis from group C streptococci causing stenosis of both the aortic and mitral valves. Thorax **1981**;36:69-71
28. Ghoneim ATM, Cooke EM. Serious infection caused by group C streptococci. J Clin Pathol **1980**;33:188-90
29. 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**;174:511-22
30. Brown J, Savage D. Group C streptococcal endocarditis. South Med J **1980**;73:86
31. Kirby WMM, Rantz LA. Streptococcic bacteremia cured with sulfadiazine. Report of a case of infection caused by hemolytic streptococci

of Lancefield group C, with a review of the literature and presentation of immunologic data. Arch Intern Med **1943**;71:620–9
32. Lawrence MS, Cobbs CG. Endocarditis due to group C streptococci. South Med J **1972**;65:487–9
33. Hill AM, Butler HM. Haemolytic streptococcal infections following childbirth and abortion. II. Clinical features with special reference to infections due to streptococci of groups other than A. Med J Aust **1940**;1:293–9
34. Rosenthal AH, Stone FM. Puerperal infection with vegetative endocarditis: report of sulfanilamide therapy in two fatal cases due to *Streptococcus haemolyticus* groups B and C. JAMA **1940**;114:840–3
35. Feingold DS, Stagg NL, Kunz LJ. Extrarespiratory streptococcal infections: importance of the various serologic groups. N Engl J Med **1966**;275:356–61
36. Finnegan P, Fitzgerald MXM, Cumming G, Geddes AM. Lancefield group C streptococcal endocarditis. Thorax **1974**;29:245–7
37. Jack CM, Khan MM, Adgey AAJ. Group C streptococcal endocarditis associated with intubation-induced tracheal stenosis. Int J Cardiol **1984**;5:376–9
38. Robinson P, Jacobs RF, Bradsher RW. Group C β-hemolytic streptococcal endocarditis: report of a pediatric case. Pediatr Cardiol **1984**;5:61–4
39. Sanders V. Bacterial endocarditis due to a group C beta hemolytic streptococcus. Ann Intern Med **1963**;58:858–61
40. Kuskie MR. Group C streptococcal infections. Pediatr Infect Dis J **1987**;6:856–9
41. Stewardson-Krieger P, Gotoff SP. Neonatal meningitis due to group C beta hemolytic streptococcus. J Pediatr **1977**;90:103–4
42. Patey O, Buisson CB, Soussy CJ. Group C streptococcal meningitis in adults [letter]. Rev Infect Dis **1990**;12:157–8
43. Breiman RF, Silverblatt FJ. Systemic *Streptococcus equi* infection in a horse handler—a case of human strangles. West J Med **1986**;145:385–6
44. Von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. Ann Intern Med **1981**;94:505–18
45. Matthieu DE Jr, Wasilauskas BL, Stallings RA. A rapid staphylococcal coagglutination technic to differentiate group A from other streptococcal groups. Am J Clin Pathol **1979**;72:463–7
46. Hare R. Sources of haemolytic streptococcal infection of wounds in war and in civil life. Lancet **1940**;1:109–12
47. Lancefield RC, Hare R. The serological differentiation of pathogenic and non-pathogenic strains of hemolytic streptococci from parturient women. J Exp Med **1935**;61:335–49
48. Forrer CB, Ellner PD. Distribution of hemolytic streptococci in respiratory specimens. J Clin Microbiol **1979**;10:69–71
49. Deibel RH, Seeley HW Jr. Streptococcaceae. In: Buchanan RE, Gibbons NE, eds. Bergey's manual of determinative bacteriology. 8th edition. Baltimore: Williams & Wilkins, **1974**:490–509
50. Stableforth AW. Streptococcal diseases. In: Stableforth AW, Galloway IA, eds. Infectious diseases of animals. Diseases due to bacteria. New York: Academic Press, **1959**:589–650
51. Quinn RJM, Hallett AF, Appelbaum PC, Cooper RC. Meningitis caused by *Streptococcus dysgalactiae* in a preterm infant. Am J Clin Pathol **1978**;70:948–50
52. Hare R. The classification of haemolytic streptococci from the nose and throat of normal human beings by means of precipitin and biochemical tests. J Pathol Bacteriol **1935**;41:499–512
53. Edwards PR. Further studies on the differentiation of human and animal strains of hemolytic streptococci. J Bacteriol **1933**;25:527–36
54. Hutchinson RI. Pathogenicity of group C (Lancefield) haemolytic streptococcus. BMJ **1946**;2:575–6
55. Evans AC. Studies on hemolytic streptococci. VIII. Streptococcus equisimilis. J Bacteriol **1944**;48:267–84
56. Ross RF. Streptococcal infections in swine. In: Wannamaker LW, Matsen JM, eds. Streptococci and streptococcal diseases: recognition, understanding, and management. New York: Academic Press, **1972**: 339–48
57. Bryans JT, Moore BO. Group C streptococcal infections of the horse. In: Wannamaker LW, Matsen JM, eds. Streptococci and streptococcal diseases: recognition, understanding, and management. New York: Academic Press, **1972**:327–38
58. Barnham M, Cole G, Efstratiou A, Tagg JR, Skjold SA. Characterization of *Streptococcus zooepidemicus* (Lancefield group C) from human and selected animal infections. Epidemiol Infect **1987**;98:171–82
59. Rose HD, Allen JR, Witte G. *Streptococcus zooepidemicus* (group C) pneumonia in a human. J Clin Microbiol **1980**;11:76–8
60. Low DE, Young MR, Harding GKM. Group C streptococcal meningitis in an adult. Probable acquisition from a horse. Arch Intern Med **1980**;140:977–8
61. Fehrs LJ, Flanagan K, Kline S, Facklam RR, Quackenbush K, Foster LR. Group A β-hemolytic streptococcal skin infections in a US meatpacking plant. JAMA **1987**;258:3131–4
62. Martin TA, Hoff GL, Gibson V, Biery RM. Foodborne streptococcal pharyngitis Kansas City, Missouri. Am J Epidemiol **1985**;122:706–9
63. Centers for Disease Control. Group C streptococcal infections associated with eating homemade cheese—New Mexico. MMWR **1983**;32:510, 515–6
64. Auckenthaler R, Hermans PE, Washington JA II. Group C streptococcal bacteremia: clinical study and review of the literature. Rev Infect Dis **1983**;5:196–204
65. Baker CJ, Barrett FF. Transmission of group B streptococci among parturient women and their neonates. J Pediatr **1973**;83:919–25
66. Barg NL, Kish MA, Kauffman CA, Supena RB. Group A streptococcal bacteremia in intravenous drug abusers. Am J Med **1985**;78:569–74
67. Venezio FR, Gullberg RM, Westenfelder GO, Phair JP, Cook FV. Group G streptococcal endocarditis and bacteremia. Am J Med **1986**;81: 29–34
68. Francis J, Warren RE. *Streptococcus pyogenes* bacteraemia in Cambridge—a review of 67 episodes. Q J Med **1988**;68:603–13
69. Skogberg K, Simonen H, Renkonen O-V, Valtonen VV. Beta-haemolytic group A, B, C and G streptococcal septicaemia: a clinical study. Scand J Infect Dis **1988**;20:119–25
70. Bibler MR, Rouan GW. Cryptogenic group A streptococcal bacteremia: experience at an urban general hospital and review of the literature. Rev Infect Dis **1986**;8:941–51
71. Vartian C, Lerner PI, Shlaes DM, Gopalakrishna KV. Infections due to Lancefield group G streptococci. Medicine (Baltimore) **1985**;64: 75–88
72. Gallagher PG, Watanakunakorn C. Group B streptococcal bacteremia in a community teaching hospital. Am J Med **1985**;78:795–800
73. Verghese A, Mireault K, Arbeit RD. Group B streptococcal bacteremia in men. Rev Infect Dis **1986**;8:912–7
74. Hammersen G, Bartholme K, Oppermann HC, Wille L, Lutz P. Group B streptococci: a new threat to the newborn. Eur J Pediatr **1977**;126: 189–97
75. Shlaes DM, Lerner PI, Wolinsky E, Gopalakrishna KV. Infections due to Lancefield group F and related streptococci (*S. milleri*, *S. anginosus*). Medicine (Baltimore) **1981**;60:197–207
76. Lerner PI, Gopalakrishna KV, Wolinsky E, McHenry MC, Tan JS, Rosenthal M. Group B streptococcus (*S. agalactiae*) bacteremia in adults: analysis of 32 cases and review of the literature. Medicine (Baltimore) **1977**;56:457–73
77. Libertin CR, Hermans PE, Washington JA II. Beta-hemolytic group F streptococcal bacteremia: a study and review of the literature. Rev Infect Dis **1985**;7:498–503
78. Pringle SD, McCartney AC, Marshall DA, Cobbe SM. Infective endocarditis caused by *Streptococcus agalactiae*. Int J Cardiol **1989**; 24:179–83
79. Bouza E, Meyer RD, Busch DR. Group G streptococcal endocarditis.

Am J Clin Pathol **1978**;70:108-11
80. Savage D, Brown J. Endocarditis due to group A streptococcus. Am J Med Sci **1981**;282:98-103
81. Gallagher PG, Watanakunakorn C. Group B streptococcal endocarditis: report of seven cases and review of the literature, 1962-1985. Rev Infect Dis **1986**;8:175-88
82. Backes RJ, Wilson WR, Geraci JE. Group B streptococcal infective endocarditis. Arch Intern Med **1985**;145:693-6
83. Scully BE, Spriggs D, Neu HC. *Streptococcus agalactiae* (group B) endocarditis—a description of twelve cases and review of the literature. Infection **1987**;15:169-76
84. Duca E, Teodorovici G, Radu C, Vita A, Talasman-Niculescu P, Bernescu E, Feldi C, Rosca V. A new nephritogenic streptococcus. J Hyg **1969**;67:691-8
85. Barnham M, Thornton TJ, Lange K. Nephritis caused by *Streptococcus zooepidemicus* (Lancefield group C). Lancet **1983**;1:945-8
86. Poon-King T, Mohammed I, Cox R, Potter EV, Simon NM, Siegel AC, Earle DP. Recurrent epidemic nephritis in south Trinidad. N Engl J Med **1967**;277:728-33
87. Gnann JW Jr, Gray BM, Griffin FM Jr, Dismukes WE. Acute glomerulonephritis following group G streptococcal infection [letter]. J Infect Dis **1987**;156:411-2
88. Barnham M, Kerby J, Chandler RS, Millar MR. Group C streptococci in human infection: a study of 308 isolates with clinical correlations. Epidemiol Infect **1989**;102:379-90
89. Matsen JM, Coghlan CR. Antibiotic testing and susceptibility patterns of streptococci. In: Wannamaker LW, Matsen JM, eds. Streptococci and streptococcal diseases. Recognition, understanding, and management. New York: Academic Press, **1972**:189-204
90. Finland M, Garner C, Wilcox C, Sabath LD. Susceptibility of beta-hemolytic streptococci to 65 antibacterial agents. Antimicrob Agents Chemother **1976**:9:11-9
91. Barnham M, Cole G. Erythromycin-resistant beta-haemolytic streptococci in north Yorkshire [letter]. J Infect **1986**;13:200-2
92. Portnoy D, Prentis J, Richards GK. Penicillin tolerance of human isolates of group C streptococci. Antimicrob Agents Chemother **1981**;20:235-8
93. Rolston KV, LeFrock JL, Schell RF. Activity of nine antimicrobial agents against Lancefield group C and G streptococci. Antimicrob Agents Chemother **1982**;22:930-2
94. Handwerger S, Tomasz A. Antibiotic tolerance among clinical isolates of bacteria. Rev Infect Dis **1985**;7:368-86