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# Infections Caused by Group C and G Streptococcus (*Streptococcus dysgalactiae* subsp. *equisimilis* and Others): Epidemiological and Clinical Aspects

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**ABSTRACT** Streptococci carrying serogroup C and G antigens, and in particular, *Streptococcus dysgalactiae* subsp. *equisimilis* (SDSE), are emerging human pathogens that are increasingly isolated from patients with a myriad of infections that range from mundane to life-threatening. SDSE is microbiologically similar to *Streptococcus pyogenes*. These streptococci frequently cause infections of the throat and skin and soft tissues. Moreover, they may invade the bloodstream and disseminate widely to many deep tissue sites, including the endocardium. Life-threatening invasive infections due to SDSE, including the streptococcal toxic shock syndrome, occur most frequently in patients with severe underlying medical diseases. Treatment with penicillin is adequate under most circumstances, but treatment failure occurs. SDSE may also be resistant to other antibiotic classes including tetracyclines, macrolides, and clindamycin. Most human infections caused by groups C and G streptococci are transmitted from person to person, but infections due to *Streptococcus equi* subsp. *zooepidemicus* (and, rarely, to *S. equi* subsp. *equi*) are zoonoses. Transmission of these latter species occurs by animal contact or by contamination of food products and has been associated with the development of poststreptococcal glomerulonephritis. Members of the *Streptococcus anginosus* group, usually classified with the viridans group of streptococci, are associated with a variety of pyogenic infections.

Conrary to the homogeneity typical of streptococci belonging to Lancefield groups A (*S. pyogenes*) and B (*S. agalactiae*), groups C and G streptococci (GCGS) represent a variety of species that are widely variable in regard to biochemical reactions, hemolytic characteristics, predilection for host species, and clinical illnesses produced in

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humans and animals. These organisms are found as commensals in the throat, skin, and occasionally the female genitourinary tract, and their epidemiologic patterns and clinical manifestations reflect this distribution.

## HISTORY AND TAXONOMY

The classification of GCGS is complex and has been continuously evolving over the past few decades. Most human infections with GCGS are caused either by members of the *S. anginosus* group (SAG) (*S. anginosus*, *S. constellatus*, and *S. intermedius*, also formerly known as the *S. milleri* group), which form small colonies (<5 mm), can be alpha-, beta-, or nonhemolytic, and may also express Lancefield group F (most common) or group A (rare) antigens or no group antigen at all, or by *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE), which forms large colonies (>5 mm) that resemble those of *S. pyogenes* when cultivated on sheep blood agar plates and is typically beta-hemolytic. SDSE and SAG may express either group C or G antigens. Certain uncommon strains of SDSE may also express Lancefield group L or group A antigens (1–3). In addition, *S. dysgalactiae* subsp. *dysgalactiae* (SDSD), *S. equi* subsp. *equi*, and *S. equi* subsp. *zooepidemicus* express group C antigens, while *S. canis* strains are group G (4).

While well known to veterinarians as a cause of bovine mastitis, *S. dysgalactiae* (from the Greek for "bad milk") was dropped from the Approved List of Bacterial Names in 1980 (5). It is unclear whether this was an oversight or if there was a more concrete reason such as the absence of a reference strain, but in 1983 Garvie sought to correct this error and published an article that included a detailed microbiological description and a reference strain (6). In 1996 Vandamme proposed distinguishing two subspecies of *S. dysgalactiae* based on their host of origin, with animal isolates designated as *S. dysgalactiae* subsp. *dysgalactiae* and human isolates receiving the name *S. dysgalactiae* subspecies *equisimilis* (4). Vieira et al. agreed with the separation into two subspecies but suggested that the distinction be based on the type of hemolysis produced, designating nonhemolytic and alpha-hemolytic GCGS strains as SDSD and beta-hemolytic strains as SDSE (7). This is the currently accepted taxonomic classification, although it has continued to be challenged (8). In 2001 it was proposed that SDSD and SDSE be recognized as distinct species based on clinical and epidemiological grounds, but the motion was rejected by the International Committee on Systematic Bacteriology because taxonomic evidence did not support it (9). Multiple reports of exceptions to the Vieira subdivision have been published, and some authors have found it to be very inaccurate when assessed by DNA fingerprinting (10). It is possible that some of these discrepancies can be explained by continued evolution of the species through horizontal transfer of genes from other beta-hemolytic streptococci, especially *S. pyogenes*, to SDSE (10, 11). In the absence of widespread availability of genomic identification, many clinical laboratories continue to designate animal strains as SDSD and human strains as SDSE or continue to report these bacteria using the Lancefield classification.

In this article we will, to the extent possible, focus on the species-based nomenclature of streptococci. However, many of the studies reviewed, particularly those in the older literature, employed the Lancefield classification, making it impossible to know the causative species.

## EPIDEMIOLOGY

The SAG members are normal commensals in the oral cavity. All three species, but especially *S. intermedius*, have been found in gingival crevices, dental plaque, dental root canals, and the naso- and oropharynx. *S. anginosus* isolates are also commonly isolated from urogenital and gastrointestinal sources (1, 12).

SDSE is a common commensal of humans (13). It is thought that the horizontal transfer of virulence factors such as fibronectin-binding protein, M protein, and bacteriocin-like inhibitory substance activity from human streptococci to animal strains of *S. dysgalactiae* enabled them to colonize humans (14). Some studies have suggested that pharyngeal colonization with SDSE may be protective against infection with other pathogens, since its presence has been found to have an inverse correlation with the incidence of pharyngitis (15). On the other hand, invasive infections caused by SDSE have been emerging in many parts of the world (16). SDSE is responsible for over 80% of invasive infections caused by beta-hemolytic streptococci of groups other than A and B (2). The incidence of bacteremia caused by SDSE has increased 2- to 3-fold and approaches that of *S. pyogenes* in many countries. In Finland, the incidence of group G streptococcal bacteremia increased from 1.8 cases/100,000 population in 1995 to 4.3 cases/100,000 population in 2004 (17). In Norway, the incidence of invasive GCGS infections increased from 1.4/100,000 inhabitants in 1999 to 6.3/100,000 in 2013 (18). The increased virulence of SDSE seems to be related to clonal expansion of a few clades carrying specific virulence factors, such as *cbp*, *fbp*, *speG*, *sicG*, *gfbA*, and *bca* (19, 20). Most SDSE strains express a functional

homolog of the potent *S. pyogenes* beta-hemolysin/cytolysin streptolysin S that contributes to the pathogenesis of necrotizing soft tissue infection (21). SDSE strains also express M proteins that share structural and functional properties with *S. pyogenes* M proteins (22, 23). Similar to invasive GAS infections, a high percentage of patients with invasive SDSE infections have comorbid illnesses, including diabetes mellitus, malignancies, immunosuppression, intravenous drug use, and breakdown of the skin (1, 16, 24).

Transmission of SDSE, when it occurs, is likely to be from person to person, and most cases are sporadic in nature, rather than associated with common source outbreaks. When outbreaks do occur, they are generally associated with close personal contact or perhaps with environmental contamination. By contrast, *S. equi* subsp. *zooepidemicus* is generally associated with exposure to animals or to common source outbreaks, especially consumption of contaminated dairy products.

## ANIMAL INFECTIONS

SDSD is a major cause of mastitis in cows and dromedary camels and various infections in lambs (25–27). *S. equi* subsp. *equi* is occasionally found in the upper respiratory tract of normal horses and is the causative agent of equine strangles. This acute, contagious, and deadly respiratory disease has led to explosive epidemics in horse stables and has serious potential economic consequences for horse fanciers (28). *S. equi* subsp. *zooepidemicus* is a cause of infection in a variety of animal species, including horses, cows, dogs, rabbits, llamas, alpacas, guinea pigs, and swine (25, 26, 29–33).

## HUMAN INFECTIONS

The SAG is usually classified, and described, with the "viridans" group of streptococci. These species are characterized for their disposition to form abscesses in various organs, including lung, pleural space, brain, oral and abdominal cavities, skin and soft tissues, and the genitourinary tract with or without associated bacteremia (34–36). Although less common than other viridans streptococci, *S. anginosus* may also cause endocarditis (12, 37, 38). Many invasive SAG strains, however, belong to serogroups other than C or G or are nongroupable (34, 39).

This review will focus on the more common infections caused by SDSE, as well as on the few reported human cases caused by *S. equi* subsp. *zooepidemicus*, *S. equi* subsp. *equi*, and *S. canis*. Strains of these streptococci have been associated with infections of many body sites (14, 26, 40–45).

### Pharyngitis and Acute Glomerulonephritis

The role of SDSE in sporadic cases of pharyngitis remains somewhat controversial. Although occasionally isolated from patients with pharyngitis, streptococci of this species are also often cultured from the throats of healthy individuals (12). Marchello and Ebell conducted a meta-analysis of the prevalence of group C streptococci in patients with sore throat. They found a prevalence of 6.1%. However, the absence of a healthy control group did not allow the authors to conclude whether these bacteria were the actual pathogens (46). Several clinical and laboratory-based studies have looked at the clinical manifestations of patients with pharyngitis in whom SDSE was isolated. In general, signs and symptoms of patients with pharyngitis in whom SDSE is isolated are indistinguishable from those in whom *S. pyogenes* is found (47, 48). Turner et al. (49) studied students reporting to a college health service with acute pharyngitis and compared them with controls without infectious problems. Group C streptococci were cultured at a higher rate from students with pharyngitis than from the control group. Patients with positive cultures for group C streptococci were more likely to have features suggestive of a bacterial infection, such as exudative tonsillitis and anterior cervical lymphadenopathy, than were those with negative cultures. Furthermore, these group C strains resisted phagocytosis in human blood and contained genomic DNA encoding an M protein similar in structure to that of group A streptococci, providing further evidence of possible human virulence (50). In a later study, the same group of authors described 265 students with exudative pharyngitis and compared them with 75 patients with rhinovirus infection and 162 students with noninfectious problems. SDSE was isolated significantly more frequently from patients with exudative pharyngitis than from either control group (51). Twenty-two cases of pharyngitis from which group C streptococci were isolated occurred during the fall of 1974 in a school for boys with learning disabilities. Although it is likely in this epidemiologic setting that the infecting strains were SDSE, they were unfortunately not speciated (52). On the more severe side of the spectrum, SDSE has rarely been reported as the cause of severe and even necrotizing tonsillitis (53, 54).

Streptococci expressing group G antigen have clearly been linked to outbreaks of pharyngitis. Many of those outbreaks were related to a common source, usually a food product. In one such outbreak during a single

week in 1968, 176 students at a college were evaluated for pharyngitis. The attack rate in the student body was 31%. Signs and symptoms were similar to those characteristic of group A streptococcal pharyngitis, suggesting an etiologic role for the organism. Epidemiologic investigation linked the outbreak to contaminated egg salad (55). In another common source outbreak, 72 people who attended a convention developed pharyngitis, with group G streptococci isolated from most who had cultures performed. All the patients had consumed chicken salad prepared by a single cook whose throat culture was positive for the organism (56). Another epidemic of group G streptococcal pharyngitis involving 68 students occurred over a 1-week period at a North Carolina college. Because no common food source could be identified, the author concluded that the mode of spread was most likely person to person. The very sharp epidemic curve and brief duration of the outbreak suggest, however, that contamination of a common food vehicle is more likely. In support of this conclusion are the facts that all students interviewed had eaten in the campus cafeteria in the week preceding illness and that one student with a positive culture was a food handler (57). A community-wide outbreak of group G streptococcal pharyngitis, unrelated to any common source, was documented among private pediatric patients in the winter and spring of 1986 to 1987 in Connecticut (58).

Epidemics and clusters of pharyngitis cases due to *S. equi* subsp. *zooepidemicus* are typically related to a common source, usually consumption of unpasteurized dairy products. A remarkable feature of such outbreaks is their association with poststreptococcal acute glomerulonephritis. From December 1997 to July 1998, 253 cases of acute glomerulonephritis due to *S. equi* subsp. *zooepidemicus* occurred in Nova Serrana, Brazil, among people who had consumed locally produced unpasteurized cheese. Ten patients required dialysis and three died (59). A follow-up report 2 years later of 134 of these patients showed that five of them required continuing dialysis. Of the 69 patients from that cohort who could be found and reevaluated, 42% had hypertension, and there was a high proportion of patients (up to 30%) with persistent renal function abnormalities (60). Duca et al. described 85 patients with pharyngitis due to *S. equi* subsp. *zooepidemicus* following the ingestion of improperly pasteurized milk, 87% of which were adults. Approximately one-third of the patients developed acute glomerulonephritis, generally in the second or third week of illness (61). In a smaller outbreak, five members of a family developed an upper respiratory infection related to *S. equi* subsp. *zooepidemicus* after consuming unpasteurized milk (62). Three of the five family members subsequently developed poststreptococcal glomerulonephritis, which was confirmed in one case by renal biopsy.

## Infections of Skin and Soft Tissue

SDSE is a frequent cause of skin and soft tissue infections, and the skin is often the portal of entry for serious invasive disease and bacteremia. These infections can manifest as pyoderma, cellulitis, erysipelas, surgical wound infections, abscesses, necrotizing soft tissue infections, and pyomyositis (63–67). In some series, GCGS have been isolated with as much or greater frequency than *S. pyogenes* in patients with cellulitis and erysipelas (68, 69). Infection caused by these organisms may complicate ulcers associated with diabetes mellitus, immobility, or venous and lymphatic compromise of any cause (14). Recurrent cellulitis may occur, for example, in the limb that underwent saphenous venectomy of patients who have experienced coronary artery bypass grafting or in the extremities of individuals who have had axillary, pelvic, or femoral node dissection for cancer (70). Severe skin and soft tissue infections caused by SDSE include cases of necrotizing fasciitis, Fournier's gangrene, and necrotizing myositis (67, 71). Bruun et al. described a series of 70 cases of necrotizing fasciitis, 9 of which were caused by SDSE. The in-hospital case fatality rate of patients with SDSE was 33%, compared to 11% for those caused by *S. pyogenes* (67). These infections typically occur in patients who are older and have underlying comorbid conditions, such as malignancy, cardiovascular disease, alcoholism, and diabetes mellitus (44, 72). Injectable-drug users seem to be at increased risk for cellulitis and skin abscesses caused by SDSE, and the skin is the usual source of bacteremia in such patients (64). Burn patients are also at risk for skin and skin graft infections with SDSE; such individuals accounted for 8% of cutaneous group G streptococci infections in one series (63, 73).

There are numerous reports of streptococcal toxic shock syndrome (STSS) in patients with severe infections caused by SDSE (74–83). Sachse et al. studied 24 pathogenic isolates of SDSE and found a gene encoding the streptococcal pyrogenic exotoxin G (speG$^{dys}$), demonstrating that this species has the potential to produce superantigen-like proteins. They failed, however, to show the presence of genes related to the superantigens SPEA, SPEC, SPEZ (SMEZ), SPEH, and SPEI (84). Another study, however, demonstrated that some strains of SDSE do carry the bacteriophage-associated genes *speA*, *speC*, *speM*, *ssa*, or *smeZ* identical to their counterparts in *S. pyogenes*. This suggests that these genes

may be transferred from one species to the other, conferring enhanced pathogenicity (85).

In contrast to SDSE, the rare cases of skin and soft tissue infection due to *S. equi* subsp. *zooepidemicus* and *S. equi* subsp. *equi* usually involve exposure to animals. One case of cellulitis with bacteremia due to *S. equi* subsp. *zooepidemicus* was reported in a renal transplant patient who was exposed to horses at a show (86); a case of severe facial cellulitis due to *S. equi* subsp. *equi* was reported in another man who also had equine exposure (87), and a case of necrotizing myositis was reported in a previously healthy Norwegian farmer with two asymptomatic Shetland ponies in his stable (88). Two cases of streptococcal toxic shock syndrome caused by *S. equi* subsp. *zooepidemicus* have also been described (74, 89).

## Joint and Bone Infections

While not common, SDSE is a known etiology of infectious arthritis, in both native and prosthetic joints (90–92). A group of reference hospitals in France published their experience with streptococcal bone and joint infections. They found SDSE to be present in 12% of cases and *S. anginosus* in 11%. These species were second only to *S. agalactiae* in frequency. In this series, the isolation of SDSE was associated with an unfavorable clinical outcome (93).

González Terán et al. reviewed 24 patients with group C streptococcal arthritis, two from their experience and the other 22 from the literature. Twelve (50%) cases were caused by SDSE, three by *S. equi* subsp. *zooepidemicus*, and the other nine were not speciated. Nine of the patients had polyarticular involvement. One-third (eight patients) had a pre-existing arthropathy, including rheumatoid arthritis, gout, seronegative arthropathy, osteoarthritis, and others. Four of the patients were immunosuppressed, two had HIV infection, and two were on chemotherapy. Only two patients, one infected with *S. equi* subsp. *zooepidemicus*, and the other with SDSE, had a history of animal exposure (horses in both cases) (94).

Numerous cases of infectious arthritis due to group G streptococci have been reported. Serious medical illnesses and previous joint disease were common features in these patients. In five cases of group G streptococcal infectious arthritis from the UCLA hospital system, all patients had prior joint disease and two had infected prostheses (95). In a series of seven patients, only one patient had no underlying systemic or rheumatologic illness. The remaining six patients all had prior trauma, surgery, or inflammation of the affected joint, and four of the six patients also had underlying medical conditions, including diabetes mellitus, alcoholism, and cardiovascular disease (96). In another review of 50 previously reported cases of group G streptococcal arthritis, more than one-third of patients had chronic joint disease, while just under half of the patients had one of four underlying conditions: malignancy, alcoholism, diabetes mellitus, or injectable-drug use (97). Osteomyelitis has also been described with GCGS, but it is reported less frequently than infectious arthritis. In these cases, there is also often a significant underlying disease (44, 63).

## Maternal and Neonatal Infections

Although SDSE can be found as part of the normal female genitourinary flora, its presence in clinical specimens often indicates infection. There have been at least two published outbreaks of puerperal fever caused by SDSE. In the first, 33 confirmed cases in England were caused by a single strain of SDSE. Clinical features included fever and signs of perineal infection. Sources of infection were postulated by the authors to be environmental, because the organism was cultured from toilet seats and bath plug holes. However, the organism was also cultured from the throats of many of the nursing staff (98). In the second outbreak, which occurred 4 years later in England, seven women developed puerperal fever caused by SDSE (99). Interestingly, the isolates shared the same M serotype with the strain responsible for the first outbreak. Though the microorganism was not isolated from the environment, it was speculated that transmission may have occurred through use of a common toilet seat. These epidemiologic and microbiologic data suggesting transmission by fomites must be interpreted with caution. The role of environmental contamination versus health care-related person-to-person transmission in such outbreaks remains to be determined.

Neonatal group C streptococcal infection is rare. In one reported case, meningitis due to SDSE developed in an infant whose mother was being treated for chorioamnionitis at the time of delivery (100). In another case, a preterm infant developed meningitis due to SDSD; the source of infection was not determined, because the mother was not ill and the organism could not be cultured from her (101).

Although clinical infection is rare, colonization of neonates with group G streptococci seems to be a common finding. In one study, cultures were taken from the nose and umbilicus of more than 3,000 neonates over a 1-year period at a New York hospital. The monthly incidence of positive cultures for group G streptococci ranged from 41 to 76%. Seven cases of neonatal sepsis due to these organisms were diagnosed over the same

time period. Five of the seven cases occurred in the setting of complications of pregnancy or childbirth (102). In a larger review, which included this series, premature or prolonged rupture of the amniotic membranes was the most common risk factor associated with group G streptococcal infection (103).

## Bacteremia, Endocarditis, and Other Serious Invasive Diseases

SDSE, *S. equi* subsp. *zooepidemicus*, and other streptococci with either group C or G antigen have been reported with increasing frequency to cause bacteremia, most commonly secondary to skin and soft tissue infection (16, 24, 42, 104). Many patients affected by these organisms (up to 70% in some series) have serious underlying diseases, especially malignancy, cardiovascular disease, diabetes mellitus, immunosuppression, and alcohol or injectable-drug use (40, 41, 44, 45, 105).

Bacteremia due to SDSE may be primary in approximately 20% of cases or secondary to a focal site of infection, most often from the skin or soft tissues. Auckenthaler et al. reviewed 38 patients who were bacteremic with group G streptococci at the Mayo Clinic-affiliated hospitals, representing 0.25% of all patients with positive blood cultures over a 10-year period. Seventy percent of the patients acquired the infection in the community, and the skin was the portal of entry in approximately three-quarters of the patients. Most of the hospital-acquired bacteremias involved a postoperative wound or a transcutaneous procedure. The patients tended to be older, with most being in the sixth to eighth decades. Many patients had venous insufficiency, lymphedema, or another cause of chronic lower extremity edema (40). Carmeli et al. reported 10 cases of group C streptococcal bacteremia in Israel and reviewed several other case series. In this review, some patients had primary bacteremia, but most cases were secondary to pharyngitis, epiglottitis, pericarditis, pneumonia, skin and soft tissue infection, endocarditis, or an infected aneurysm (41). In a review from Boston University, 29 patients with group G streptococcal bacteremia were identified over a 3-year period. The median age of the affected patients was 68 years, and one-half had a skin infection as the primary source of the bacteremia (45). In another series, six cases of bacteremia were reported in injectable-drug users. The portal of entry for these patients was the skin. All of the infected patients had injected drugs for at least 10 years (64).

Some studies have noted a high rate of relapsing or recurring bacteremias caused specifically by organisms carrying the group G antigen. A series of 84 cases of group G SDSE in Israel included 6 patients (7%) who developed recurrent bacteremia, ranging from two to four episodes per patient. Two of the six patients had SDSE with the same *emm* type (*emm stG*840.0) isolated from their subsequent bacteremias, and the other four had different isolates in each incident (42). Another series, in Singapore, reported a rate of recurrent bacteremia of 5.8% (106). This finding suggests that, although group G streptococci contain M proteins, infections with these organisms may not induce solid protective immunity (22). This assumption is supported by studies in a murine model of group G streptococcal cellulitis (107).

Bacteremia caused by *S. equi* subsp. *zooepidemicus* is generally associated with animal contact and tends to occur in outbreaks associated with exposure to animals or animal products. In 1999, Bradley et al. (108) reviewed 88 cases of bacteremia caused by group C streptococci reported in the literature. Of these patients, 21 reported exposure to animals or animal products and, as expected, most of these had bacteremia due to *S. equi* subsp. *zooepidemicus*. Ten patients had consumed unpasteurized milk, four patients were farmers, one was a butcher, and several had other contact with animals. In the same series, 24 patients with definite or probable endocarditis were described. Of these, five cases were due to *S. equi* subsp. *zooepidemicus*, four were due to SDSE, and the remainder were unspecified. Animal exposure was noted only in patients with infection due to *S. equi* subsp. *zooepidemicus* or unspeciated organisms. Underlying cardiac disease was seen in 60% of the patients for whom adequate information was available. Edwards et al. described an outbreak of 11 cases of bacteremia due to *S. equi* subsp. *zooepidemicus* in West Yorkshire. Presentations included primary septicemia, endocarditis, infected aneurysm, and meningitis. All 11 patients had consumed unpasteurized milk from the same source (43). Yuen et al. (109) reported 11 cases of *S. equi* subsp. *zooepidemicus* bacteremia with sepsis over a 4-year period in Hong Kong. The patients had a variety of presenting syndromes, and 55% had a serious underlying illness. None of the patients reported exposure to animals or animal products. After further investigation, it was believed that the infections were acquired from ingestion of undercooked pork. Furthermore, condemned septicemic pigs were found to be infected with *S. equi* subsp. *zooepidemicus* strains whose DNA fingerprints were identical to the human isolates. More recently, a fatal *S. equi* subsp. *zooepidemicus* bacteremic infection was reported associated with equine exposure (110).

Endocarditis due to GCGS is also an emerging disease. Like bacteremia from other sources, endocarditis tends to occur in older patients with serious underlying conditions and carries a high risk of severe disease, embolic events, metastatic infections, and death (111, 112). Clinical manifestations are similar to those seen with *S. pyogenes* endocarditis. Oppegaard et al. (113) reported a series of nine cases of definite endocarditis caused by SDSE in Norway between 1999 and 2013. The median age was 64 years, and all but two had underlying comorbid conditions. In general, the patients were acutely and severely ill. The median time of illness to admission was 1 day. Mitral and aortic valves were affected with similar frequency. Four of the nine patients had embolic events, and seven had cardiac complications. Valve replacement was needed in three of the nine patients. Mortality at 30 days was 22%. In a literature review of 40 cases of group G streptococcal endocarditis, the average age was 56 years and the overall mortality was 36%. Underlying disease was present in about one-half of the patients; six patients had a malignancy, six were diabetic, four were alcoholics, and three were injectable-drug users. Also, one-half of the patients had known preexisting valvular disease, with mitral regurgitation being the most common abnormality. Three cases occurred in patients with prosthetic valves (114). In a series of seven cases not included in the above review, the average age of the patients was 72 years, and only one patient was younger than 60 (115). Underlying medical conditions and/or preexisting valvular disease were noted in most cases.

Some patients with SDSE and *S. equi* subsp. *zooepidemicus* bacteremia develop multifocal metastatic infections, including meningitis, peritoneal abscesses, pericarditis, and pneumonia (116–120).

## TREATMENT

SDSE and the other large-colony group C and G streptococci are typically susceptible to penicillin, which is considered the drug of choice to treat infections caused by these organisms. Their range of MICs to penicillin G is between 0.03 and 0.06 μg/ml (121). Besides beta-lactams, glycopeptides, daptomycin, and linezolid are also consistently active *in vitro* (122).

Lam and Bayer found that bacterial killing by penicillin is impaired when high concentrations of organisms (>$10^8$ colony-forming units/ml) are found (123). This phenomenon is well described for *S. pyogenes*, which downregulates the production of penicillin-binding proteins during its stationary phase of growth, resulting in a paucity of targets for penicillin (the "Eagle effect") (124). Another observation has been that in certain patients with endocarditis or septic arthritis, but also in some patients with pharyngitis, there is a poor or delayed response to therapy (125). The reason for this suboptimal response is unclear, and it may be from a combination of microbiological and host factors. The addition of gentamicin to a cell wall active antibiotic has been shown to be synergistic *in vitro*, and some have suggested its use in certain patients with severe and invasive SDSE infections, provided there is no contraindication to use an aminoglycoside antimicrobial agent (126, 127). However, there are no definitive clinical data to support that recommendation at this time. Recently, a penicillin-resistant strain was isolated from the blood of three epidemiologically linked patients in Denmark. The four isolates had a penicillin MIC of 0.5 to 2 mg/liter, belonged to a single clone, and had mutations in multiple penicillin-binding proteins (PBPs), including PBP2x mutations similar to those found in *Streptococcus pneumoniae* and *S. agalactiae*, and mutations in PBP1a and PBP1b (128).

Susceptibility to tetracyclines, macrolides, clindamycin, and fluoroquinolones is variable and cannot be assumed without proper testing (123, 129, 130). Megged (131) reported resistance rates of 38.8% and 27.8% to erythromycin and clindamycin, respectively, in Israel. Mechanisms of resistance are varied, with strains expressing constitutive macrolides-lincosamides-streptogramin B ($MLS_B$), inducible $MLS_B$, and M phenotypes. Another study, also from Israel, found resistance to clindamycin, erythromycin, azithromycin, and tetracycline in 11.1%, 18.2%, 21.2%, and 49.5% of SDSE, respectively (132). Similar high rates of resistance have been found in such distant geographical locations as Taiwan, Austria, and Brazil (133–136). Investigators in Portugal reviewed a collection of 314 human isolates of SDSE and found a levofloxacin resistance rate of 12%. Resistance was found in multiple *emm* types and genetic lineages and was associated with mutations in both *gyrA* and *parC*. The data also showed evidence of recombination between SDSE and *S. pyogenes*, but not between SDSE and SDSD (137).

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