Soft tissue infection caused by *Streptococcus dysgalactiae* subsp. *equisimilis* possessing group A antigen: a case report and review of the literature

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Abstract

The study presents microbiological characteristics, identification, pathogenicity, epidemiology and antimicrobial susceptibility of *Streptococcus dysgalactiae* subsp. *equisimilis* (SDSE). The SDSE shows a close relationship to *Streptococcus pyogenes*. The SDSE strains usually have a group G antigen, less commonly a group C one. Like *S. pyogenes*, most of SDSE strains can cause complete hemolysis (β-hemolysis) on a blood agar medium, and some of them possess the same A type of group-specific cell wall antigen. These common phenotype traits lead to confusion between both species. For this reason, microbiological diagnosis of streptococci should not be finished at the stage of serogrouping. A case of soft tissue infection of the left lower limb of a 30-year-old man is described. The etiological factor of the infection was β-hemolytic SDSE of group A. Antimicrobial susceptibility tests revealed that the strain is susceptible to penicillin, erythromycin, clindamycin and levofloxacin, while it is resistant to tetracycline. Treatment with first-generation cephalosporin (cefadroxil) was successfully applied, resulting in a complete remission of the infection symptoms.

Key words: *Streptococcus dysgalactiae* subsp. *equisimilis*, group A streptococci, group C, G, and L streptococci.

Introduction

Streptococcus dysgalactiae subsp. *equisimilis* (SDSE) is a taxonomic name, proposed by Vandamme *et al.*, 1996 [1], for β-hemolytic streptococci isolated from people, possessing group G or C cell wall carbohydrate antigens, producing streptokinase active on human plasminogen, and displaying proteolytic activity on human fibrin. Usually SDSE strains have the group G antigen, more rarely the group C one. According to results of several large investigations (on more than 100 isolates), SDSE isolates with G antigen consisted from 70% to more than 90%, and those with C antigen – from 5% to 26% of the examined SDSE population [2-8]. The SDSE strains with group A and L antigens are isolated much less frequently [2, 9-16]. In SDSE populations, the participation of strains with group A antigen may amount up to some 3.5% [2, 17], and those with L antigen – up to 0.5% [4, 6, 8]. Group A antigen is carried by some strains of both SDSE and *S. anginosus* [18], which is why the term "group A streptococci" (GAS) should not be treated as synonymous to *S. pyogenes*. For the same reason, microbiological diagnosis of streptococci should not be finished at the stage of determination of the group antigen.

The SDSE forms large (> 0.5 mm in diameter) grayish colonies surrounded by a wide zone of β-hemolysis on sheep blood agar, after incubation at 37°C in 5% CO_2 atmosphere [10, 19]. However, some strains are found to induce α-hemolysis or no hemolysis at all, in the above-described standard conditions [20-22]. As in the case of *S. pyogenes*, there exist strains of SDSE which produce oxygen-labile streptolysin O, and no streptolysin S [20, 23, 24]. The occurrence of such strains has been an incentive to search for media and conditions of incubation which would enhance the activity of streptolysin O [20]. Some authors suggest parallel incubation of three plates aerobically, anaerobically and in 5% CO_2 atmosphere [25]. Similarly as with culture test for *S. pyogenes* [26], it is necessary to stab the inoculated agar with an inoculation loop

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in order to discover subsurface hemolysis [20]. Due to the occurrence of strains displaying changed hemolytic activity, neither α-hemolytic nor nonhemolytic streptococci should be treated as non-pathogenic, especially if they are isolated from patients showing clinical symptoms such as tonsillopharyngitis, rheumatic fever, erythema marginatum, reactive arthritis or glomerulonephritis [25].

Microbiological diagnosis

The SDSE is most often resistant to bacitracin [2, 9, 18, 19], but there are also reports on strains susceptible to that antibiotic [13, 14, 18, 21, 27]. The susceptibility to bacitracin is typical of SDSE strains with a group L antigen [21, 27], but susceptible SDSE isolates with a group A antigen have been described as well [13, 14]. Typically, SDSE strains produce no L-pyrrolidonyl arylamidase, and display a negative result of the Voges-Proskauer test, positive result of β-glucuronidase and negative result of α- and β-galactosidase test [9, 18]. Most of them do not hydrolyze hippurate, except for SDSE strains with group L antigen [21, 27].

For SDSE identification, the following molecular methods were used: 16S rRNA gene sequencing [5, 12, 28-30], polymerase chain reaction (PCR) [15, 28], 23S rRNA gene sequencing [31] and *in situ* hybridization [29].

The basic methods for genotyping SDSE strains are Multilocus Sequence Typing (MLST), Pulse Field Gel Electrophoresis (PFGE) and *emm* typing [2, 6-8, 12, 19, 32-34]. About 50 *emm* types have been described in SDSE so far [6]. It has been observed that different *emm* types dominate in different geographical regions [19]. Several intercontinental clonal complexes of SDSE have been characterized [6].

Virulence factors and pathogenicity

The closest species for SDSE is *S. pyogenes* [35, 36], with sequence similarity at 72% [35], in spite of the highest similarity with *S. agalactiae* in the 16S rRNA gene sequence [35, 37]. The SDSE has a range of genes showing a high degree of homology with corresponding genes of *S. pyogenes*. These are, among others, genes encoding different virulence factors such as: fibronectin binding protein, laminin binding protein, streptolysin S, streptolysin O, streptokinase, hemolysin, hyaluronidase, C5a peptidase and C3-degrading proteinase [35]. Both species have antiphagocytic M protein, encoded by *emm* [10, 35, 36] and hyaluronic capsule [10, 35]. There are, however, marked differences between them: SDSE, for example, lacks the whole set of genes encoding superantigens, which are mostly of phage origin (*spe A*, *spe B*, *spe C*, *spe H*, *spe I*, *spe J*, *spe K*, *spe L*, *spe M*, *ssa*, *smez*) [12, 15, 24, 35, 38-42]. However, scarce occurrences of SDSE strains have been described, having one of those genes [32, 43]. The only superantigen gene which is often found in SDSE strains is *spe G*, which encodes exotoxin G [12, 22, 24, 32, 35, 36, 39-42, 44]. Between both of these closely related bacteria, interspecies DNA transfer occurs [6, 45, 46] by means of mobile genetic elements.

As a result of similar virulence factors possessed by SDSE and *S. pyogenes*, both microorganisms show similar pathogenicity. The SDSE can be isolated as normal flora of human skin, nasopharynx, digestive tract and genitourinary system [10, 19, 27]. Pharyngeal [12, 33, 47-49] and nasal [31] carrier-state of that pathogen has been reported. The frequency of pharyngeal carrier-state is different in particular populations. Zaoutis *et al.* [50] discovered SDSE in 1.5% of American children aged 6-13 (average of 10 years). Steer *et al.* found SDSE in 18.9% of children in a group aged 5-14 in Fiji [49]. McDonald *et al.* discovered pharyngeal carrier-state in 5% of individuals in Australian Aboriginal communities [51], with 5.8% in children under 15 years of age [52]. The latter work showed that pharyngeal SDSE carrier-state is most common between 5 and 14 years of age, exceeding 10% [52].

The SDSE may cause toxic shock syndrome [2, 4, 12, 17, 19, 22, 23, 31, 32, 34, 35, 42, 53, 54] and other invasive infections, such as bacteremia without identified focus (primary bacteremia) [4, 19, 30, 32, 34, 55, 56], meningitis [4, 19, 34, 56, 57], pneumonia [3, 4, 19, 30, 34, 56-58], peritonitis [4, 22], sepsis [2, 16, 17, 31, 57, 58] including urosepsis [3], osteomyelitis [4, 19, 34, 57], including spondylodiscitis [59], arthritis [2-4, 19, 30, 34, 57, 58, 60], necrotizing fasciitis [2, 4, 12, 19, 32, 34, 41], cellulitis [2-4, 17, 19, 29-31, 33, 34, 41, 54, 55, 57, 61], including erysipelas [11, 16, 62], patellar bursitis [57], appendicitis [4], salpingitis [22], abscesses of various locations [4, 19, 30, 34], endocarditis [4, 19, 30, 34, 56, 57], pyomyositis [21], gas gangrene [29, 63], diabetic gangrene [12], and cystitis [31]. The SDSE may also cause non-invasive infections: cutaneous (impetigo [47, 48]) and mucous (tonsillopharyngitis [2, 7, 20, 25, 31, 53, 64], otitis media [2, 40]). Sporadically, infections caused by SDSE are followed by acute glomerulonephritis [65-67]. There is also a growing number of evidence for the connection between SDSE and rheumatic fever [46, 68].

The portal of entry for SDSE may be venous ulcers of legs [59]. Some works reported recurrent bacteremia induced by SDSE [55]. There is a description of toxic shock syndrome in a neonate that took place 12 h after birth and was caused by a strain having the same *emm* type and PFGE pattern as the maternal one, which suggests a possibility of SDSE carrier-state in pregnant women and vertical transmission of the microorganism to a newborn, as in the case of *S. agalactiae* [53]. Three cases of iatrogenic SDSE infection following transfusion of platelet concentrates were described [19], as well as cases of nosocomial infections [30]. It was found that most patients with invasive infections caused by SDSE were suffering from additional disorders, especially with cardiovascular diseases of atherosclerotic etiology, diabetes, obesity,

chronic disorders of soft tissues (diabetic foot, decubitus ulcers, chronic lymphedema, venous stasis), impaired renal or liver function, and malignant neoplasms [2-4, 30, 34, 57]. The SDSE infections occur in all age groups, but the frequency of invasive infections significantly increases after 50 years of age [2, 19, 30, 34], when the above-mentioned risk factors are more common.

The SDSE, unlike *S. pyogenes*, has also been isolated from animals: horses [69-71], pigs [72, 73], dogs [74], camels [75], cattle [44] and sea otters [76]. Marked differences have been found between SDSE strains deriving from humans and animals [44, 73]. Kawata *et al.* [73] discovered no streptokinase activity on human plasminogen in any of 11 SDSE strains isolated from pigs, such activity being one of the most important distinctive features of this bacterium [1]. Due to lack of data, it is not yet certain whether animals participate in transmission of that microorganism to people [70]. The available literature gives no documented cases of zoonotic infections, in contrast with *S. equi* subsp. *zooepidemicus*, which is rather closely related [35] to SDSE [77].

Antimicrobial susceptibility

The SDSE strains remain susceptible to penicillin and other β-lactams [2, 4, 10, 19, 23, 25, 30, 57]. Penicillin is the drug of choice in infections caused by that microorganism. One of recent works describes 2 isolates with minimal inhibitory concentration (MIC) for penicillin of 0.25 µg/ml, in a group of 472 (1997-2004) β-hemolytic streptococci deriving from Europe and North America, possessing group G or C antigens [78], but there is no clear information on species identification of those two strains. This value (MIC = 0.25) is a breakpoint, and it is still interpreted as "susceptibility" according to binding European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations [79], while Clinical and Laboratory Standards Institute (CLSI) guidelines of 2011 [80] treat it as "non-susceptibility".

The SDSE, like *S. pyogenes*, may enter cells of pharyngeal mucous membrane cells and, as an intracellular pathogen, avoid penicillin or other β-lactams, which may be a reason for the described therapeutic failures [25]. In this connection, should a β-lactam be ineffective in therapy of SDSE-induced infections, a cell-penetrating antibiotic ought to be used, chosen according to the antimicrobial susceptibility test (preferably a macrolide, or, in the case of a macrolide-resistant strain, antibiotic of tetracycline or a new fluoroquinolone group, or clindamycin) [25, 64]. In treatment of more serious infections, particularly those associated with toxic shock syndrome, a β-lactam should be administered together with clindamycin [10].

Investigations showed a different percentage of strains resistant to macrolides, lincosamides and streptogramins B in SDSE. There are several phenotypes of resistance, which result from presence and expression of specific genes: *mef*(*A*) encodes an efflux pump that pumps out 14- and 15-membered macrolides, which results in resistance to these antibiotics (M phenotype); *erm*(*A*) and *erm*(*B*) encode ribosomal methylases which mediate resistance to macrolides, lincosamides and streptogramins B by the inducible ($iMLS_B$ phenotype) and constitutive mechanism ($cMLS_B$ phenotype). $iMLS_B$ and $cMLS_B$ phenotypes exclude use of macrolides, lincosamides and streptogramins B, while M phenotype excludes treatment with 14- and 15-membered macrolides [81-83]. Zaoutis *et al.* stated that among 23 SDSE isolates, 3 (13.0%) were resistant to erythromycin (1991-1996) [57]. Lopardo *et al.* discovered one isolate (3.7%) having *erm(TR)*, subclass *erm(A)*, among 27 invasive SDSE isolates coming from Argentina (1998-1999) [17]. Woo *et al.* [30], in a group of 66 isolates (1997-2000), found two (3.0%) resistant to erythromycin and clindamycin, and one (1.5%) resistant to erythromycin and susceptible to clindamycin. Broyles *et al.* discovered resistance to erythromycin in 28.8%, and to clindamycin in 4.2% of isolates coming from invasive infections in California and Georgia (n = 212), however giving no specification of types of resistance (2002-2004) [4]. Uh *et al.*, in a group of 32 SDSE isolates, discovered 3 (9.4%) erythromycin-resistant isolates. Each of them had a different phenotype of resistance (M, $iMLS_B$, $cMLS_B$) (2003-2004) [84]. Hashikawa *et al.* detected *ermB* in one strain among 11 SDSE isolates which caused streptococcal toxic shock syndrome (9.1%). The other ones were susceptible to erythromycin, clarithromycin and clindamycin [23]. Sunaoshi *et al.*, in a group of invasive and non-invasive infection isolates in Japan (n = 145), detected *mef*(*A*) in 4.8%, *erm*(*A*) in 2.1%, and *erm*(*B*) in 3.4% of strains. In total, genes for resistance to macrolides were detected in 10.3% of isolates (2003-2005) [2]. Takahashi *et al.* examined a group of isolates coming from invasive infections in Japan (2006-2007) (n = 231). *mef*(*A*) was present in 1.7%, *erm*(*A*) in 5.6%, and *erm*(*B*) in 2.6% of isolates [19, 34].

Resistance to tetracyclines is very common, which excludes use of these antibiotics in the empirical therapy of infections caused by SDSE [10]. Lopardo *et al.* discovered (1998-1999) 40.7% of strains resistant to tetracyclines [17]. All of them contained *tet*(*M*) [17]. Broyles *et al.* (2002-2004) discovered that 58% of isolates were intermediate to tetracycline [4]. Uh *et al.* (2003-2004) [84] discovered 68.8% of strains resistant to tetracycline. Hashikawa *et al.* detected *tetM* in two SDSE isolates (18.2%) [23]. Liu *et al.* detected *tetS* in 6.4% (n = 12) of 188 (1998-2004) SDSE isolates resistant to tetracycline [85]. Both these genes encode ribosomal protection proteins (RPP) that prevent binding the antibiotic to the ribosome, which allows protein synthesis (translation) [86].

Biedenbach *et al.* [78] detected the lowest inhibitory concentrations for levofloxacin ≥ 2 µg/ml in 2.9% (n = 14) strains out of 472 (1997-2004) β-hemolytic streptococci deriving from Europe and North America, possessing group G or C antigens. All isolates with elevated levofloxacin MIC

Table 1. Antimicrobial susceptibility of the tested isolate of *Streptococcus dysgalactiae* subsp. *equisimilis*

Antimicrobial agent	Disc content	Zone diameter [mm]	Interpretation
Penicillin	10 IU	29	S
Erythromycin	15 µg	22	S
Clindamycin	2 µg	21	S
Levofloxacin	5 µg	18	S
Tetracycline	30 µg	14	R

S – susceptible, R – resistant

values were identified as SDSE. With one exception, they had mutations of *gyrA*, which encodes one of gyrase subunits, of *parC* encoding one of topoisomerase subunits, or of both genes. Some of them exhibited also resistance to moxifloxacin and gatifloxacin. Broyles *et al.* (2002-2004) observed resistance to fluoroquinolones in 2 isolates (0.9%) [4]. Sunaoshi *et al.* (2003-2005) noted a high degree of resistance to levofloxacin (with MICs of ≥ 32 µg/ml) in 2.8% of isolates, which was due to a mutation of *gyrA* and *parC* [2]. A markedly higher percentage of strains resistant to levofloxacin (12.1% (*n* = 38)) was found among 314 β-hemolytic strains, forming large colonies (> 0.5 mm in diameter), possessing group C or G antigens, deriving from invasive and non-invasive infections from Portugal (1998-2005). In that work, a time-related increase of resistant strains was noted, from 11.4% in 2003 to 20.2% in 2005 [45]. Takahashi *et al.* (2006-2007) [19, 34] discovered a high degree of resistance to levofloxacin (the MICs of ≥ 32 µg/ml) in 0.9% of isolates, which was due to a mutation of *gyrA* and *parC*. Hashikawa *et al.* reported all isolates to be susceptible to levofloxacin [23].

In 3 investigations where SDSE susceptibility to vancomycin was tested, all isolates were found to be susceptible to the antibiotic [23, 30, 57]. In one of these works [57], a part of the isolates exhibited tolerance to it (Minimal Bactericidal Concentration, MBC being 32 times or more higher than MIC).

Hashikawa *et al.* noted that all isolates were susceptible to trimethoprim-sulfamethoxazole, chloramphenicol and rifampicin (with rifampicin MIC ≤ 1.0 µg/ml) [23]. Uh *et al.* discovered resistance to chloramphenicol in 9.4% of SDSE isolates [84].

In the work of Lopardo *et al.*, one SDSE isolate was found to produce the bifunctional enzyme (AAC(6')APH(2'')) mediating high-degree resistance to gentamicin [17].

Case report

A 30-year-old white man, with moderate obesity and interdigital tinea pedis, presented with a relapse of infection of soft tissue in the left lower limb. Over 2 years preceding the infection, the patient experienced two episodes of erysipelas of the left crus, with redness, edema, pain, immobility and fever. He received topical and general antibiotic treatment, with a positive result. The patient did not suffer from diabetes, vascular diseases or immune disorders. The bacterial strain isolated from erythematous, suppurative skin lesions on the left foot, when cultured in sheep blood agar, after 24 h of incubation in CO_2 enriched atmosphere, formed grayish colonies, about 1 mm in diameter, surrounded by β-hemolysis zone, about 3 mm in diameter. Microscopic examination of the Gram-stained preparation revealed presence of Gram-positive cocci forming short chains and small clusters. The strain did not produce catalase. It had a group A antigen (Streptex, Remel, Lenexa, Kans., USA). It also did not produce L-pyrrolidonyl arylamidase (PYR 50 Test, Remel). Three identification tests, one for manual identification (API 20 Strep, bioMerieux, Marcy l'Etoile, France) and the other two for automatic identification (rapid ID 32 Strep, bioMerieux; VITEK 2 GP identification card, bioMerieux), basing on biochemical properties, allowed to identify the strain as *Streptococcus dysgalactiae* subsp. *equisimilis* (a number in the collection of the National Medicines Institute: 3932/09). Susceptibility of the isolate to several chosen antibiotics was tested using a disc diffusion method. The measurement of antimicrobial susceptibility and interpretation of the results were performed in accordance with the standards of the Clinical and Laboratory Standards Institute (2011) [80].

The results of antimicrobial susceptibility tests are presented in Table 1.

First-generation cephalosporin (cefadroxil) was used in the treatment, resulting in a complete remission of the infection symptoms. No events of relapse were noted during the next 12-month observation period.

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