

# STREPTOCOCCUS ANGINOSUS GROUP - BRIEF CHARACTERIZATION AND ITS CONTRIBUTION TO THE BRAIN ABSCESS PATHOGENESIS

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## Abstract

**Background:** The oral streptococci are microorganisms whose major habitat is the oral cavity and oropharynx. The *Streptococcus anginosus* group, formerly known as *Streptococcus milleri* group, comprises the following commensal species: *S. anginosus*, *S. constellatus* and *S. intermedius*. Sometimes these species may produce different oral or extraoral infections, especially oro-maxillo-facial infections and deep-seated abscess.

**Objective:** The aim of the present article was to provide the reader with the essential knowledge about *S. anginosus* group characteristics and a useful updated review of its important contribution to develop brain abscess.

**Data sources and selection:** The most important evidence concerning the recent taxonomical data, main phenotypical features and findings referring to the involvement of these bacteria in causing cerebral abscess in adults and children were collected from PubMed/Medline database. Only articles published between January 2011 - November 2015 were selected and the significant data have been presented in a synthesized form, without performing a meta-analysis.

**Conclusion:** The *S. anginosus* group merits greater attention from both clinicians and microbiologists due to its importance in human pathology, especially in life-threatening infections, like brain abscesses, which often require a multidisciplinary team for proper diagnosis and treatment.

**Keywords:** *S. anginosus*, *S. constellatus*, *S. intermedius*, *S. milleri* group, brain abscess

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## Introduction

The oral streptococci are commensal microorganisms that predominate in the normal flora of the mouth and oropharynx. These bacteria have been classified into: *Streptococcus salivarius*, *Streptococcus mutans*, *Streptococcus anginosus* and *Streptococcus mitis* groups. The species: *Streptococcus sanguinis*, *Streptococcus parasanguinis* and *Streptococcus gordonii* have been included in some publications in the group last mentioned, while Facklam considered them to belong to a distinct group, called *S. sanguinis* group.<sup>1</sup>

The *S. anginosus* group was formerly known as *Streptococcus MG - intermedius*, *Streptococcus anginosus - constellatus* or mostly as *Streptococcus milleri* group.

At present, the *S. anginosus* group comprises the following species: *Streptococcus*

*anginosus*, *Streptococcus constellatus* and *Streptococcus intermedius*. *S. anginosus* contains the following 3 subspecies: genomosubspecies AJ1, subsp. *anginosus* and the subsp. *whileyi*, the last one being previously recognized as the DNA group 2 taxon<sup>2</sup> *S. constellatus* is divided into: *constellatus* subsp., *pharyngis* subsp.<sup>3</sup> and *viborgensis* subsp. nov.<sup>2</sup>

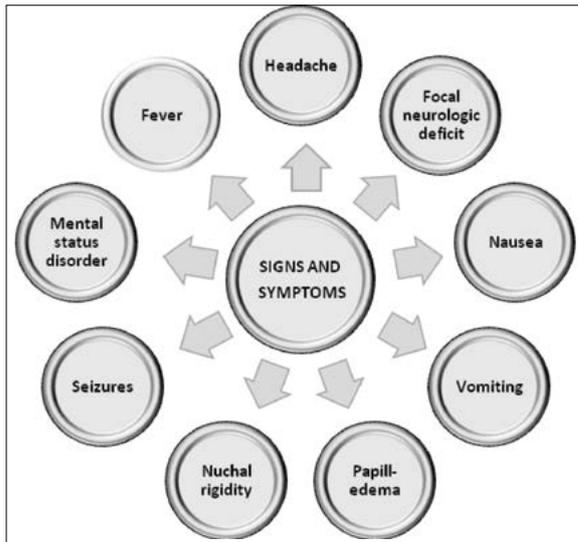
The *S. anginosus* group is phenotypically *heterogeneous*. The strains produce colonies on blood-agar which can be alpha- or gamma-haemolytic and less frequently beta-haemolytic, while the culture has a distinct caramel smell. The isolates of *S. anginosus* group are either non-groupable or belong to one of the following Lancefield groups: F, C, G or A.

The isolates of *S. anginosus* subsp. *whileyi* commonly originate from a sore throat and

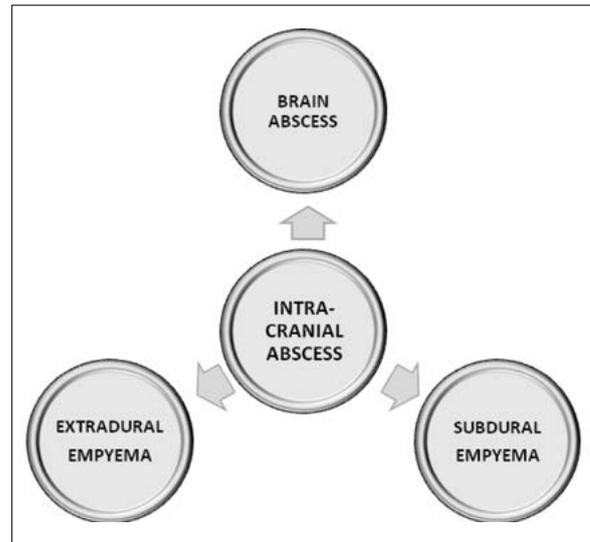
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**Figure 1.** The most frequent clinical signs and symptoms found in brain abscess cases



**Figure 2.** Classification of the intracranial abscesses

seldom from blood, abscess or different intra-abdominal infections. The strains of this subspecies are beta-haemolytic, belong to Lancefield group C and produce larger haemolytic zones compared to *S. constellatus* subsp. *pharyngis* and *viborgensis*. The isolates of *S. constellatus* subsp. *viborgensis* have been isolated from the pharynx, are beta-haemolytic and carry the Lancefield group C antigen.<sup>3</sup>

The *anginosus* streptococci colonizing the mouth, pharynx, genitourinary and intestinal tract can cause severe opportunistic infections, especially when immunity is affected. Sometimes they can spread intracranial leading to meningitis and inflammation of the internal carotid artery or cavernous sinus with consecutive thrombosis.<sup>4, 5</sup> Another serious central nervous system infection produced by these bacteria is the brain abscess, characterized by the clinical triad: headache, fever and focal neurological deficit, which may be associated with other symptoms too (Fig. 1).

Intracranial abscess (Fig. 2) is a life-threatening medical problem despite the progress registered in its diagnosis and therapy.

The etiology of this infection remains unknown in 10-40% cases, but many authors consider the streptococci of *anginosus* group the most commonly isolated bacteria.<sup>6</sup> Thereby, besides making a brief description of *S. anginosus* group, the aim of the present paper has been to underline the role of these bacteria in producing brain abscess. For this, important evidence of *S. anginosus* group involvement in pathogenesis of brain abscess has been extracted from the publications indexed in PubMed/Medline. Only scientific papers written in English and English abstracts of articles written in other languages have been selected, papers published in the last 5 years, from January 2011 to November 2015, using all the combinations between the key words brain or cerebral abscess and: *S. anginosus*, *S.*

*constellatus*, *S. intermedius* or *S. milleri*.

The *anginosus* streptococci may produce cerebral abscess by contiguous spread from a focal infection, such as: dental infections, sinusitis, mastoiditis, otitis media.<sup>7, 8</sup> The frontal lobe is the main location of the brain abscess in most patients<sup>9</sup>, but the temporal lobe is more affected in case of otitis media complications<sup>10</sup> Pansinusitis may lead also to subperiosteal scalp abscess, epidural abscess and other intracranial abscess.<sup>11</sup> However, some brain abscesses develop as posttraumatic complications, including neurosurgery and other cranial trauma followed by wound infection and cerebritis. Another possibility of bacterial dissemination is the haematogenic spread at distance from the oral cavity, respiratory or gastrointestinal tract. These streptococci, like other microorganisms belonging to the normal oropharyngeal flora, may produce bacteremia also after common tooth brushing or dental procedures. As opposed to the contiguous dissemination which usually leads to solitary abscess, the bacteraemia frequently generates multiple abscesses, produced in different internal organs.

Many papers showed that the *anginosus* streptococci as the most common microorganisms involved in brain abscess pathogenesis, followed by the anaerobic bacteria. Thus, a consecutive case series study from Pakistan indicated that *S. milleri* was the most frequent etiological agent (20.7%) of the brain abscess cases investigated, closely followed by the anaerobic isolates (15.1%).<sup>9</sup> Each of the 3 species may be the single etiological agent of the brain abscess, but usually they are isolated in association with other microorganisms, especially with the anaerobic bacteria.

The *S. anginosus* group causes infections mainly in an immunocompromised host, but there are many articles describing life-threatening infections in previously healthy subjects too. Sometimes the evolution might be fatal, as happened in a

case presented by Matamala et al. referring to a previously healthy woman who developed a severe intracranial hypertension due to a brain abscess and a subdural empyema produced by these streptococci.<sup>12</sup>

*S. intermedius* is the most frequent species belonging to *anginosus* group isolated from brain abscess and there are several research works which described the pathogenic factors and mechanisms of this microorganism involved in cerebral abscess.<sup>13</sup> A very important virulence factor detected in *S. intermedius* strains is the cholesterol-dependent cytolysin named intermedilysin, which is strongly associated with brain and liver abscess production<sup>14</sup> *S. intermedius* may express surface proteins belonging to antigen I/II family with a role in pathogenesis, which bind to fibronectin and laminin and may induce the release of interleukine (IL) -8 from monocytes, followed by chemotaxis and activation of neutrophilic leucocytes. *S. intermedius* produces high levels of ammonia from the amino acids released by proteolysis associated to brain tissues destruction, which contribute to brain aedema and different symptoms observed in brain abscess.<sup>15</sup> The brain suppurative process due to this species may induce host inflammatory response, especially high levels of Th1 and T17 cytokines, like: TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$  and IL-17, IL-23, respectively.<sup>16</sup>

*S. intermedius* can also cause multiple cerebral abscesses as it was shown by a study published in 2012, describing a case of a young man hospitalized for pneumonia and multiple brain abscesses<sup>17</sup> The Gram-stained smear of the bronchoalveolar lavage fluid showed Gram-positive cocci, while *S. intermedius* was detected by a polymerase chain reaction and by electrospray ionization with mass spectrometry in both cerebrospinal fluid and fixed tissue from subcarinal lymph node biopsy sample. Multiple cerebral abscesses developed more frequently in immunocompromised persons, and Hanna and Das reported a case of multiple brain abscesses due to *S. intermedius* in a patient with oesophageal adenocarcinoma<sup>18</sup>

*S. intermedius* can produce concomitant solitary brain abscess and other deep-seated abscesses, like spleen abscess<sup>19</sup> or lung abscess<sup>20</sup> in either immunocompromised individuals or previously healthy persons. *S. intermedius* and the other species of *anginosus* group may cause brain abscess in children too<sup>21,22</sup>, and like in adult cases, the frequency of this infection was found to be 2-3 times higher in male than in female patients.<sup>22</sup> Moskovitz et al. reported a case of cerebral abscess in a pediatric patient with cyanotic heart disease and extensive dental caries.<sup>23</sup> The authors considered a dentoalveolar abscess to be the source of the *S. intermedius* strain isolated from the cerebrospinal fluid of the patient. Besides craniotomy with abscess drainage, the child was treated with antibiotics for some months and underwent proper dental procedures. Another recent paper presented 4 cases of pediatric

patients with fever, meningeal syndrome and seizures, diagnosed with cerebral abscess by brain imaging, with *S. intermedius* isolated from cerebrospinal fluid.<sup>24</sup> All 3 boys and the girl were over 12 years of age and recovered well after abscess puncture and antibiotic treatment.

In a systematic review of intracranial abscesses of odontogenic origin, 60 reported cases in PubMed database have been analysed for the predisposing condition of the patients, the clinical outcome of the infection and the microbiological findings.<sup>25</sup> The conclusions were that the odontogenic brain abscess predominated in adult men and more than half of the patients presented signs of dental lesions, mainly periapical lesions due to caries and periodontitis, while many patients underwent dental extractions.

The viridans streptococci and especially *S. anginosus* group were the most frequently isolated microorganisms from the brain abscesses, while the rest of the isolates belonged to the following genera or species: *Peptostreptococcus*, *Prevotella*, *Fusobacterium*, *Actinomyces*, *Eikenella corrodens* and *Aggregatibacter actinomycetemcomitans*. The abscesses have developed in different brain regions with no correlation between the respective site and the side of dental infection, which suggested the haematogenous spread. The mortality rate found in this study was of 8.3%.

The mortality rate increases when the brain abscess is associated with intraventricular rupture, but full recovery has been registered also in such situations. Nishizachi et al. reported a case of a 69-year-old patient with brain abscess due to *S. intermedius*, who underwent a neuroendoscopic evacuation of the intraventricular pus.<sup>26</sup> The patient has been discharged completely recovered after one month, during which he received intraventricular gentamicin and intravenous cefotaxime, continuing afterwards with oral cefcapene.

Simone and colab. presented a case of a disseminated infection with *S. intermedius* in a 61-year-old man with brain abscess and multiple pulmonary and liver lesions.<sup>6</sup> The same authors also reviewed literature on the disseminated infections produced by *S. anginosus* group and concluded that both surgical and antibiotic therapy were very important for the complete recovery of the patients, mentioning that the infections caused by these streptococci responded satisfactorily to penicillin or cephalosporins.

Lee et al. isolated *S. intermedius* from a brain abscess developed in a 47-year-old woman with congenital heart conditions with right-to-left shunting and thromboemboly.<sup>27</sup> The patient was treated by surgery (craniotomy and corticectomy) and antibiotics (penicillin G and metronidazole). Yanagihara et al. found *S. intermedius* as the etiological agent in a cerebellar abscess case secondary to a hepatopulmonary syndrome in a 76-year-old woman with interstitial pneumonia. Stereotactic burr-hole drainage and antibiotic treatment (vancomycin, piperacillin

and cefotaxime) were applied.<sup>28</sup> An unusual etiological agent association has been found in a case of a 56-year-old man with a right fronto-ethmoido-maxillary sinusitis, type II diabetes and a history of myocardial infarction, who developed a subdural empyema in the right fronto-temporo-parietal region and a right frontal lobe abscess.<sup>29</sup> Culture and polymerase chain reaction performed with pus sample collected by needle-aspiration revealed *S. intermedius*, while the abscess aspirate imaged by both Nomarski differential interference contrast microscopy and transmission electron microscopy indicated the presence of *Encephalitozoon cuniculi*. In addition, the genotype of this microsporidian was detected by a polymerase chain reaction in the abscess aspirate, urine and stool samples. The patient was cured with intravenous chloramphenicol and antiparasitic agents (first albendazol, which was changed to mebendazol due to circumstances).

The other 2 species of the *anginosus* group may express pathogenic factors too. One of the putative virulence factors responsible for the beta-hemolytic activity of the *S. anginosus* strains is the streptolysin S-like peptide with a different amino acid structure than streptolysin S of *S. pyogenes*, which is encoded by two *sagA* homologues.<sup>30</sup>

A brain abscess often requires both surgery treatment and antibiotic administration for a period of 1-2 months. Sim and Watson published a case of brain abscess due to *S. anginosus* in a 23-year-old woman who previously suffered several tooth extractions.<sup>31</sup> The patient recovered after intravenous penicillin G administration for a period longer than one month.

Lin presented a case of a temporal lobe abscess and a thalamus haematoma in a 78-year-old man with fever and haemiplegia after 5 days from the incision of a masticator space abscess due to a tooth extraction.<sup>32</sup> The culture of the aspirated pus was positive for *S. anginosus* and the patient was treated intravenously with penicillin G for 2 months, but was left with hemiparesis. This species may produce multiple intracranial abscesses even in previously healthy individuals.<sup>33</sup> A 30-year-old man with a medical history of asthma developed a left lower lobe lung abscess and multiple brain abscesses located in both frontal lobes and in parietal-occipital junction with extension in the ventricle and cerebellum.<sup>34</sup> Treatment with vancomycin intrathecally and ceftriaxone intravenously has been started, but the patient developed an extensive venous thromboembolism and died despite the urgent fasciotomy.

Specialist literature offers several case reports with concomitant brain and other deep seated abscesses caused by *S. anginosus*, such as lung abscess<sup>35</sup> or spleen and liver abscesses.<sup>36</sup>

Walsh et al. described a case of a 53-year-old woman with fronto-parietal abscess with atrial septal aneurysm and patent foramen ovale, and a history of asthma and epilepsy.<sup>37</sup> The cerebral abscess was found during the neuronavigation-

guided left fronto-parietal craniotomy, performed in order to debulk the presumed brain neoplasm revealed by neuroimaging. The microorganism grown from the drained pus was *S. constellatus* and the authors assumed that it originated from the mouth flora, entered the bloodstream during the dental extraction underwent by the patient 3 weeks prior to admission, and bypassed the pulmonary circulation developing an embolism through foramen ovale. The clinical status improved very much after neurosurgery and antimicrobial treatment for 7 weeks.

Chheda et al. isolated *S. constellatus* from a biopsy sample collected from a frontal brain lesion in a 54-year-old male patient with endogenous endophthalmitis and multiple brain abscesses. The patient also suffered from diabetes mellitus and had undergone a tooth extraction 2 months before admission.<sup>38</sup> Ceftriaxone and metronidazole were given initially and the treatment continued with intravenous cephalosporine. The patient left the hospital after 3 months, with improved neurological status.

A Polish patient with orbital complication during an acute episode of rhinosinusitis was diagnosed with brain abscess by computed tomography, which is strongly recommended for both sinus and brain in most acute rhinosinusitis complications.<sup>39</sup>

The pus culture of the surgical evacuated abscess was positive for *S. constellatus* and *Parvimonas micra*, and the patient recovered after half a month of treatment with penicillin and metronidazol.

Besides cranial computed tomography, magnetic resonance imaging is very often necessary to confirm the diagnosis. It is also the case of a 38-year-old female patient with a fronto-parietal lobe abscess who was diagnosed during the hospitalization with Osler's disease too.<sup>40</sup> *S. constellatus* was isolated in association with *Fusobacterium* spp. and *Aggregatibacter aphrophilus*.

The empiric treatment with chloramphenicol and metronidazole has been replaced by cefotaxime, due to acquired thrombocytopenia.

The diffusion-weighted imaging has already demonstrated its usefulness in distinguishing a pyogenic abscess from necrotic and cystic tumors. Thus, the gadolinium enhanced T1-weighted images indicated the presence of a pituitary abscess in a 74-year old man who suffered a transsphenoidal surgery for pituitary adenoma one year ago.<sup>41</sup> Neurosurgery was repeated and a pituitary abscess was revealed, with detection of *S. intermedius* in the abscess pus.

A national prospective research focusing on the microbiology of the brain abscess was performed in Norway between 2011 - 2013.<sup>42</sup> One hundred and sixty strains were detected by massive parallel sequencing in 31 samples originated from spontaneous abscesses. Most of the strains originated from dental or oro-maxillo-facial primary focus and only 31% and 61% of them were isolated by culture or detected by Sanger DNA sequencing,

respectively. Twenty-four strains of *S. intermedius*, 16 strains of *Fusobacterium nucleatum* and 11 strains of *Aggregatibacter aphrophilus* were present in different combinations in all the samples and therefore, the authors concluded that these species should be considered key pathogens for the establishment of polybacterial abscesses. In the respective research, *S. constellatus* was detected only in 2 cases of polymicrobial brain abscesses, while *S. intermedius* and *F. nucleatum* represented the only microorganisms found in monobacterial abscesses too. All *anginosus* streptococcal isolates were susceptible to ceftriaxone and cefotaxime. These cephalosporins associated with metronidazole represent the first line antimicrobial therapy for brain abscess in Norway.<sup>42</sup>

The species of *anginosus* group involved in cerebral abscess may originate not only from the mouth and upper respiratory tract, but also from the gut flora. Thus, Zhou et al. reported a very recent case of a 30-year-old patient with a brain abscess secondary to a recurrent sigmoid diverticular abscess, with isolation of the same strain of *S. anginosus* from both abscesses.<sup>43</sup> A Dutch team published a case report of a 51-year-old patient who developed a temporo-parieto-occipital abscess with leakage into the ventricle following a transanal hemorrhoidal dearterialization done under spinal anesthesia 2 weeks ago.<sup>44</sup> The initial treatment consisted in dexamethasone and intravenous penicillin, metronidazole (for 2 weeks) and ceftriaxone (for 3 days). Antibiotic treatment was continued with penicillin and ventriculostomy with abscess drainage were performed after 3 weeks. A penicillin-susceptible strain of *S. milleri* group was isolated from the pus culture.

Unfortunately, there are more studies in which the isolates of the *anginosus* group were not identified at species level, and were reported using the present or the former name of this streptococcal group. Thus, in a case-report of a 51-year-old man with concomitant brain and lung abscess associated with T4-T5 spondylodiscitis, treated with surgical drainage and antibiotics, the etiological agent found was *S. milleri*.<sup>45</sup> The isolation of *S. milleri* was also reported in a case of a 28-year-old man with headache, fever, limited homonymous hemianopsia and a drift leg, who was diagnosed by magnetic resonance imaging with parafalcine subdural empyema and occipital brain abscess.<sup>46</sup> The patient was treated with penicillin G.

The logistic regression analysis applied for a 20-year review of medical records of pediatric patients with intracranial complications following rhinosinusitis indicated that *S. anginosus* group was involved in about one third of the total 50 cases, developed more severe intracranial complications, with permanent neurologic deficit, and required frequent surgical treatment and longer period of intravenous antimicrobial administration.<sup>47</sup>

A Chinese team conducted a retrospective study on the etiology, management and outcome of the brain abscesses recorded in a single hospital in

Shanghai, between 2001- 2011 (48). Sixty patients were treated by stereotactic guided aspiration or craniotomy excision during that period. Because many of them received antibiotics before neurosurgery, the cultures were positive only in 13,33% cases, with the streptococcal isolates predominating, including *S. anginosus* and *S. intermedius* strains. Another retrospective study made in a Japanese hospital indicated the same predominance of *S. milleri* isolates in the brain abscess etiology, either the source of infection was known or not.<sup>49</sup> A retrospective study performed by a British team in a tertiary pediatric infectious diseases and neurosurgical center showed that there were 17 children diagnosed and treated with brain abscesses, 22 children with subdural empyema and 2 children with both types of suppuration, between 2001 - 2009.<sup>50</sup> The main underlying condition was sinusitis and the most isolated bacteria were the streptococci of *anginosus* group.

A 5-year period research by another British team, based on clinical data, radiological and microbiological findings, surgical management and outcomes in pediatric patients with sinogenic intracranial abscesses from a university hospital, found the streptococci belonging to *anginosus* group involved in more than 2/3 of the investigated cases.<sup>51</sup>

An Australian team performed a retrospective study focused on the clinical, microbiologic and treatment data obtained from 118 pediatric patients with brain abscesses recorded between 1999 - 2009 in 4 neurosurgical centers.<sup>52</sup> More than half of those children received antimicrobial agents before diagnosis, while the classical symptom triad, long-term neurological sequelae and fatal evolution were noticed only in: 13%, 35% and 6% of the cases, respectively. The most frequent etiological agent was *S. milleri* (38%), except for the head trauma cases, when *S. aureus* predominated. The ceftriaxone/cefotaxime and metronidazole represented the main empiric antimicrobial treatment and it was effective in more than 80% of cases; it is worth mentioning that metronidazole should have been required only in 7% of cases.

*S. milleri* was isolated also from a thalamic abscess in a 56-year-old man with type 2 diabetes, periodontitis and dental abscess.<sup>53</sup> The patient was cured within 2 months by stereotactic puncture, external drainage and both intrathecally and systemically administered antibiotics.

In 2012 a Danish team published the results of a 15-year retrospective review of 102 cases of adult patients with brain abscess, treated between January 1994 and April 2009, at the Departments of Neurosurgery, Infectious Medicine and Neurology of a university hospital in Copenhagen.<sup>54</sup> In addition to logistic regression analysis of the prognostic factors associated with the Glasgow Outcome Score (referred to severe disability/vegetative state and death), the

authors also discussed the laboratory findings, neuroradiological investigation and the treatment applied.

Of the total number of isolates, 55% were streptococci, with *S. milleri* isolates predominating, followed by anaerobic bacteria (17%) and staphylococci (15%) isolates. Most of the patients were treated surgically (burr-hole aspiration in 67% cases and craniotomy in 20% cases), while antibiotics alone were given in 13% patients, for a median period of 2 months. The authors found no solid arguments to consider the administration of 3<sup>rd</sup> generation cephalosporin or meropenem superior to a combination of high-dose penicillin with metronidazole, which represented the first-line treatment in brain abscess in Denmark for many years.<sup>54</sup>

The *anginosus* streptococci are usually susceptible to beta-lactam antibiotics.

However, there have been found isolates of *S. milleri* group from head and neck infections with intermediate susceptibility to ampicillin and third-generation of cephalosporins<sup>55</sup>, and one paper indicated a proportion of 29% ampicillin-resistant isolates.<sup>56</sup>

A 2-year study regarding the antimicrobial susceptibility of more than 1000 isolates of viridans streptococci from different sites of infection indicated that all *anginosus* streptococcal

isolates (166 strains of *S. anginosus*, 74 strains of *S. constellatus* and 50 strains of *S. intermedius*) were susceptible to vancomycin, while the susceptibility rates for: penicillin, ampicillin, cefotaxime, ceftriaxone, clidamycin, erythromycin, levofloxacin and tetracycline were of: 93.8%, 94.8%, 97.1%, 96.9%, 86.4%, 84.8%, 97.9% and 44.2%<sup>57</sup> In the same study, the penicillin intermediate and resistance rates were found much higher in case of: *S. salivarius* (70.2% and 8.8%), *S. mitis* (39.4% and 20.9%), *S. mutans* (14.3% and 28.6%) and *S. sanguinis* (35.2% and 5%).

However, the proportion of 4.5% (1.8% of the *S. anginosus* strains, 8.2% of the *S. constellatus* strains and 8% of the *S. intermedius* strains) penicillin intermediate and 1.7% (1.2% of the *S. anginosus* strains, 0% of the *S. constellatus* strains and 6% of the *S. intermedius* strains) penicillin resistant isolates of *S. anginosus* group indicated the unpredictable susceptibility of these bacteria to beta-lactam antibiotics and the necessity of the *in vitro* susceptibility testing when viridans streptococcal strains of clinical significance are isolated from infections requiring antimicrobials.<sup>57</sup> The data presented in this paper underline the role of *anginosus* streptococci in human pathology and is meant to raise awareness of the clinicians about the life-threatening infections, like cerebral abscess, produced by these bacteria.

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CV

## Questions

### Which are the species belonging to *Streptococcus anginosus* group?

- a. *S. anginosus*, *S. oralis*, *S. mitis*;
- b. *S. anginosus*, *S. salivarius*, *S. intermedius*;
- c. *S. anginosus*, *S. constellatus*, *S. intermedius*;
- d. *S. anginosus*, *S. constellatus*, *S. mutans*.

### What type of haemolysis can the strains of *S. anginosus* group produce on blood-agar?

- a. Only alpha-haemolysis;
- b. Only beta-haemolysis;
- c. Only gamma-haemolysis;
- d. Alpha-haemolysis, beta-haemolysis or gamma-haemolysis.

### Which Lancefield groups may the strains of *S. anginosus* group belong to?

- a. Group A, group B, group C or group D;
- b. Group A, group C, group G, group F or none of the Lancefield groups;
- c. Group C, group D, group G or group F;
- d. Group B, group C, group D or group F.

### Intermedilysin is an important pathogenic factor produced only by:

- a. *S. intermedius*;
- b. *S. anginosus*;
- c. *S. constellatus*;
- d. *S. anginosus* and *S. constellatus*.