Brief report

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Clinical and microbiologic characteristics of pleuro-pulmonary infection due to *Streptococcus intermedius*

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ABSTRACT

The clinical and microbiological characteristics of pleuro-pulmonary infection (PPI) caused by *Streptococcus intermedius* is described, including 6 cases in the literature and 9 cases handled at the present centre. Out of the 15 patients, 12 were male; mean age at diagnosis was 62.06 ± 15 years. Twelve had risk factors for *S. intermedius* infection such as alcoholism in 5 (35.7%) patients, periodontal disease in 3 (24.6%) cases, chronic obstructive pulmonary disease in 3 (24.6%), and diabetes mellitus in 2 (14.2%). Cough was present in 12 (80%) patients and chest pain and dyspnea in 9 (60%). The mean diagnosis interval was 34 days. The diagnosis was obtained from pleural fluid aspirate in 13 (86.6%) cases and from biopsy/tissue samples in 2. The most frequently antimicrobials used for treatment were ceftriaxone + levofloxacin. Ten patients cured with a combination of medical and surgical treatment and 2 patients died as a consequence of infection. The incidence of PPI caused by *S. intermedius* is increasing in our health area; drainage along with antibiotic therapy is recommended for treatment.

Key Words: Pleuro-pulmonary infection, *Streptococcus intermedius*, pleural effusion, antimicrobials, drainage.

Características clínicas y microbiológicas de la infección pulmonar causada por *Streptococcus intermedius*

RESUMEN

Se describen las características clínicas y microbiológicas de la infección pleuro-pulmonar producida por *Streptococcus intermedius*, incluyendo 6 casos de la literatura y 9 casos diagnosticados en nuestro centro. De los 15 pacientes, 12 eran varones; la media de edad al diagnóstico fue de 62,02 ± 15 años. Doce tenían factores de riesgo para la infección por *S. intermedius*, tales como alcoholismo en 5 (35,7%) pacientes, enfermedad periodontal en 3 (24,6%) casos, enfermedad pulmonar obstructiva crónica en 3 (24,6%), y diabetes mellitus en 2 (14,2%). Se presentó tos en 12 (80%) pacientes y dolor torácico y disnea en 9 (60%). La media del intervalo diagnóstico fue de 34 días. El diagnóstico se obtuvo de aspirado de líquido pleural en 13 (86,6%) casos y de muestras de biopsia/tejido en 2. Los antimicrobianos más frecuentemente utilizados fueron ceftriaxona + levofloxacino. Diez pacientes curaron con una combinación de tratamiento médico y quirúrgico y dos pacientes fallecieron como consecuencia de la infección. La incidencia de infección pleuro-pulmonar causada por *S. intermedius* se ha incrementado en nuestra área de salud; el tratamiento recomendado es el drenaje junto con la terapia antibiótica.

Palabras Clave: infección pleuro-pulmonar, *Streptococcus intermedius*, derramen pleural, antimicrobianos, drenaje

INTRODUCTION

Pleuro-pulmonary infection (PPI) is a common entity which are mainly caused by bacteria. A wide range of microorganisms can cause PPI, although the most common bacteria that are involved in immunocompetent adults in the community adquired setting include *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, viruses and

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Chlamydophila pneumoniae [1]. In elderly patients and in those with other underlying diseases *Haemophilus influenzae*, *Legionella pneumophila* and *Moraxella catarrhalis* may be also causes of PPIs [1]. *Streptococcus milleri* group is mainly associated with abscesses and supurated infections and is an uncommon cause of PPI. This group is currently known as *Streptococcus anginosus* group (SAG), term suggested by Kawamura et al. [2], and includes *S. anginosus*, *S. constellatus*, and *S. intermedius*. Of them, *S. constellatus* is generally isolated from samples of respiratory tract. However, *S. intermedius* is mainly involved with both liver and cerebral abscesses [3,4]. Until now, only few cases of PPI due to *S. intermedius* have been reported in the medical literature [5-10]. Another study shows 14 patients with PI due to *S. intermedius* in a period of 10 years [11].

In the last 3 years, we have diagnosed in our laboratory 9 cases of PPI caused by *S. intermedius*. Due to its rarity, the literature has provided only limited guidance on the characteristics of patients with this condition, so a review was performed on diagnostic and therapeutic approaches to this entity.

METHODS

We describe 15 patients with PPI due to *S. intermedius*. Using the key words "*Streptococcus intermedius* pleural infection" and "*Streptococcus intermedius* pulmonary infection" we searched MEDLINE (National Library of Medicine, Bethesda, MD), Web of Science, CINAHL, and Cochrane systematic review databases for case reports of this condition. We also checked the references cited in the papers for additional case reports published before 1966.

We traced 6 cases caused by *S. intermedius* and described in sufficient detail. These cases, along with our 9 patients, are the basis of the present report. Data on age and sex, risk factors or underlying diseases, time until diagnosis, clinical manifestations, radiological and laboratory findings, microbiologic diagnosis, treatment, outcome and follow-up were recorded over a period of two years (June 2015-June 2017).

In the microbiology laboratory the pleural fluid was processed as follows: after centrifugation, the sample was inoculated in blood agar (either aerobic or anaerobic) (BD Columbia Agar 5% Sheepblood®, Becton Dickinson), chocolate agar (BD Choco Agar, Becton Dickinson) and thioglycolate broth (BD™ Fluid Thioglycollate Medium, Becton Dickinson). All media were incubated at 37º C. A mass spectrometry method (Bruker Biotyper, Billerica, MA) was employed to identify the strain. All cases of *S. intermedius* infection in our laboratory were obtained in pure culture

RESULTS

The first case of PPI due to *S. intermedius* here reviewed was published by Roy et al. in 1991 [5]. A review of the medical literature identified 29 cases of PPI caused by this pathogen. Fourteen cases were excluded because no individualized data were available [11]. This review therefore comprised 15 patients, including our cases.

General characteristics. Table 1 summarizes the clinical and microbiologic findings for the 15 patients, and table 2 compiles the features of pleural effusion. There were 12 (80%) men and the mean age of patients was 62.06 ± 15 years (range: 38-89 years). The mean interval from clinical onset to infection diagnosis was 34 days (range: 3 to 150 days). This interval was not reported for one patient [9].

No risk factors for Streptococcal infection were found in one patient (6.6%) 5. Major risk factors for Streptococcal infection were alcoholism in 5 (33.3%) patients, chronic obstructive pulmonary disease and periodontal disease in 3 (20%) cases each one, and diabetes mellitus in 2 (13.3%). Thirteen (86.6%) patients were smokers and 3 (20%) patients had more than one risk factor for this infection.

Empyema was seen in 7 (46.6%) patients, and both pneumonia and pleural effusion in 2 patients each one (13.3%).

Clinical manifestations. Cough was reported by 12 (80%) patients, and chest pain and dyspnea by 9 (60%) patients each one. Finally, fever was recorded in 8 (53.3%) patients. Five patients (33.3%) had two symptoms, while 10 (66.6%) had three or more symptoms.

Microbiology and laboratory findings. At the diagnosis of PPI, data on C-reactive protein (CRP) level were not reported in 6 (40%) patients and data on white blood cell (WBC) were not reported in only 2 (13.3%). The mean CRP level was 208.6 mg/L (range: 33.6-480), and the mean WBC level was 21,418/mm3 (range: 3,130-40,000).

Regarding data on pleural fluid, protein level was elevated in all patients tested, except for one patient (case 10); the mean protein level was 4 g/dL (range: 1.7-5.2). LDH level was also elevated in all patients tested (n=11), being the mean LDH level 2777 g/dL (range 571-6280). Finally, the mean white cell count level was 89,484 mm3 (range 370-466,000).

S. intermedius was diagnosed by culture of pleural fluid (PF) aspirate in 13 (86.6%) cases, and culture of biopsy or tissue samples in 2 (13.3%).

Susceptibility tests for *S. intermedius* were reported in 12 (80%) isolates (table 3). Antimicrobial susceptibility was completely performed in cases 7 to 15. In these 9 cases, 100% of isolates were susceptible to cefotaxime, levofloxacin, linezolid, vancomycin and daptomycin, and 45.5% of isolates were resistant to both clindamycin and erythromycin. Only one strain of *S. intermedius* was intermediate to penicillin (case 7; MIC 1 mg/L). In case 4, susceptibility to levofloxacin was reported, and in cases 5 and 6 susceptibility to penicillin was also reported.

Antimicrobial and surgical treatment. Fourteen (93.3%) patients underwent antibiotic treatment, with a single drug in 2 cases (14.2%), with two drugs in 8 cases (57.1%) and

Table 1 | **Main findings in 15 patients with pleural effusion caused by *Streptococcus intermedius*.**

Patient (year of publication) Author [reference]	Age (years)/ sex	Clinical manifestations	Risk factors	Time until diagnosis (days)	Radiological findings	Laboratory findings	Microbiologic diagnostic	Antimicrobial treatment	Other treatments	Outcome/follow-up (months)
1 (1991) Roy [5]	38/M	Chest pain, cough, dyspnea, fever, lightheadedness	Smoker Caries	7	Large left pleural density	WBC 12,600/mm3	Pleural fluid culture	Cefotaxime Penicillin	Drainage Thoracotomy + decortication	Cure/NR
2 (2000) Khatib [6]	55/M	Fever, cough, hemoptysis, headache	Alcoholic cirrhosis	10	Right upper-lobe consolidation	NR	Lung biopsy culture	Ceftriaxone + ampicillin	NR	Died
3 (2000) Mautner [7]	80/M	Chest pain, cough, fever, shortness of breath	Smoker	14	Left hemithorax opacification	WBC 22,000/mm^3	Pleural fluid culture	NR	Drainage Thoracotomy + decortication	NR
4 (2006) Iskandar [8]	52/M	Cough, shortness of breath, loss weight	Smoker Caries, gingivitis	150	Loculated pleural effusion	NR	Pleural fluid culture	Levofloxacin + clindamycin	Drainage	Cure/NR
5 (2014) Noguchi [9]	79/M	Fever, cough	Empyema 4 months ago Smoker Drinker Poor oral hygiene	NR	Left hemithorax opacification	WBC 39,600/mm^3 CRP 33,6 mg/dL	Pleural fluid culture	Meropenem	Drainage Pleurectomy	Improved /NR
6 (2016) Hannoodi [11]	52/F	Cough, shortness of breath, fever	Asthma Smoker	42	Bilateral multilobular lung infiltrate Loculated pleural effusion	WBC 29,200/mm^3	Tissue sample culture	Erythromycin Ciprofloxacin Aztreonam + vancomycin + azithromycin Ceftriaxone	Drainage Pleurectomy + decortication	Cure/NR
7 (PR) Cobo	75/M	Cough, dyspnea, chest pain, hemoptysis	Smoker Asthma COPD	5	Right hemithorax opacification	WBC 24,000/mm^3 CRP 200 mg/dL	Pleural fluid culture	Ceftriaxone Levofloxacin	Drainage	Cure/3
8 (PR) Cobo	63/M	Cough, chest pain	DM Smoker COPD	7	Pulmonary abscess and empyema Right hemithorax opacification	WBC 20,600/mm3 CRP 353.7 mg/dL	Pleural fluid culture	Ceftriaxone Levofloxacin	Drainage	Cure/3
9 (PR) Cobo	62/F	Fever, dyspnea	Smoker COPD Thoracic trauma	2	Right basal pulmonary opacification Pleural effusion	WBC 20,080/mm^3	Pleural fluid culture	Ceftriaxone Levofloxacin	Drainage + pleural debridement	Cure/5
10 (PR) Cobo	89/M	Increase of dyspnea, cough	DM	15	Pulmonary empyema	WBC 18,520/mm^3 CRP 156.5 mg/dL	Pleural fluid culture	Ceftriaxone	Drainage	Cure/NR
11 (PR) Cobo	48/M	Dyspnea, fever, chest pain, cough, chills	Smoker Amigdalitis and cervical abscess	5	Pulmonary abscesses Bilateral pleural effusion	WBC 3,130/mm^3 CRP 480 mg/dL	Pleural fluid culture	Ceftriaxone Levofloxacin	Drainage	Died
12 (PR) Cobo	72/M	Cough, dyspnea, chest pain	Smoker Drinker	3	Right basal opacification Pleural effusion	WBC 21,210/mm^3 CRP 284 mg/dL	Pleural fluid culture	Ceftriaxone Levofloxacin	Drainage	Improved/new pleural effusion 1 month later Cure/2
13 (PR) Cobo	49/M	Chest pain, dyspnea, fever	Smoker Drinker	7	Right pleural effusion	WBC 40,000/mm3 CRP 33.7 mg/dL	Pleural fluid culture	Levofloxacin Clarithromycin Cefditoren Clindamycin	Drainage	Improved/new pleural effusion 15 days later
14 (PR) Cobo	74/M	Chest pain, dyspnea	Smoker Drinker Pulmonary epidermoid carcinoma	6	Right pleural effusion Nodular lesions in the right lung	WBC 15,100/mm3 CRP 80.2 mg/dL	Pleural fluid culture	Imipenem Ceftriaxone Clindamycin	Drainage	Cure/1
15 (PR) Cobo	43/F	Chest pain, cough, dyspnea	Smoker	4	Left pleural effusion	WBC 12,400/mm3 CRP 256 mg/dL	Pleural fluid culture	Levofloxacin	Drainage	Cure/2

M: male; F: female; NR: not reported; PR: present report; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood count; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus

Table 2 **Pleural effusion characteristics from 13 patients with *S. intermedius* infection.**

Patient[b] (year of publication) Author [reference]	pH	Glucose (mg/dl)	Proteins (g/dl)	LDH (IU/L) LDH (IU/L) in blood[a]	WCC (mm^3)/ % neutrophils
1 (1991) Roy [5]	7.04	NR	NR	NR	370/NR
3 (2000) Mautner [7]	6.89	5	4.7	NR	2,900/96
4 (2006) Iskandar [8]	NR	10	4.2	6280 113[a]	466,000/90
5 (2014) Noguchi [9]	NR	1	4.3	2873 236[a]	NR
6 (2016) Hannoodi [11]	NR	93	4	1372	NR
7 (PR) Cobo	NR	1	2.8	3540 198[a]	5,727/96
8 (PR) Cobo	NR	32	3.5	4860 292[a]	63,298/95
9 (PR) Cobo	NR	1	3.9	1790 204[a]	44,924/92
10 (PR) Cobo	NR	1	1.7	687 173[a]	295,000/54
12 (PR) Cobo	NR	10	4.2	1535 211[a]	19,212/91
13 (PR) Cobo	7.5	1	5.2	2278 217[a]	45,800/85
14 (PR) Cobo	7.07	26	4.8	4762 116[a]	38,552/82
15 (PR) Cobo	7.2	74	4,7	571 289[a]	2,549/32

NR: not reported; LDH: lactate dehydrogenase; ADA: adenosin-deaminase; WCC: white cells count
Normal values: pH: 7.37-7.45; Glucose: >60 mg/dL; Proteins: 1-2 gr/dL; LDH: <50% plasma value; WCC: 1000-5000/mm^3.
[b]Cases 2 and 11 did not reported any data about pleural effusion

more than two in 3 (21.4%). Ceftriaxone plus levofloxacin was the antimicrobial regimen most used (5/35.7%).

Drainage of PF was performed in all patients, 9 of whom (60%) underwent only this procedure. Thoracotomy plus decortication was undertaken in 2 (13.3%) patients and pleurectomy in another 2 cases. Debridement was undergone only in one (6.6%) patient.

Outcome. The final outcome was not reported in one patient, and a favourable outcome was recorded in 12 (80%) patients after antibiotic plus surgical treatment. Two patients (13.3%) died. The follow-up was reported in 6 (40%) patients, with a mean time of 2.6 months (range 1-5 months).

DISCUSSION

SAG is part of the normal biota of the oropharyngeal, urogenital, and gastrointestinal tracts [12]. These microorganisms are strongly associated with abscess formation in the brain, peritoneal cavity, and oropharynx [13], although *S. intermedius* and *S. constellatus* are generally more frequently associated with abscess formation than *S. anginosus* [14]. Moreover, it is well known that *S. anginosus* is frequently found in specimens from the urogenital or gastrointestinal tracts and *S. constellatus* can be found in infections of the respiratory tract or blood, as well as *S. intermedius* is most often identified in abscesses of the brain or liver [15].

PPI caused by *S. intermedius* is an uncommon event. Only few case reports with this condition have been published until now [5-10], and other report found some cases of this infection in a period of 10 years [11]. However, in our hospital we were able to trace 9 cases of PPI caused by this microorganism in the last 3 years, showing an increase of incidence of this infection in our health area. The main cause of this increase is unknown, but the use of new diagnostic tools such as MALDI-TOF techniques may be related to a better identification.

Risk factors for *S. intermedius* infection, including periodontal disease, diabetes mellitus, alcoholism and COPD [16] were recorded in 14 patients and may play an important role in the development of these infections. Moreover, 13 patients were smokers and, although the smoker status is not strictly a risk factor for this infection, this condition may lead to produce COPD in the future and to contribute to the infection. Once *S. intermedius* have entered the body, their pathogenicity has been attributed to their trend to form abscesses and suppurated infections [13,15].

Several mechanisms for *S. intermedius* infections have been suggested; among others, aspiration of oral secretions is of particular importance especially in elderly patients.

Table 3 **Antimicrobial susceptibility in 9 strains of *S. intermedius*.**

Antibiotic	% susceptibility
Cefotaxime	100
Clindamycin	55.5
Erythromycin	55.5
Levofloxacin[a]	100
Linezolid	100
Penicillin[b]	90,9
Vancomycin	100
Daptomycin	100

[a]Including the strain of Iskandar et al. [b]Including the strains of Noguchi et al. and Hannoodi et al.

Regarding to this fact, it has been reported that *S. intermedius* infection tend to be more frequently produced in older patients. However, the mean age of *S. intermedius* infection in this series was 62 years and 7 patients here included were in their fifties or less, indicating the involvement of other factors in triggering the infection. On the other hand, *S. intermedius* tended to be more frequently detected in male patients [16]; in the present manuscript 12 from 15 patients were male. The reasons for the gender differences remain unclear, and further studies will be necessary to elucidate it.

According to our results, cough, chest pain and dyspnea are the main symptoms of PPI due to *S. intermedius*. Moreover, the onset of symptoms and development of the disease is generally rapid. Based on data for 14 patients, the mean time between onset of symptoms and PPI diagnosis was 34 days.

CRP level has a good sensitivity but it is limited by it poor specificity. Out of 9 patients in the present series for whom CRP studies were requested, all cases had CRP > 30 mg/L, which might suggest the presence of infection. In the majority of cases, the CRP level was elevated with a mean value of 208 mg/L. Also, the number of WBC was also elevated in almost all cases with a mean value of 21,400 cells/mm3.

Characteristics of PF were also analyzed. In patients in whom proteins, LDH and WCC levels were reported, in almost all of them the levels of these markers were increased (see table 2). The mean values of proteins, LDH and WCC were 4 mg/dL, 2777 IU/L and 89,484 cells/mm3 respectively. In the same way, the glucose levels were diminished, except in two cases (case 6 and 15) and the mean value was 21.25 mg/dL.

Treatment of infections due to *S. intermedius* should be guided by susceptibility studies although some clinical laboratories do not routinely perform antimicrobial susceptibility testing for these pathogens. *S. intermedius* as well as other members of the SAG are generally susceptible to β-lactam agents. The treatment of choice for these infections has not yet been established but ceftriaxone seems to be the preferred antimicrobial used due to both an excellent activity and tissue penetration. Regarding penicillin susceptibility, some strains intermediate with this antibiotic have been reported, and there are rare strains with resistance to penicillin [17]. Penicillin-intermediate or -resistant strains are more likely to be *S. anginosus* or *S. intermedius* than *S. constellatus* [17]. If allergy or resistance to β-lactam agents may be demonstrated, vancomycin is an appropriate alternative to treatment. Overall, fluoroquinolones are susceptible to SAG although MICs are high, but these microorganisms tend to develop resistance quickly and seems to be not appropriate for empirical treatment [18]. Most strains of the SAG are resistant to aminoglycosides and macrolide resistance appears to be increasing [17,19]. In the present study, 100% of susceptibility was obtained for cefotaxime, levofloxacin, linezolid, vancomycin and daptomycin, whereas only 55% of susceptibility was found for erythromycin and clindamycin. Only one isolate was intermediate to penicillin. Overall, susceptibility to several antibiotics is shown and antibiotic resistance in *S. intermedius* may be initially not considered a problem, although monitoring through susceptibility testing is advisable.

In the majority of cases, the diagnosis was carried out by culture of PF. In fact, drainage of pleural effusion was performed in all patients; other surgical procedures were pleurectomy, thoracotomy, decortication, and debridement.

The outcome was generally favourable and cure was documented in 10 patients. Two patients improved of the disease and in two cases the treatment fails and finally died as a consequence of the infection.

PPIs caused by *S. intermedius* are uncommon infections with few cases published in the medical literature. These infections tend to occur in males, smokers and with different risk factors such as periodontal diseases, alcoholism and COPD. The diagnosis may be suspected by elevation of CRP and WBC and must be confirmed microbiologically, taking samples of pleural fluid and/or lung tissue. Antimicrobial susceptibility testing of *Streptococcus* strains is also highly recommended. The association of antimicrobial drugs with drainage of pleural effusion is recommended to eradicate the infection.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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None to declare

REFERENCES

1. Menéndez R, Torres A, Aspa J, Capelastegui A, Prat C, Rodríguez de Castro F. Neumonía adquirida en la comunidad. Nueva normativa de la sociedad española de neumología y cirugía torácica (SEPAR). Arch Bronconeumol 2010; 46: 543-58. doi: 10.1016/j.arbres.2010.06.014.

2. Kawamura Y, Hou XG, Sultana F, Miura H, Ezaki T. Determination of 16S rRNA sequences of *Streptococcus mitis* and *Streptococcus gordonii* and phylogenetic relationships among members of the genus *Streptococcus*. Int J Syst Bacteriol 1995; 45: 406-8. PMID:7537076

3. Khaja M, Adler D, LominadzeG. Expressive aphasia caused by *Streptococcus intermedius* brain abscess in an immunocompetent patient. Int Med Case Rep J 2017; 10: 25-30. doi: 10.2147/IMCRJ.S125684.

4. Parthvi R, Amin M, Mehra S. Antimicrobial therapy for pyogenic liver abscess secondary to *Streptococcus intermedius* bacteremia. Am J Ther 2017; 24: e770-e771. doi: 10.1097/MJT.0000000000000537.

5. Roy WJ, Roy TM, Davis GJ. Thoracic empyema due to *Streptococcus intermedius*. J Ky Med Assoc 1991; 89: 558-62. PMID:1748832.

6. Khatib R, Ramanathan J, Baran Jr. J. *Streptococcus intermedius*: a cause of lobar pneumonia with meningitis and brain abscesses. Clin Infect Dis 2000; 30: 396-7. PMID:10671350.

7. Mautner GH, Lu I, Ort RJ, Grossman ME. Transverse leukonychia with systemic infection. Cutis 2000; 65: 318-20. PMID:10826095.

8. Iskandar SB, Al Hasan MA, Roy TM, Byrd RP. *Streptococcus intermedius*: an unusual cause of a primary empyema. Tennessee Med 2006; 99: 37-9. PMID:16681236.

9. Noguchi S, Yatera K, Kawanami T, Yamasaki K, Fukuda K, Naito K, et al. Pneumonia and empyema caused by *Streptococcus intermedius* that shows the diagnostic importance of evaluating the microbiota in the lower respiratory tract. Intern Med 2014; 53: 47-50. PMID:24390528.

10. Hannoodi F, Ali I, Sabbagh H, Kumar S. *Streptococcus intermedius* causing necrotizing pneumonia in an immune competent female: a case report and literature review. Case Rep Pulmonol 2016; 2016: 7452161. doi: 0.1155/2016/7452161.

11. Noguchi S, Yatera K, Kawanami T, Yamasaki K, Naito K, Akata K, et al. The clinical features of respiratory infections caused by the *Streptococcus anginosus* group. BMC Pulm Med 2015; 15: 133. doi: 10.1186/s12890-015-0128-6.

12. Spellerberg B, Brandt C. *Streptococcus*. In: Versalovic J, Carroll KC, Funke G, Jorgensen JH, Landry ML, Warnock DW (eds). Manual of Clinical Microbiology. ASM Press, 10th edition, 2011. Washington, DC.

13. Sunwoo BY, Miller WT. *Streptococcus anginosus* infections: crossing tissue planes. Chest 2014; 146: e121-e125. doi: 10.1378/chest.13-2791.

14. Claridge JE, Attorri S, Musher DM, hebert J, Dunbar S. *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* ("*Streptococcus milleri* group") are of different clinical importance and are not equally associated with abscess. Clin Infect Dis 2001; 32: 1511-5. doi: 10.1086/320163.

15. Whiley RA, Beighton D, Winstanley TG, Fraser HY, Hardie JM. *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* (the *Streptococcus milleri* group): association with different body sites and clinical infections. J Clin Microbiol 1992; 30: 243-4. PMID:1734062.

16. Porta G, Rodriguez-Carballeira M, Gómez L, Salavert M, Freixas N, Xercavins M, et al. Thoracic infection caused by *Streptococcus milleri*. Eur Respir J 1998; 12: 357-62. PMID:9727785.

17. Tracy M, Wanahita A, Shuhatovich Y, Goldsmith EA, Clarridge JE, Musher DM. Antibiotic susceptibilities of genetically characterized *Streptococcus milleri* group strains. Antimicrob Agents Chemother 2001; 45: 1511-4. PMID:11302819.

18. Yamamoto N, Fujita J, Shinzato T, Higa F, Tateyama M, Tohyama M, et al. In vitro activity of sitafloxacin compared with several fluoroquinolones against *Streptococcus anginosus* and *Streptococcus constellatus*. Int J Antimicrob Agents 2006; 27: 171-6. PMID:16472994.

19. Asmah N, Eberspächer B, Regnath T, Arvand M. Prevalence of erythromycin and clindamycin resistance among clinical isolates of the Streptococcus anginosus group in Germany. J Med Microbiol 2009; 58: 222-7. doi: 10.1099/jmm.0.001560-0.