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# Thoracic infection caused by *Streptococcus milleri*

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*Thoracic infection caused by* Streptococcus milleri. *G. Porta, M. Rodríguez-Carballeira, L. Gómez, M. Salavert, N. Freixas, M. Xercavins, J. Garau. ©ERS Journals Ltd 1998.*
**ABSTRACT: The objective of this study was to increase our understanding of the importance of members of the *Streptococcus milleri* (SM) group as respiratory pathogens, by studying the epidemiological and clinical features of thoracic infections caused by this group and comparing the epidemiology and prognosis of empyema caused by SM with cases of pneumococcal aetiology.**

**The clinical histories and microbiology reports were reviewed in 27 cases of thoracic infection caused by SM over a period of 8 yrs. Cases of pneumococcal empyema that occurred during the same period were also analysed.**

**Diagnoses were made of cases of empyema, including six with pneumonia and one with pulmonary abscess, three cases of pneumonia and two of mediastinitis. In 17 cases, SM was the only pathogen isolated. There was a history of instrument or surgical procedures on the digestive or respiratory tract in 59%. Secondary bacteraemia was documented in three cases. The treatment administered, a combination of antibiotics and surgery, was successful in 22 of 27 (81%) of cases. All strains were susceptible to penicillin. When the characteristics of the empyemas caused by monomicrobial SM infection were compared with those of pneumococcal aetiology from the same period of study, significant differences were found with respect to age, origin of the infection and the need for surgery.**

**In conclusion, thoracic infections caused by *Streptococcus milleri* are largely pleural. They are polymicrobial in one-third of cases, commonly acquired in hospital and, in most patients, associated with major surgery and/or surgical procedures of the respiratory or digestive tract. The empyema frequently requires thoracotomy for complete resolution.**
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The group *Streptococcus milleri* (SM) includes several species of pathogenic streptococci associated with pyogenic infections. In 1956 O. Guthof was the first to use the name SM when referring to nonhaemolytic species of streptococci found in the oral cavity [1]. Whiley and coworkers [2, 3], through phenotypic and deoxyribonucleic acid (DNA)-DNA hybridization studies, affirmed the existence of at least three well-differentiated species: *S. constellatus*, *S. intermedius* and *S. anginosus*. Many authors prefer to continue using the term SM for the three species for two reasons: firstly, because the term is useful to the clinician, since it warns of the presence of a suppurative process [4, 5] and secondly, because the three species appear to be equally represented as a cause of thoracic infection [6, 7].

The SM group is part of the usual flora of the mouth, but its true prevalence is unknown. It is also found among normal faecal flora in 16–67% of healthy adults and has been isolated from normal appendix and from vaginal secretions [3, 8–10]. The most important clinical feature of these micro-organisms is their tendency to cause suppurative infections at various sites, ranging from dental abscesses to deep visceral abscesses [1, 4, 8, 11–15].

The purpose of this study was to contribute to a better understanding of the importance of members of the SM group as respiratory pathogens, by studying the epidemiological and clinical features of thoracic infections caused by SM and contrasting the features of empyema caused by SM with those in cases of pneumococcal aetiology.

## Patients and methods

A review was undertaken of the clinical histories and microbiological reports of episodes of infection by SM isolated from clinically significant samples in our institution, an acute care general hospital serving around 250,000 inhabitants, between January 1988 and December 1995. Only those cases in which some type of thoracic infection was diagnosed were analysed. The cases of pneumococcal empyema that occurred during the same period were also analysed. For the purposes of this study, thoracic infection was defined as all processes of an infectious nature localized to any of the organs, systems or anatomical structures in the thoracic cavity, except intravascular lesions with endothelial infection. Infections were considered to be acquired

in the hospital when they occurred at least 72 h after admission. Information was gathered on a series of epidemiological, clinical, diagnostic, therapeutic and prognostic variables, as well as on predisposing factors and underlying diseases in each case.

Samples were taken in aseptic conditions and sent to the microbiology laboratory, where they were processed according to standard procedures. (Blood was cultured using a conventional biphasic aerobe/anaerobe system and, bottles were incubated at 35°C for 7 days. They were occasionally subcultured in blood agar and incubated in a $CO_2$-enriched atmosphere for 48 h). Isolated streptococci were tentatively identified by morphology and colony size, haemolysis pattern, sensitivity to optoquine and reaction to the bileesculin test. The SM group was identified by the API 20 STREP (bio-Mérieux; Marcy, L'Etoile, France) system, which includes *S. anginosus*, *S. constellants*, *S. $MG_1$*, *S. intermedius* and certain β-haemolytic streptococci from Lancefield groups C, F and G. The battery was inoculated, read and interpreted according to the manufacturer's instructions and recommendations. Antibiotic susceptibility was determined by the Kirby-Bauer diffusion technique according to National Committee for Clinical Laboratory Standards (NCCLS) recommendations. In selected cases, minimal inhibitory concentrations (MIC) of the strains were determined by microdilution (Sensititre, East Grinstead, W. Sussex, UK).

Data were analysed using the SPSS-PC package, Windows 6.1 version (SPSS, Munich, Germany). Quantitative variables were treated with the Kolmogrov-Smirnow test, which showed compatibility with a normal distribution and, therefore, analyses were performed with the Student's t-test for comparison between means. Comparisons between qualitative variables were analysed by Fisher's exact test. A level of $p<0.05$ was deemed significant.

## Results

Thoracic infections were found in 27 (19%) of the 141 episodes of SM infection diagnosed during the period of study. Of these, 20 (74%) were in males. The age at presentation was 53±14 yrs (mean±SD) (range 23–83). A diagnosis of empyema was made in 22 cases (81%), pneumonia in three cases (11%) and mediastinitis in two cases (7%). Of the 22 cases of empyema, six were associated with pneumonia (27%) and one with a pulmonary abscess (5%) (table 1).

The infection was acquired in the hospital in 15 cases (55%): 12 cases of empyemas, including two of pneumonia, two pneumonia and one postsurgical mediastinitis. One of the cases of pneumonia was associated with intraabdominal surgery and the other with intubation and mechanical ventilation in a patient with cranioencephalic trauma. The other 10 patients with hospital-acquired empyema had a history of surgery or endoscopy; furthermore, six of these had fistulae (one gastropleural and five bronchopleural).

Secondary bacteraemia was observed in three cases (11%), which corresponded to two cases of pneumonia and one of empyema. There were four cases of shock: two septic, one haemorrhagic and one cardiogenic. The two cases of septic shock were in a patient with empyema and in one patient with mediastinitis; neither developed bacteraemia and in both the infection was polymicrobial in nature. The two other cases of shock were not related to infection (see table 1).

Predisposing factors included instrumental and/or surgical procedures on the respiratory tract in 10 cases (37%), including two endotracheal intubations with mechanical ventilation and two videothoracoscopies, and instrumental and/or surgical procedures on the digestive tract in six cases (22%), including two endoscopic oesophageal dilatations. Other factors present were: septic mouth in three (11%) and rib contusion and Ludwig's angina in two other cases. No predisposing factor was observed in the case of pulmonary abscess.

Underlying diseases are described in table 1. They included 12 pulmonary pathology (44%), seven gastrointestinal disease (26%), four alcoholism (15%), three diabetes mellitus (11%), two human immunodeficiency virus (HIV) infection (7%) and one epilepsy (4%).

Microbiological diagnosis was made by culture of pleural exudate in the 22 cases of empyema and of pus obtained from drainage in the two cases of mediastinitis. The three cases of pneumonia were diagnosed by selective bronchoalveolar lavage culture, by protected catheter brush culture and by the presence of pulmonary consolidation and bacteraemia, respectively.

Twelve cases were acquired in the community. When compared with those acquired in hospital (table 2), the only significant difference found was the universal presence of predisposing factors in all hospital-acquired infections.

In 10 cases (37%) the infection was polymicrobial in nature. In infections related to digestive procedures, other organisms isolated were *Candida albicans*, *Pseudomonas* spp., *Eikenella corrodens* and enterococci. In infections related to thoracic procedures, the other organisms isolated were: *Staphylococcus aureus*, *Pseudomonas aeruginosa* and unidentified anaerobic Gram-negative bacteria. In the patient with Ludwig's angina, bacteroides were isolated and mixed oropharyngeal flora was isolated from the patient with pulmonary abscess. Diagnoses in the cases of polymicrobial infections were: seven empyema (70%) (one with pulmonary abscess), two mediastinitis (20%), and one hospital-acquired pneumonia (10%). No significant differences were found with respect to monomicrobial infections regarding either the need for surgery or the evolution, nevertheless, the cases of polymicrobial infection were related to a diagnosis of empyema ($p=0.02$).

Antibiotics were administered in all cases and chest tube insertion or thoracotomy was necessary in 22 cases (85%). Of the 22 cases of empyema, five required simple drainage and 15 required thoracotomy (including two decortications and two myoplasties); in two of the empyemas, the patients did not undergo surgery due to the rapid and fatal evolution of the disease (patient number 6 and 11). The two patients with mediastinitis required thoracotomy. All of the patients with polymicrobial infections required surgery, except for the patient with pneumonia.

Various antibiotics were administered, penicillin or derivatives in 74% of the cases and clindamycin in 26%. All SM isolates were susceptible to penicillin (MIC <0.03 $mg \cdot L^{-1}$), 21/23 to erythromycin and 23/24 to clindamycin. Tetracycline resistance was observed in 7/7, all of which were susceptible to cotrimoxazole.

With regard to evolution, 22 patients (81%) were cured and three patients (11%) died from the infection (one from respiratory insufficiency and the other two from septic shock,

Table 1. – Twenty seven cases of thoracic infection caused by *Streptococcus milleri*

| Case | Age yrs | Sex | Diagnosis | Bact. Y/N | Predisposing factors | Underlying disease | PI Y/N | Treatment | Evolution |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 41 | F | Pleural empyema | N | Pulmonary aspergillosis; pneumonectomy | Alcoholism, dilated myocardiopathy; congestive heart failure; pulmonary fibrosis | N | S+Atb | Cured |
| 2 | 54 | M | Pneumonia (diagnosis confirmed by positive blood culture) | Y | Surgery for upper GI, haemorrhage secondary to marsupialization of pancreatic pseudocyst | Ishaemic heart disease; acute pancreatitis; pancreatic pseudocyst | N | Atb | Cured |
| 3 | 57 | F | Hospital-acquired multilobar pneumonia (diagnosed by telescoping catheter) | Y | Intubation and mechanical ventilation; corticotherapy | Cranioencephalic trauma | Y | Atb | Cured |
| 4 | 40 | M | Pneumonia and empyema | N | | Chronic bronchitis | N | S+Atb | Cured |
| 5 | 59 | F | Empyema | N | Rib contusion | Hepatic cirrhosis; diabetes mellitus; duodenal ulcer | N | S+Atb | Cured |
| 6 | 76 | M | Pneumonia and empyema | N | GI surgery; parenteral nutrition: upper GI haemorrhage | Colonic adenocarcinoma: hiatal hernia | N | Atb | Exitus |
| 7 | 52 | F | Pneumonia and empyema | N | Septic mouth | Epilepsy | N | S+Atb | Cured |
| 8 | 23 | M | Empyema | N | | Smoker | N | S+Atb | Cured |
| 9 | 36 | M | Postpneumothorax empyema | N | Drainage of pneumothorax 2 weeks earlier; videothoracoscopy 2 days earlier | Spontaneous pneumothorax (relapsed) | Y | S+Atb | Cured |
| 10 | 62 | M | Pneumonia and empyema | N | | Alcoholism; COPD; diabetes mellitus | N | S+Atb | Cured |
| 11 | 70 | M | Empyema | N | Lung carcinoma and obstructive pneumonitis | COPD; peptic ulcer | N | Atb | Exitus |
| 12 | 62 | M | Postquirugic haemopyothorax | N | Lobectomy; bronchial fistula | Scamous carcinoma; COPD; alcoholism | N | S+Atb | Cured |
| 13 | 28 | M | Pneumonia and empyema | N | | IVDU; HIV infection; chronic hepatitis; duodenal ulcer operated 2 yrs earlier | N | S+Atb | Cured |
| 14 | 48 | M | Empyema | N | Pulmonary biopsy with bronchopleural fistula; corticotherapy; septic mouth | Pulmonary vasculitis; chronic bronchitis | Y | S+Atb | Cured |
| 15 | 62 | M | Empyema | N | Oesophageal perforation postsclerosis of oesophageal varices and placement of Seenstaken tube | Hepatic cirrhosis with bleeding oesophageal varices | Y | S+Atb | Exitus |
| 16 | 54 | M | Mediastinal abscess | N | Oesophagectomy and gastroplasty with secondary gastrocervical fistula | Alcoholism; COPD; oesophageal carcinoma | Y | S+Atb | Cured |
| 17 | 68 | M | Empyema | N | Oesophagectomy, gastroplasty and gastrocervical anastomosis; gastropleural fistula | Oesophageal neoplasm; COPD | N | S+Atb | Cured |

Table 1 continued on the next page.

table 1. – continued.

| Case | Age yrs | Sex | Diagnosis | Bact. Y/N | Predisposing factors | Underlying disease | PI Y/N | Treatment | Evolution |
|---|---|---|---|---|---|---|---|---|---|
| 18 | 61 | M | Empyema | N | Pneumothorax and postsurgical bronchopleural fistula | Lung carcinoma; diabetes mellitus; COPD; ishaemic heart disease | Y | S+Atb | Cured |
| 19 | 41 | M | Empyema | N | Oesophageal perforation secondary to repeated dilations | Oesophageal stenosis by caustics | Y | S+Atb | Cured |
| 20 | 43 | M | Mediastinitis | N | Ludwig's angina | | Y | S+Atb | Exitus |
| 21 | 63 | M | Empyema | Y | Pneumonectomy followed by bronchopleural fistula | Lung carcinoma | Y | S+Atb | Cured |
| 22 | 64 | M | Empyema | N | Lobectomy | Lung carcinoma | N | S+Atb | Cured |
| 23 | 38 | M | Pneumonia (diagnosed by selective BAL culture) | N | Septic mouth | AIDS, IVDU | N | Atb | Cured |
| 24 | 83 | F | Pneumonia and empyema | N | | Senile dementia | N | S+Atb | Cured |
| 25 | 49 | M | Empyema | N | Lobectomy | Lung carcinoma | N | S+Atb | Cured |
| 26 | 57 | F | Empyema | N | Intubation and mechanical ventilation | Congestive heart failure; dilated cardiomyopathy; hypertension | N | S+Atb | Exitus |
| 27 | 37 | M | Pulmonary abscess and empyema | N | | Smoker | Y | S+Atb | Cured |

F: female; M: male; BAL: bronchoalveolar lavage; N: no; Y: yes; Bact.: bacteraemia; GI: gastrointestinal; PI: polymicrobial infection; COPD: chronic obstructive pulmonary disease; IVDU: intravenous drug use; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; S: surgery; Atb: antibiotic.

Table 2. – *Streptococcus milleri* thoracic infections: comparison between community and hospital-acquired infections

| Characteristics | Community-acquired | Hospital-acquired |
|---|---|---|
| Number | 12 | 15 |
| Age yrs (mean±SD) | 56±10 | 48±18 |
| Sex male/female | 8/4 | 11/4 |
| Bacteraemia % | 0 | 3 (20) |
| Predisposing factors % | 6 (50) | 15 (100)+ |
| Polymicrobial % | 2 (17) | 8 (53) |
| Surgery % | 10 (83) | 12 (80) |
| Mortality % | 2 (17) | 3 (20) |

+: p=0.02, significant difference.

patient number 6, 15 and 20, respectively). The two remaining cases (7%) died of causes unrelated to the infection at days 3 and 5 following the start of treatment (massive haemoptysis and cardiogenic shock, patient number 11 and 26, respectively). No relationship between evolution and type of infection (focal or bacteraemic) was found (p=0.56). The mean hospital stay was 45 days (range 7–128).

Data obtained from the 15 cases of empyema due to monomicrobial SM infection were compared with those of the 10 cases of pneumococcal empyema documented during that period. The mean age at presentation in the cases of pneumococcal empyema was 79±11 yrs, compared with 53±14 yrs in those with SM empyema (p= 0.0003). Infection was acquired in the hospital in 7/15 of the cases of SM empyema and in none of the cases of pneumococcal empyema (p=0.01). Nine of 15 of the patients in the SM group required thoracotomy, while this was necessary in only 1/10 of the cases of pneumococcal empyema (p=0.017). There were no differences with regard to mortality.

## Discussion

In the authors experience, one in every five SM infections is localized to the thorax [16]. According to other reports, the incidence of thoracic infection due to SM has ranged between 10–32% of all SM infections [12, 17–22] and between 24–57% of suppurative thoracic infections [23, 24]. Most patients in the present series were adult males (3:1), as has been the experience of others [11, 21].

Of the various types of thoracic infection caused by SM, empyema is the most common, which in this series accounted for 78% of all cases, confirming the experience of others [11, 12, 19, 20, 25]. The present study included two cases of mediastinitis, although no differences were found with regard to predisposing factors for this site. It is noteworthy that only one case of pulmonary abscess was found, with no predisposing factor or underlying disease that could help to explain the genesis of the infection. It was, however, polymicrobial with oropharyngeal flora; since the patient was a smoker, perhaps this could be explained by microaspiration associated with defects in tracheobronchial clearance, as suggested in the study reported by Lorber and Swenson [26].

SM reaches the thoracic cavity by several routes: 1) aspiration of oral secretions; 2) direct implantation by

trauma or surgery; 3) extension by contiguity; and 4) haematogenous dissemination [23]. No cases of haematogenous dissemination were found. Aspiration cannot be eliminated as the route in the three cases of pneumonia, in the four cases of empyema associated with pneumonia or in the pulmonary abscess. The majority of cases, however, were attributable to direct implantation (64%) through the diagnosis on therapeutic intervention procedures in the respiratory or gastrointestinal tracts. Finally, one case was clearly related to extension by contiguity (Ludwig's angina).

Underlying diseases observed were: periodontal disease, diabetes mellitus, neoplasm, alcoholism, HIV infection and chronic obstructive pulmonary disease (COPD); these associations have been recognized previously [9, 11, 17, 21, 27].

In the present study almost two-thirds of patients (17/27) had SM infections in pure culture, similar to the percentage (64%) recently reported by WONG *et al.* [28] in a series of 25 patients, in other studies this figure ranged 14–35% [11, 13, 29]. This emphasizes the importance of SM as a cause of suppurative thoracic infection.

In contrast to other series in which the polymicrobial origin of the thoracic infection was associated with gastrointestinal origin and the presence of gastropleural fistulae [17, 24], this study revealed that polymicrobial infection was also associated with respiratory origin and bronchopleural fistulae. This is probably related to the fact that all polymicrobial infections in this series, except for one (mediastinitis in Ludwig's angina), were linked to respiratory or gastrointestinal tract procedures, indicating that the procedure is a decisive factor for the concomitant presence of other pathogens. Similarly, the apparent synergy between SM and strict anaerobic bacteria [7] could explain the frequency of polymicrobial infections. Finally, a higher rate of hospital-acquired infections (60%) was found than that described in the literature [23, 28].

As in other published studies [17, 18, 20, 21, 23, 28, 30], the need for a combined treatment with antibiotics and surgery in most cases of empyema, abscess and mediastinitis, was apparent in the present series. With regard to antibiotic susceptibility, this study differed from others, which showed a moderate resistance to penicillin [11, 18, 31], in that the SM strains were uniformly susceptible to penicillin. Susceptibility to clindamycin was 96% and to erythromycin was 91%. With regard to surgical treatment, it should be noted that thoracotomy was required in more than three-quarters of cases; this has also been found in other series [17, 18, 20, 21, 23, 28], indicating that these infections have a high morbidity and require early and vigorous treatment.

The percentage of patients cured in the present study was 81%. In other series of general SM infection, rates have been lower, between 40–50% [18, 21], and in the recent pulmonary infection series reported by WONG *et al.* [28] the cure rate was 76%, which may indicate that infection at the thoracic site has a better prognosis. However, the high mortality that accompanies this infection cannot be underrated.

From a comparative analysis of SM empyema and pneumococcal empyema, the former was found to occur in younger patients and was largely acquired in the hospital, whereas those of a pneumococcal aetiology were acquired in the community. SM empyemas tend to loculate and frequently require thoracotomy, in contrast with pneumococcal empyema where loculation is uncommon [5]. This could explain the need for thoracotomy and the more prolonged hospital stay in the former, which almost doubles the duration of hospital stay of the cohort of patients with pneumococcal empyema (27 *versus* 51 days, p=0.06).

In conclusion, thoracic infection represents one-fifth of all infections caused by *Streptococcus milleri*. In one-third of cases the infection is polymicrobial and, in contrast with infection at other sites, bacteraemia is rare [16]. More than half of the episodes are acquired in the hospital and the majority of these are secondary to major surgical and/or instrumental procedures on the respiratory and gastrointestinal tracts. In the author's experience, *Streptococcus milleri* empyema is more frequent than that caused by *Streptococcus pneumoniae*, has considerable morbidity, significantly prolongs hospital stay and often requires thoracotomy. Penicillin remains the treatment of choice. The better prognosis for thoracic infection caused by *Streptococcus milleri* is probably related to early surgery in patients who have been adequately treated with antibiotics.

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