


# The Clinical Features and Management of Empyema Caused by *Streptococcus constellatus*

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**Background:** *Streptococcus constellatus*, a commensal, plays an important role in purulent infections. It has been reported as aggressive pathogen causing pleural empyema. But the role of *S. constellatus* in empyema has not been taken seriously. There are no studies about clinical characteristics of empyema caused by *S. constellatus* domestically and abroad. This study aimed to explore the clinical features and management of empyema caused by *S. constellatus*.

**Methods:** A retrospective review of 9 patients diagnosed with empyema caused by *S. constellatus* in a hospital between January 2010 and August 2021 was performed.

**Results:** *S. constellatus* empyema were mostly seen in old males (66.7%) with comorbid diseases. The high-risk factors include diabetes mellitus, oral infection, and oral surgery. All were unilateral encapsulated empyema (right-side, 55.6%), diagnosed with pneumonia (bilateral pneumonia, 88.9%; ipsilateral lung abscess, 44.4%). 33.3% of patients had *S. constellatus* and anaerobes co-isolated. *S. constellatus* were sensitive to penicillin G, linezolid, levofloxacin, vancomycin, ceftriaxone, and chloramphenicol, resistant to erythromycin, tetracycline, and clindamycin. 33.3% of the patients needed ventilator support. The primary treatment to *S. constellatus* empyema was timely pus drainage, intravenous antibiotics, and enough nutrition support, intrapleural fibrinolytics and surgery (VAST recommended first) in necessity.

**Conclusion:** *S. constellatus* may cause pneumonia and lung abscess first and then spread to cause empyema mainly in old males with comorbid diseases. *S. constellatus* often co-isolated with anaerobes in empyema. Antibiotics should cover simultaneously both *S. constellatus* and anaerobes.

**Keywords:** *S. constellatus*, empyema, clinical features, anaerobes

## Introduction

*Streptococcus constellatus* (*S. constellatus*) is a gram-positive and catalase test-negative coccus, first isolated from periodontal abscess and described by Guthof in 1956.<sup>1</sup> *S. constellatus*, a member of *Streptococcus milleri* group (SMG), is commensal in the mouth, upper respiratory tract, and gastrointestinal tract.<sup>2</sup> It was considered as pathogen in purulent infections including subdural empyema,<sup>3</sup> liver abscess,<sup>4</sup> frontal sinus abscess,<sup>5</sup> head and neck infections.<sup>6</sup> SMG is identified as one of the main pathogens causing community-acquired pleural infections.<sup>7</sup> It was reported that 54.5% of patients with SMG pulmonary infections had pleural effusion, and that pleural effusion was more frequently observed in patients with SMG infections than that infected with other pathogens.<sup>8</sup> In an animal study of 21 mice with SMG pulmonary infections, 66.7% were found to have empyema, and *S. constellatus* was commonly observed as pathogen, especially in empyema (8/21).<sup>9</sup> A case of *S. constellatus* causing empyema was also reported in our previous study.<sup>10</sup> Empyema caused by *S. constellatus* has not been taken seriously. The possible reasons are as follows: (1) the special culture conditions of *S. constellatus* that has access to oxygen and higher concentration of carbon dioxide,<sup>11</sup> make it difficult to be detected. (2) As commensal bacteria, the isolated *S. constellatus* is not

generally considered as the pathogen of respiratory infections. The present study aimed to explore the clinical features of *S. constellatus* empyema and provide some ideas for the diagnosis and treatment of *S. constellatus* empyema.

## Methods

This retrospective review was performed in a hospital. Patient diagnosed with pleural empyema with positive *S. constellatus* cultures or (and) sequence detected by Next-Generation Sequencing (NGS) from pleural fluid from January 2010 to August 2021 was enrolled. Pleural empyema was defined by pleural effusion indicated by images and macroscopic purulent fluid in this study. We collected clinical information of patients, including epidemiology, past-history, clinical manifestation, laboratory examination results, therapy. To explore the possible mechanism of *S. constellatus* causing empyema, we focused on the presence of pneumonia, lung abscess, and bronchopleural fistula. The antibiotics susceptibility test (AST) of *S. constellatus* isolates from pleural fluid was performed by K-B AGAR and minimum inhibitory concentration of antibiotics (MIC) test. It is divided into three grades: sensitive (S), intermediate (I) and resistant (R). The study was approved by the First Affiliated Hospital of Guangxi Medical University Medical Ethics Committee [NO.2022-KY-E-(142)].

## Results

### Clinical and Laboratory Characteristics

Nine patients diagnosed with empyema with *S. constellatus* isolated from pleural fluid were enrolled in this study. The clinical features and laboratory findings were summarized in Table 1 (Table 1). The average age was  $53.78 \pm 11.96$  years, and 66.7% of the patients were male. 77.8% had underlying conditions, diabetic mellitus commonly. The average time

**Table 1** The Clinical and Laboratory Features of Patients with *S. constellatus* Empyema

Term	Total (n = 9)
Age (y); mean $\pm$ SD	53.78 $\pm$ 11.96
Gender-male n (%)	6 (66.7%)
BMI; mean $\pm$ SD (kg/m <sup>2</sup> )	23.73 $\pm$ 2.16
Comorbidity diseases n (%)	7 (77.8%)
Chronic pulmonary disease and heart failure	1 (11.1%)
Atrial septal defect	1 (11.1%)
Diabetes mellitus	4 (44.4%)
Chronic anemia (hemoglobin <90g/L)	1 (11.1%)
Hypoalbuminemia n (%)	9 (100%)
Smoking history n (%)	4 (44.4%)
Acohol n (%)	1 (11.1%)
From symptom onset to purulent pleural fluid drained (days)	14.2 $\pm$ 6.14
Symptoms at presentation n (%)	
Fever	9 (100%)
Cough	8 (88.9%)
Sputum	6 (66.7%)
Chest pain	6 (66.7%)
Chest distress	2 (22.2%)
Dyspnea	7 (77.8%)
Previous antibiotic treatment n (%)	2 (22.2%)
Laboratory findings at presentation	
White blood cell counts (10 <sup>9</sup> cells/L)	17.37 $\pm$ 7.10
Neutrophil percentage	0.85 $\pm$ 0.05
c-reactive protein (normal 0–10 mg/L)	198.6 $\pm$ 56.78

(Continued)

**Table 1** (Continued).

Term	Total (n = 9)
Procalcitonin (normal 0–0.05ng/mL)	1.55±1.64
Erythrocyte sedimentation rate (normal 0–20mm/h)	89.57±14.50
serum albumin (normal 40–45 g/L)	30.91±4.09
Bacteriology of thoracic drainage fluid n (%)	
Only <i>S. constellatus</i>	6 (66.7%)
Mixed infection	3 (33.3%)
Blood culture n (%)	8
Bacteremia	0
No bacteria cultured	8 (88.9%)

from onset of clinical symptoms to admission for drainage of purulent pleural effusion was  $14.22 \pm 6.14$  days. All patients had fever, and most had cough, sputum production, dyspnea, chest pain and tightness. On admission, all patients showed hypoproteinemia ( $30.91 \pm 4.09$ , normal 40–45g/L) with average BMI  $23.73 \pm 2.16$  kg/m<sup>2</sup>, and the remaining liver function and renal function showed no abnormality. Abdominal and urinary ultrasonography revealed no significant kidney or liver lesion that may cause pleural effusion. Inflammatory markers of all patients were significantly rising. Average WBC count, neutrophil percentage, C-reactive protein, and procalcitonin were  $17.37 \pm 7.10$  (cells  $10^9$ /L),  $0.85 \pm 0.05$ ,  $198.6 \pm 56.78$  (mg/L),  $1.55 \pm 1.64$  (ng/mL), respectively. No pathogen was found in the blood cultures of all patients. None of the patients had a history of immunodeficiency or use of hormone or immunosuppressive agents. Lymphocyte subgroup analysis of six patients was unremarkable. Four patients had hypogammaglobulinemia, with IgM 0.787, 0.630, 0.54, and 0.46 g/L, respectively (normal 0.84–1.32 g/L). Unfortunately, we cannot assess the remaining patients' immune status as they did not receive related laboratory tests.

## Characteristics of Pleural Fluid

As the table showed ([Supplementary Table 1](#)), all were macroscopically purulent and turbid liquid with Rivalta test positive, and the WBC counts were more than  $500 \times 10^6$  cells/L, mainly multinucleated cells. Pleural effusion was exudate in all patients, according to the Light standard that LDH level of pleural effusion was more than 2/3 of the upper limit of serum normal value ( $>245$ U/L). *S. constellatus* can be isolated from primal pleural fluid in all patients, except case 9 of whom sequences of *S. constellatus* was detected by NGS of pleural fluid. As shown in [Table 1](#) ([Table 1](#)), *S. constellatus* was mainly found as a solitary isolate from pleural fluid of 66.7% of patients. *S. constellatus* and anaerobes were co-isolated from pleural fluid of three patients (two co-isolated with *P. oris*, one co-isolated with *P. buccae*) ([Supplementary Table 1](#)). Based on clinical experience and previous published studies, we considered *S. constellatus* was a significant isolate rather than a commensal. The results of AST of *S. constellatus* isolates of patients were showed ([Table 2](#)). Antibiotics 100% efficacy against *S. constellatus* were penicillin G, linezolid, levofloxacin and vancomycin. Ceftriaxone (87.5%) and chloramphenicol (75%) showed relatively high efficiency. *S. constellatus* was observed resistant to erythromycin (57%), tetracycline (50%) and clindamycin (62.5%).

## Image Features

As shown in [Table 3](#) ([Table 3](#)), all patients had unilateral empyema, mostly right-side (55.6%) and encapsulated empyema. The average pleural fluid thickness was  $10.71 \pm 2.88$  cm. All patients with empyema were diagnosed with pneumonia, bilateral pneumonia especially (88.9%). One patient had left-side pneumonia, and his empyema was also left-side. 44.4% of the patients had lung abscess, which was consistently ipsilateral to empyema. Chest CT indicated that more than half of patients had intrathoracic lymphadenectasis, including hilus pulmonic and mediastinal lymph nodes. Two patients had bronchopleural fistula and two patients had pyopneumothorax.

**Table 2** Antibiotics Susceptibility Test of *S. constellatus* Isolates from Pleural Fluid

ID	Penicillin G	Ceftriaxone	Linezolid	Levofloxacin	Vancomycin	Erythromycin	Tetracyclines	Clindamycin	Chloramphenicol
Case1	S	S	S	S	S	R	R	R	S
Case2	S	S	S	S	S	S	S	S	S
Case3	S	S	S	S	S	R	R	R	R
Case 4	S	R	S	S	S	/	I	R	S
Case 5	S	S	/	S	S	R	S	R	S
Case 6	S	S	S	S	S	S	S	S	S
Case 7	S	S	S	S	S	S	R	S	S
Case 8	S	S	S	S	S	R	R	R	I
Case 9	/	/	/	/	/	/	/	/	/
Sensitive (%)	100%	87.5%	100%	100%	100%	42.9%	37.5%	37.5%	75.0%

**Table 3** The Image Features of 9 Patients with Empyema Caused by *S. constellatus*

Term	Total (n = 9)
Empyema n (%)	
Left	4 (44.4%)
Right	5 (55.6%)
Encapsulated empyema	9 (100%)
Pyopneumothorax	2 (22.2%)
Pleural fluid thickness (cm)	10.71±2.88
Pneumonia (n/%)	9 (100%)
Left/right/both	1/0/8
Lung abscess	4 (44.4%)
Lymphadenectasis(n/%)	6 (66.7%)
Only mediastinal lymph node	3 (33.3%)
Hilus pulmonis and mediastinal lymph nodes	3 (33.3%)
Bronchopleural fistula (n/%)	2 (22.2%)

## Treatment and Outcome

Treatment and prognosis of patients were shown in Table 4. All patients received intravenous antibiotic and pleural effusion drainage, and 33.3% received additional therapy, including intrapleural urokinase and surgery. The average

**Table 4** The Treatment and Prognosis of 9 Patients with *S. constellatus* Empyema

Term	Total (n = 9)
Therapy (n/%)	
Antibiotics+ drainage	6 (66.7%)
Antibiotics+ drainage + Intrapleural fibrinolytics	1 (11.1%)
Antibiotics+ drainage+ Intrapleural fibrinolytics + surgery	1 (11.1%)
Antibiotics+ drainage+ surgery	1 (11.1%)
Duration of antibiotic use (days)	44.3±22.5
Respiratory failure (n/%)	5 (55.6%)
Sever pneumonia	3 (33.3%)
ARDS	2 (22.2%)
Ventilator using (n/%)	3 (33.3%)
Hospital stays(days)	23±7.02
Outcome(n/%)	
Cured and survival	8 (88.9%)
Worsen and death	1 (11.1%)

duration of antibiotic use was  $44.3 \pm 22.5$  days. 55.6% of patients developed respiratory failure. And three patients developed severe pneumonia requiring ventilator support and two developed acute respiratory distress syndromes (ARDS). After treatment, 88.9% of patients were significantly cured. Only one patient (case 6) developed septic shock without significant improvement after comprehensive treatment and died finally. As shown in table ([Supplementary Table 2](#)), the inflammatory markers of case 6 who died after treatment were significantly higher than that before treatment. Inflammatory markers in the other 8 patients were significantly lower after treatment. To some extent, these inflammatory indicators can effectively evaluate the therapy efficacy of *S. constellatus* empyema.

## Literature Review

We searched relevant articles in databases with search terms ("*Streptococcus constellatus*" and empyema) with no language restrictions. At present, no original clinical studies on empyema caused by *S. constellatus* have been published, but case reports. 14 patients in the literature with empyema with *S. constellatus* cultured from pleural fluid was enrolled.<sup>12–23</sup> The clinical information was shown in the table ([Supplementary Table 3](#)). 92.9% of patients were male. Mostly were middle-aged and elderly patients, with an average age of  $50.21 \pm 11.37$  years. Almost all patients had underlying conditions or risk factors including alcoholism, diabetes. Three had recently exodontia. One patient developed a mediastinitis who had gastroesophageal reflux and recently underwent gastroscopy. 55.6% of patients had purulent infections besides empyema, including liver abscess, lung abscess, mandibular tissue abscess, and gingival abscess. The right-side empyema was more common (72.8%), and two patients had pyopneumothorax. 71.4% were monoinfection involving only *S. constellatus*, while 28.6% were pleural polyinfection involving *S. constellatus* and other organisms, most of which were anaerobes. The primary treatment was intravenous antibiotics and pleural fluid drainage, and nearly half of the patients also received other treatments, including intrapleural fibrinolytic agents (urokinase, streptokinase) and surgery (decortication, partial excision of lobe with lung abscess). The average duration of antibiotic use was  $43.5 \pm 9.25$  days. All patients were cured after treatment.

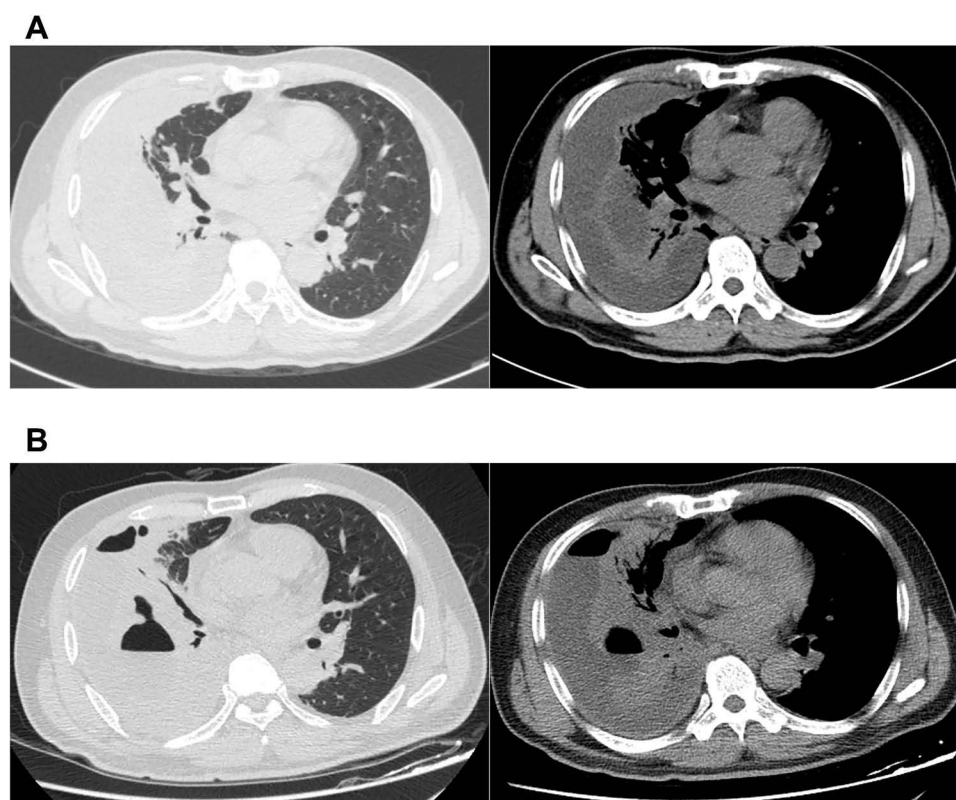
## Case Presentation of Case 6

On 19 October 2020, a 55-year-old man referred to emergency ward of our hospital with a 9-days history of progressively worsening right chest pain, dyspnea, right upper abdominal pain and a low-grade fever. He broken his right foot and recovered after surgery in 2015. He has been a smoker for more than 30 years, never taken hormones or immunosuppressive agents, with unremarkable family medical history. On admission, heart rate 105 beats/min; respiratory rate 23 breaths/min; temperature  $37.5^{\circ}\text{C}$ ; blood pressure 152/86mmHg, PaCO<sub>2</sub> 32.2mmHg, PaO<sub>2</sub> 71.8mmHg. No lymphadenopathy was detected. Weakened breath sounds were detected in the right hemithorax with small wet rales and stony-related dullness to percussion. The abdomen was soft, with tenderness in the right upper abdomen and under the xiphoid process, no rebound tenderness. The rest physical examination was unremarkable.

Results of laboratory examination on admission were as follows: WBC count,  $14.43 \times 10^9$  cells/L; neutrophils percent, 0.81; C-reactive protein,  $>192$  mg/L; procalcitonin, 1.33 ng/mL, serum albumin 27.5 g/L. Liver and kidney functions test were normal. Serum immunoglobulin test indicated hypogammaglobulinemia with IgM 0.46 g/L (normal 0.84–1.32 g/L) and lymphocyte subgroup test demonstrated no abnormality. Ultrasound suggested an atrial septal defect with a small amount of left to right shunt at the atrial level. A large right-sided pleural effusion was identified in chest radiograph. Consistently, chest CT showed bilateral pneumonia and a large right-sided encapsulated and separate pleural effusion, with almost collapsed right lung and lightly mediastinal lymphadenectasis ([Figure 1A](#)). Abdominal ultrasound and CT were unremarkable. Empirical antibiotics (cefuroxime, levofloxacin, moxifloxacin, cefodizime) were administered. And we punctured ultrasound-guided to drain empyema repeatedly, in view of encapsulated and separate pleural empyema difficult to drain via chest tube drainage.

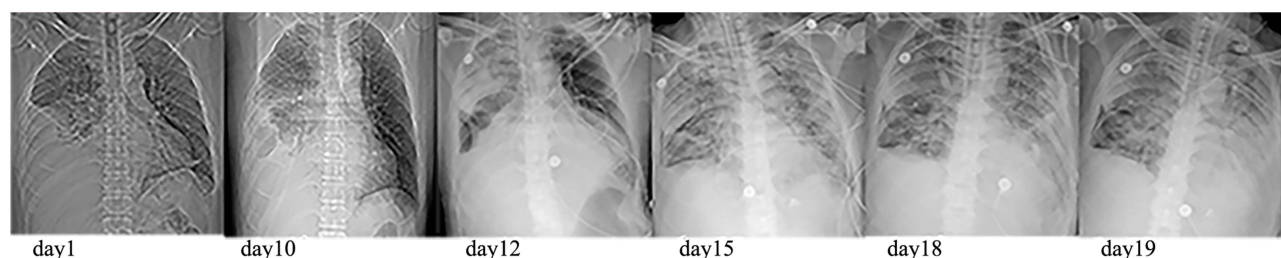
G+ cocci, G- bacillus and pharyngeal bacteria could be found in sputum smear, with no pathogen cultured. A small amount of G+ coccus was found in pleural fluid smear. *S. constellatus* and *Prevotella buccae* were cultured from initial yellow pleural fluid. AST showed the isolated *S. constellatus* susceptible to all the following antibiotics: penicillin G, ceftriaxone, linezolid, levofloxacin, vancomycin, erythromycin, tetracyclines, clindamycin, chloramphenicol. And the antibiotic regimen was adjusted (cefoperazone/sulbactam against *S. constellatus*, and morinidazole against *Prevotella buccae*).



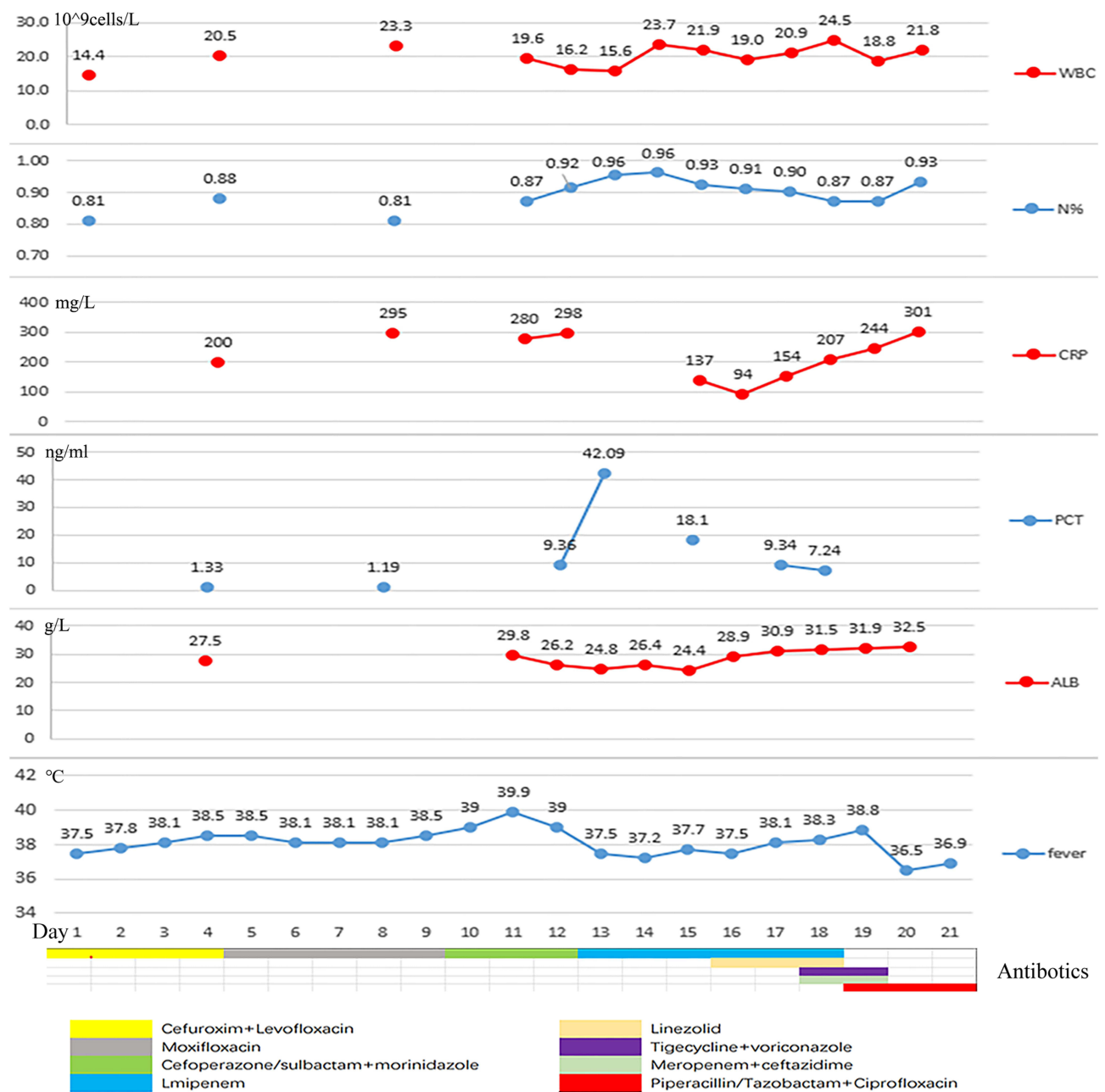


**Figure 1** CT images the dead patient (case 6). **(A)** CT on admission showed bilateral pneumonia and a large right-sided encapsulated and separate pleural effusion. **(B)** CT repeated in the 10th day showed empyema and pneumonia aggravated, lung abscess and bronchopleural fistula were found.

Although the patient had received intravenous antibiotics, albumin supplementation and pleural fluid drainage since admission, the condition was getting worse. Repeated CT showed empyema and pneumonia intensified, and lung abscess and bronchopleural fistula were found (Figure 1B). The patient developed into severe pneumonia with respiratory failure. Since the patient was too serious infected to tolerate surgery, we performed chest tube drainage and drained green-yellow purulent fluid in the 13th day. He was transferred to intensive care unit for further treatment, needing tracheal intubation and mechanical ventilation to maintain respiratory function. After several days, the patient eventually developed into severe ARDS (PaO<sub>2</sub>/FiO<sub>2</sub>: 78 mmHg) and septic shock. It required crystals and colloidal solution, continuous norepinephrine pumping (0.5µg/kg min) to boost blood pressure. Patient's dyspnea exacerbated, and aspiration of sputum and bronchoalveolar lavage were performed repeatedly via fiberoptic bronchoscopy. During ICU stays, antibiotics were adjusted several times depending on the disease. Repeated chest X-ray showed that the patient's empyema and pneumonia gradually worsened (Figure 2) and the patient demand to be discharged in the 21st day. He died shortly after leaving hospital. After the patient was discharged from the hospital, *Pseudomonas aeruginosa* (*P. aeruginosa*) was isolated from alveolar lavage fluid and sputum samples that were sent on the 19th day. The patient had already received antimicrobial treatment strongly against *P. aeruginosa* throughout clinical course, but the condition deteriorated (Figure 3). So, we considered that the isolated was difficult-to-treat resistance (DTR) *P. aeruginosa*.



**Figure 2** Chest radiograph of the patient during hospitalization.



**Figure 3** During hospitalization, the changes of body temperature, inflammatory indicators (including white blood cell count, neutrophil percentage, C-reactive protein, procalcitonin), nutritional status (plasma albumin), and antibiotic regimen adjustment process.

## Discussion

In a large trial of 434 patients from over 40 centers in the UK, Gram-positive aerobic organisms were the most frequent pathogens identified in community acquired pleural infection.<sup>24</sup> Streptococcal species including the SMG and *S. aureus* account for approximately 65% of cases.<sup>7</sup> *S. constellatus*, as a member of SMG, can reach the original sterile parts of individuals with lower immunity and cause suppurative infection. It is reported that *S. constellatus* is a common pathogen in empyema in some studies of SMG pulmonary infections. But there is no clinical study on empyema caused by *S. constellatus*. In the present study, we retrospectively analyzed the clinical characteristics of 9 patients diagnosed with empyema caused by *S. constellatus*. We found that the patients tended to be quinquagenarian men with comorbid diseases and lower immunity. The high-risk factors for *S. constellatus* empyema include diabetes mellitus, oral infection,

and oral surgery. The mean time from symptom onset to purulent pleural fluid drained was about two weeks. It was demonstrated that SMG infections occur mainly in male patients and patients with comorbid diseases, and the mean time to pus formation is 18 days.<sup>25–27</sup> This was consistent with our study.

SMG was considered causing thoracic infections via some pathways, including aspiration of oral secretions, direct implantation by trauma or surgery, extension by contiguity, and hematogenous dissemination.<sup>26,28,29</sup> In a retrospective study of 30 patients, SMG pneumonia tended to more frequently occur in males with comorbid diseases and involve pleural effusion with purulent formation, and *S. intermedius* was the most common organism followed by *S. constellatus*.<sup>30</sup> Okada et al reported that pleural effusion was observed in 54.5% of patients with SMG infections, and that pleural effusion was more frequently observed in patients with SMG infections than that were infected with other pathogens, including *S. pneumoniae*.<sup>8</sup> It was showed a low SMG detection rate in patients with pneumonia without pleural effusion.<sup>31</sup> In the present study, all patients had pneumonia, nearly half of the patients had lung abscess, and some had bronchopleural fistula. We observed right-side empyema was more common in *S. constellatus* empyema in this study. As we known, the right bronchus is wider, more vertical, and shorter than the left one. Therefore, we speculated that *S. constellatus* mainly cause pneumonia and lung abscess, and then invades the pleura and causes empyema by aspiration. Most of the patients reported in the literature had a history of recent exodontia and extra-thoracic abscesses. Hematogenous dissemination may be another important way of *S. constellatus* to cause pleural empyema. And a history of recent exodontia may be an important indication for the diagnosis of *S. constellatus* empyema.

*S. constellatus* were reported more likely to be polymicrobial in suppurative infections.<sup>31</sup> About 33.3% of empyema in our study were mixed infections involving *S. constellatus* and anaerobes. The reported rates of SMG polymicrobial infection with other bacteria ranged from 13% to 45% in respiratory infections caused by SMG.<sup>8,28,29,32</sup> And the rates of mixed infections involving the SMG combined with anaerobes range from 14% to 24%.<sup>25,33</sup> A study of in vitro and in vivo experiments demonstrated that the presence of anaerobes can positively enhance infection of *S. constellatus* related to high rate of lung abscess development and mortality. The potential mechanism was that anaerobes itself and its metabolite may impair the function of polymorphonuclear leukocytes (PMNLs) to inhibit the bactericidal activity of the host and stimulate the growth of *S. constellatus*.<sup>34</sup>

Although low mortality (11.1%) was showed in patients with *S. constellatus* empyema, more than half developed respiratory failure and 33.3% develop severe pneumonia, even ARDS and septic shock. It caused huge medical economic burden. Early diagnosis of *S. constellatus* empyema and timely treatment is very important. It is recommended all patients with pleural infection should early receive antibiotics.<sup>7</sup> When a patient is suspected to have empyema due to *S. constellatus*, it is vital to administer empirical antibiotics before bacterial culture and AST results available. As we known, there is no study on AST of *S. constellatus* related to pleural infection so far. In this study, *S. constellatus* isolates were completely sensitive to penicillin G, linezolid, levofloxacin and vancomycin. Ceftriaxone, chloramphenicol showed relatively low efficiency against *S. constellatus*. More than half of isolates were resistant to erythromycin, tetracycline and clindamycin. In a study involving 33 periodontal *S. constellatus* isolates, Thomas et al reported clindamycin was an effective antibiotic against *S. constellatus* and about 30% of the isolates were resistant to doxycycline.<sup>35</sup> Piotr et al observed that *S. constellatus* had the highest resistance rate to clindamycin (49%) and all isolates were susceptible to vancomycin in an AST data of 779 viridians group *Streptococcus* isolates from orofacial infections.<sup>36</sup> This was different from our results, which may be caused by the different sampling sources, local antibiotic policies and resistance patterns. These may have certain guiding significance for the empirically antibiotics therapy to *S. constellatus* empyema. Unfortunately, small sample sizes and frequent antibiotic adjustments in patients made it difficult to analyze the characteristics of antimicrobial treatment in patients with empyema caused by *S. constellatus*. Therefore, the use of antibiotics in the nine enrolled patients was not specified in this study. We found that *S. constellatus* was quite often co-isolated with anaerobes in empyema. Interestingly, in the process of data collection, we found that almost all patients were simultaneously treated with ornidazole, morinidazole or metronidazole against anaerobic bacteria in addition to antibiotics against *S. constellatus*. Thus, we held the opinion that antibiotics should cover both *S. constellatus* and anaerobes. In the present study, all patients received intravenous antibiotics and pleural fluid drainage, and favorable outcomes achieved in most of the cases. Duration of antibiotic use was about six weeks. It was argued that delayed pleural drainage probably leads to increased morbidity, duration of hospital stays and increased mortality of pleural infection.<sup>7</sup> In addition to antibiotic treatment, early and adequate pleural drainage is very



important for the treatment of *S. constellatus* empyema. Hypoproteinemia was very common in patients with *S. constellatus* empyema. And hypoalbuminaemia was considered associated with a poor outcome from pleural infection,<sup>7</sup> so enough nutritional support should be emphasized in the treatment of *S. constellatus* empyema. In addition to antibiotics and drainage, two patients in our study and six patients with *S. constellatus* empyema in the literature were cured by surgical treatment, including decortication and excision of the lung lobe with lung abscess. And most of them received Video-assisted Thoracoscopic Surgery (VATS) rather than open thoracotomy. Surgical treatment should be taken into consideration when persistent purulent pleural effusion cannot be effectively resolved after adequate antibiotics and drainage, and VATS may be the preferred procedure.

We explored the cause of the patient's death and concluded that empyema caused by *S. constellatus* and anaerobes and subsequently severe pneumonia caused by DTR *P. aeruginosa* contributed to the patient's death. First, the patient had separate and encapsulated empyema, making the pus difficult to be drained effectively. Pneumonia caused by DTR *P. aeruginosa* rapidly aggravated, and the result of AST was reported too late to adjust antibiotic regimen in time. Lung abscess and bronchopleural fistulas exacerbated empyema. Secondly, surgical treatment could not be performed timely to remove the infection lesions. Finally, the patient had persistent hypoproteinemia despite protein supplementation, and his serum IgM levels were low, resulting in compromised immunity. Together, the patient's infection could not be effectively controlled, and septic shock gradually worsened, leading to multiple organ failure and death.

We acknowledged several limitations of this study: (1) *S. constellatus* empyema is rare and *S. constellatus* is difficult to cultivate. This was a single-center study and sample size was small, may lead to poor reliability of this research. (2) This was a retrospective study, and we could not trace the patient's recent tooth extraction and periodontal inflammation without records in the hospital system. (3) We could not know the sequence of empyema, pneumonia/lung abscess and bronchopleural fistula and lack of microbiology of pneumonia and lung abscess. And no *S. constellatus* isolates was identified in sputum specimens of all patients. The conjecture that *S. constellatus* caused pneumonia and lung abscess first and then empyema remains further investigation to elucidate. (4) Anaerobes was reported to strengthen pathogenicity of *S. constellatus* in pulmonary infection. We did not compare the difference in disease severity and prognosis between the two groups of single *S. constellatus* and polymicrobial combined with anaerobes. (5) it was confirmed that *Pseudomonas aeruginosa* can form biofilms in the pleural cavity,<sup>37</sup> and we can further investigate whether *S. constellatus* can form biofilms in the pleural cavity.

## Conclusions

*S. constellatus* empyema was found more frequently in old males with comorbid diseases, and most were right-side encapsulated empyema with bilateral pneumonia and abscess. We speculated that *S. constellatus* mainly caused pneumonia and lung abscess first and then spread to cause empyema. *S. constellatus* empyema can lead to large medical economic burden. Timely pus drainage, antibiotics (intravenous antibiotic first) and enough nutrition support are crucial. Anaerobes may involve and aggravate *S. constellatus* empyema, antibiotics should against both *S. constellatus* and anaerobes. Intrapleural fibrinolytics and surgical treatment (VATS recommended first) should be considered if necessary.

## Abbreviations

*S. constellatus*, *Streptococcus constellatus*; SMG, *Streptococcus milleri* group; NGS, Next-Generation Sequencing; CT, computed tomography; AST, antibiotics susceptibility test; MIC, minimum inhibitory concentration; ARDS, acute respiratory distress syndromes; VATS, video-assisted thoracoscopic surgery; WBC, white blood cell counts; ALB, albumin; ADA, adenosine deaminase; GLU, glucose; PRO, protein; LDH, lactate dehydrogenase; NEU%, neutrophil percentage; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; DVT, deep venous thrombosis; PE, pulmonary embolism; DTR, difficult-to-treat resistance; *P. aeruginosa*, *Pseudomonas aeruginosa*.

## Ethics Approval and Consent to Participate

The study was approved by the First Affiliated Hospital of Guangxi Medical University Medical Ethics Committee [NO.2022-KY-E-(142)]. Written informed consent was obtained from study participants. This study complies with the Declaration of Helsinki.

## Consent for Publication

Written informed consent for publication of the clinical details was obtained from the patient (case 6).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors have no relevant financial or non-financial interests to disclose.

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