

Microbiological characteristics and outcomes of children with pleural empyema admitted to a tertiary hospital in southeast China, 2009-2018

Xueya Zhang^{ORCID}, Hailin Zhang^{ORCID}

Department of Pediatric Respiratory, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China.

ABSTRACT

Background. Pleural empyema is one of the most serious and life-threatening types of infection in children. The aim of this study was to describe the microbiological characteristics and outcomes of children with pleural empyema.

Methods. A retrospective review was conducted of the medical records of 63 children admitted to a tertiary hospital in China with pleural empyema between January 2009 and December 2018.

Results. The children had a median age of 1 year (range: 2 months to 16 years) and 33 (52.4%) were female. Bacterial isolates included *Staphylococcus aureus* (n=15, 23.8%), *Streptococcus pneumoniae* (n=10, 15.9%), *Pseudomonas aeruginosa* (n=7, 11.1%), *Escherichia coli* (n=2, 3.2%), *Burkholderia cepacia* (n=2, 3.2%), *Enterobacter cloacae* (n=1, 1.6%), *Klebsiella pneumoniae* (n=1, 1.6%), and *Streptococcus constellation* (n=1, 1.6%). All 15 *Staphylococcus aureus* isolates were found to be resistant to penicillin, and the rate of methicillin-resistant *Staphylococcus aureus* was high (66.7%, 10/15). Overall, 5 of 10 *Streptococcus pneumoniae* isolates were susceptible to penicillin. Each *Staphylococcus aureus* and *Streptococcus pneumoniae* isolate showed susceptibility to vancomycin. Ceftazidime was effective against all *Pseudomonas aeruginosa* isolates. Of the 63 children, 60 improved, no one died.

Conclusions. *Staphylococcus aureus* and *Streptococcus pneumoniae* were the leading cause of pleural empyema. Antimicrobial susceptibility testing revealed a high percentage of resistance against penicillin while vancomycin provided 100% coverage for these pathogens. *Pseudomonas aeruginosa* is the third most common pathogen mainly detected in those under 3 years old in the summer and have shown to be susceptible to ceftazidime. The prognosis is good after appropriate therapy.

Key words: children, empyema, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*.

Empyema, defined as the presence of pus in the pleural cavity, is a serious infectious condition with high morbidity and a 15–20% mortality.¹⁻³ The incidence of empyema in children has varied in recent decades. During 2006, an estimated total of 2,898 hospitalizations of children aged ≤18 years in the USA were due to empyema. The empyema-associated hospitalization rate was estimated at 3.7 per 100,000 children in 2006, compared to 2.2 per 100,000 in 1997.⁴

Liese et al.⁵ estimated the annual incidence of pediatric parapneumonic pleural effusion and pleural empyema hospitalizations in a nationwide surveillance study and found it to be 18.4 in 2010, which then decreased to 13.7 in 2013, and increased again to 17.3 in 2015 per million children. Generally, early and appropriate antibiotic therapy in children with pneumonia will avoid the development of empyema and its progression. Confirming the predominant pathogen of empyema is important to guide antimicrobial therapy. The bacteriology of pleural infection has changed over time. Recent data demonstrates that the distribution of pathogens causing empyema

✉ Hailin Zhang
zhlwz97@hotmail.com

Received 16th July 2020, revised 10th February 2021,
21st April 2021, accepted 27th April 2021.

differs according to geographical region.⁶ Following the introduction of the pneumococcal conjugate vaccines (PCVs), the incidence of empyema in children has changed.⁵ This variability according to time period and region has implications for treatment. It is important for clinicians to remain informed of the local bacteriology of empyema in order to inform their choice of antibiotic treatment.

The primary objective of the present study was to describe the microbiological characteristics and outcomes of children with pleural empyema admitted to a tertiary hospital in Wenzhou, China, in order to provide a source of reference for empiric antibiotic therapy.

Material and Methods

The study was approved by the Institutional Review Board of The Second Affiliated Hospital of Wenzhou Medical University (Protocol LCKY2019-199).

Patients

We retrospectively reviewed the clinical data of 63 children aged ≤ 18 years who had been admitted to the hospital with pleural empyema between 1 January 2009 and 31 December 2018. The inclusion criteria were as follows: (1) Children were aged 1 month to 18 years; (2) clinical symptoms of infection, including fever, cough, shortness of breath and other clinical manifestations were confirmed; (3) chest X-ray, computed tomography (CT) or ultrasound scan of the chest provided evidence of pleural effusion; (4) with any of the following additional findings: i) pus aspirated from the pleural space, and/or a positive Gram stain/culture of pleural fluid; ii) pleural fluid with a pH of < 7.2 , lactate dehydrogenase $> 1,000$ IU/L, glucose < 40 mg/dL, and/or a WBC count of $\geq 50,000$ cells/ μ L; iii) necessary for surgical decortication. Surgical and pathology reports were reviewed to confirm the diagnosis of empyema.⁷⁻⁹ Children with pleural empyema caused by trauma, surgery, tuberculous pleurisy, or carcinomatous pleuritis were excluded. For the purpose of evaluating the

bacteriology of pleural empyema, we assessed the microbiological findings according to the age group. The 63 children were divided into two age groups: < 3 years or ≥ 3 years old. Also, the 63 children were divided into two groups according to the date of the episode: in the first 5 years or in the last 5 years of the study.

Data collection

Data on the children's age, sex, underlying disease, date of the episode, laboratory data, microbiological findings, antimicrobial susceptibility testing, treatments and outcomes were extracted from electronic medical records. Information about vaccination including influenza, conjugated Haemophilus influenza type b (Hib) and conjugated pneumococcal vaccine (PCV) was collected. Haemophilus influenza type b and the 7-pneumococcal conjugate vaccine (PCV7) had been introduced to China in 1999 and 2008, respectively. All of the vaccines were considered as the second-class vaccine. The PCV7 was replaced with the 13-valent pneumococcal conjugate vaccine (PCV13) in 2016.

Microbiological methods

We also extracted data on the children's microbiology results, blood and pleural fluid cultures were carried out on admission. Bacterial cultures were performed according to standard microbiological methods. Blood and pleural fluid cultures were carried out using BD BACTEC Peds Plus/F vials in the BACTEC system (Becton, Dickinson and Company, Sparks, MD, USA). Confirmation of the species was performed by the VITEK 2 Advanced Expert System (bioMérieux, Marcy-l'Étoile, France). Susceptibility testing of cefoxitin, penicillin, ampicillin, gentamicin, rifampicin, erythromycin, clindamycin, tetracycline, levofloxacin, trimethoprim sulfamethoxazole (TMP-SMZ), cefuroxime, cefotaxime, amoxicillin clavulanic acid, amikacin, ceftazidime, cefepime, ciprofloxacin, aztreonam, imipenem, piperacillin, piperacillin-tazobactam, cefoperazone-sulbactam, tobramycin,

meropenem and ticarcillin clavulanic acid were performed using the disc-diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The minimum inhibitory concentrations (MICs) of vancomycin were determined with a gradient method (Etest, bioMérieux, Marcy-l'Étoile, France). Methicillin-resistant *Staphylococcus aureus* (MRSA) was defined as isolates of *Staphylococcus aureus* that were ceftoxitin-resistant by the disc-diffusion method.

Detection of viral pathogens from nasal swabs/washes or tracheal aspirates was carried out on admission. Samples were examined by direct immunofluorescence assays (DIAs) for respiratory syncytial virus, adenovirus, influenza A, influenza B and parainfluenza I, II and III. *Mycoplasma pneumoniae* antibody was detected by enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

Counts and percentages were used for categorical variables, and medians were used for continuous variables with a non-symmetrical distribution. Chi squared tests or Fisher's exact test were used to compare categorical variables. P values <0.05 were considered to be significantly significant. Statistical analysis was performed using SPSS for Windows, Version 19.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 63 children were enrolled in the study, of whom 33 (52.4%) were female. Children's median age was one year (range: 2 months to 16 years). Of the 63 children, 40 (63.5%) were aged <3 years (Group 1), and 23 (36.5%) were aged over 3 years (Group 2). Forty-two (66.7%) children were admitted in the winter or the spring (from December to May) and 21 (33.3%) were admitted in the summer or the autumn (from June to November). (Fig. 1). Three children were fully vaccinated with PCV7 and one child

received one dose of PCV13. Three children were vaccinated with influenza, while five children were fully vaccinated with Hib. Of the participants 39 were treated with intravenous antibiotics and only 4 children did not receive antibiotic treatment before admission. Patient characteristics are shown in Table I.

Microbiology

Of the 57 children with a pleural fluid culture result available, 29 (50.9%) had a positive culture. Of the 51 children with a blood culture result available, 10 (19.6%) had a positive culture. *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* grew in the blood culture in five, three and two patients, respectively. The blood culture results and pleural fluid culture results were both positive in four patients and they were compatible. *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* were the main pathogens. Antimicrobial susceptibility data is presented in Table II. All 15 *Staphylococcus aureus* isolates were found to be resistant to penicillin, and the rate of methicillin-resistant *Staphylococcus aureus* was high (66.7%,10/15). Overall, 5 of 10 *Streptococcus pneumoniae* isolates were susceptible to penicillin. Each *Staphylococcus aureus* and *Streptococcus pneumoniae* isolate showed 100% susceptibility

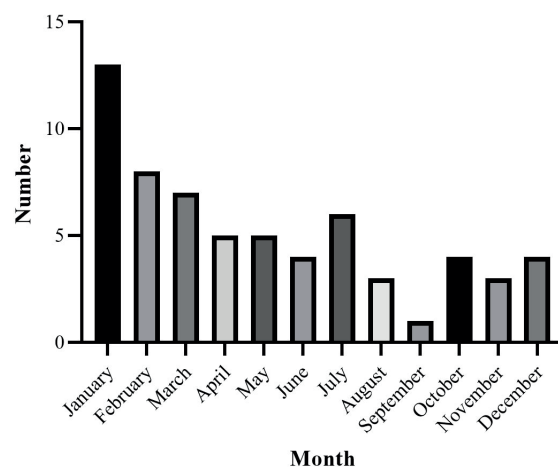


Fig. 1. Number of children admitted with pleural empyema by month, January 2009 to December 2018 (n = 63)

Table I. Patient characteristics.

Patient characteristics	<3 years old n=40 n (%)	≥3 years old n=23 n (%)	Total N=63 n (%)	P-value
Sex, female	18 (45)	15 (65)	33 (52.4)	0.122
Underlying disease				
Congenital pulmonary airway malformation	5 (12.5)	2 (8.7)	7 (11.1)	0.963
Congenital pulmonary cyst	3 (7.5)	1 (4.3)	4 (6.3)	>0.99
Pulmonary sequestration	0	1 (4.3)	1 (1.6)	—
Tracheomalacia	2 (5)	0	2 (3.2)	—
Intellectual disability	0	3 (13)	3 (4.8)	—
Primary immunodeficiency	2 (5)	0	2 (3.2)	—
Immunosuppression	0	1 (4.3)	1 (1.6)	—
Cause				
Bacterial pneumonia	20 (50)	16 (69.6)	36 (57.1)	0.131
Pulmonary abscess	12 (30)	5 (21.7)	17 (27)	0.477
Septicemia	5 (12.5)	2 (8.7)	7 (11.1)	0.644
Retropharyngeal abscess	2 (5)	0	2 (3.2)	—
Abscess of the chest wall	1(2.5)	0	1(1.6)	—
Laboratory data				
WBC (10 ³ /mm ³), median (IQR)	23.7 (20.3)	23.6 (14.9)	23.7 (17.7)	0.959
CRP (mg/L), median (IQR)	159.7 (52.4)	149.1 (127.5)	155.8 (84.2)	0.595

CRP: C-reactive protein, WBC: white blood cell, IQR: interquartile range.

to vancomycin. Ceftazidime was effective against all *Pseudomonas aeruginosa* isolates. Children aged <3 years were significantly more likely to have a positive bacterial culture result (65% versus 39.1%, $P=0.047$). (Table III). Three children had more than one bacterial infection detected. A child with a retropharyngeal abscess had *Burkholderia cepacia* and *Enterobacter cloacae* coinfection, and two children had *Streptococcus pneumoniae* and *Staphylococcus aureus* coinfection. One child who had been intubated had *Burkholderia cepacia* which was detected in their pleural fluid. The other types of coinfection are shown in Table III. Coinfection with respiratory viruses or *Mycoplasma pneumoniae* was significantly less common in children aged <3 years than those aged ≥3 years (22.5% vs 56.5%, $p=0.006$).

The number of cases of *Staphylococcus aureus* (eight cases in the first 5 years, and seven cases in the last 5 years) and *Streptococcus pneumoniae* (four cases in the first 5 years, and six cases in

the last 5 years) infection remained relatively stable over time. The number of cases of *Pseudomonas aeruginosa* infection declined from five in the first 5 years to two in the last 5 years of the study.

Staphylococcus aureus and *Streptococcus pneumoniae* infections were more common in the winter and the spring. Conversely, *Pseudomonas aeruginosa* was more common in the summer. The distribution of pathogens according to month is shown (Fig. 2).

Treatment and outcome

The study flow chart is presented in Figure 3. Thirty (47.6%) children were treated with empirical antibiotics and a chest tube insertion and did not require surgery. Ten patients received intravenous antibiotics and simple drainage alone, and 20 children required closed thoracic drainage. Thirty-three children (52.4%) required surgery, of whom 21 had an open thoracotomy,

Table II. Antimicrobial susceptibility data for the main pathogens of empyema.

Pathogen	<i>Staphylococcus aureus</i> (n=15)			<i>Streptococcus pneumoniae</i> (n=10)			<i>Pseudomonas aeruginosa</i> (n=7)		
	S	I	R	S	I	R	S	I	R
Agent									
Penicillin	0	0	15	5	0	5	—	—	—
Cefuroxime	—	—	—	3	2	5	—	—	—
Cefotaxime	—	—	—	6	2	2	—	—	—
Ampicillin	0	0	15	—	—	—	—	—	—
Cefoxitin	5	0	10	—	—	—	—	—	—
Clindamycin	4	1	10	—	—	—	—	—	—
Erythromycin	4	0	11	0	0	10	—	—	—
Rifampicin	12	1	2	—	—	—	—	—	—
Tetracycline	12	0	3	2	0	8	—	—	—
Gentamicin	14	0	1	—	—	—	6	1	0
Levofloxacin	15	0	0	10	0	0	7	0	0
TMP-SMZ	14	0	1	1	1	8	—	—	—
Amoxicillin clavulanic acid	—	—	—	8	2	0	—	—	—
Vancomycin	15	0	0	10	0	0	—	—	—
Amikacin	—	—	—	—	—	—	7	0	0
Ceftazidime	—	—	—	—	—	—	7	0	0
Cefepime	—	—	—	—	—	—	7	0	0
Ciprofloxacin	—	—	—	—	—	—	7	0	0
Aztreonam	—	—	—	—	—	—	7	0	0
Imipenem	—	—	—	—	—	—	7	0	0
Piperacillin	—	—	—	—	—	—	7	0	0
Piperacillin-tazobactam	—	—	—	—	—	—	7	0	0
Cefoperazone-sulbactam	—	—	—	—	—	—	7	0	0
Tobramycin	—	—	—	—	—	—	7	0	0
Meropenem	—	—	—	—	—	—	7	0	0
Ticarillin clavulanic acid	—	—	—	—	—	—	6	1	0

S: susceptible, I: intermediate, R: resistant, TMP-SMZ: trimethoprim sulfamethoxazole

six had video-assisted thoracoscopic surgery, two had a right inferior pulmonary lobectomy, and one with a congenital pulmonary cyst had a left upper pulmonary lobectomy. Two patients with retropharyngeal abscesses were treated by incision and drainage, and one patient with a thoracic abscess was managed with debridement and drainage. The most common serious complication was pneumothorax. One patient experienced septic shock, and another developed a bronchopleural fistula. One experienced multiple organ failure, and another had hemolytic uremic syndrome. The mean (SD) duration of total hospital stay was

33 (12) days. Of the 63 children, 60 improved, while three did not complete their treatment and left the hospital against medical advice. One was readmitted to the hospital 3 months' post-discharge. Outcomes are summarized in Table IV.

Discussion

According to previous research, pleural empyema is usually secondary to acute bacterial pneumonia. In our study, 57.1% of the cases of empyema were preceded by bacterial pneumonia. Lamas-Pinheiro et al.¹⁰ reported

Table III. Pathogens detected in children with pleural empyema.

Pathogen	<3 years old	≥3 years old	Total	P-value
	n=40 n (%)	n=23 n (%)	N=63 n (%)	
Bacteria	26 (65.0)	9 (39.1)	35 (55.6)	0.047
<i>Staphylococcus aureus</i> ^{a,b,d}	12 (30.0)	3 (13.0)	15 (23.8)	—
<i>Streptococcus pneumoniae</i> ^{a,b,d}	8 (20.0)	2 (8.7)	10 (15.9)	—
<i>Pseudomonas aeruginosa</i> ^d	6 (15.0)	1 (4.3)	7 (11.1)	—
<i>Escherichia coli</i>	0	2 (8.7)	2 (3.2)	—
<i>Burkholderia cepacia</i> ^{b,c}	2 (5)	0	2 (3.2)	—
<i>Enterobacter cloacae</i> ^c	1 (2.5)	0	1 (1.6)	—
<i>Klebsiella pneumoniae</i>	1 (2.5)	0	1 (1.6)	—
<i>Streptococcus constellatus</i>	0	1 (4.3)	1 (1.6)	—
<i>Mycoplasma pneumoniae</i>	3 (7.5)	9 (39.1)	12 (19.0)	0.006
Viruses	6 (15.0)	4 (17.4)	10 (15.9)	0.803
Influenza A virus	1 (2.5)	4 (17.4)	5 (7.9)	0.105
Influenza B virus	1 (2.5)	0	1 (1.6)	—
Human adenovirus	2 (5)	0	2 (3.2)	—
Respiratory syncytial virus	1 (2.5)	0	1 (1.6)	—
Human parainfluenza virus type3	1 (2.5)	0	1 (1.6)	—

^a*Staphylococcus aureus* co-infected with *Streptococcus pneumoniae* in one patient aged <3 years.

^b*Staphylococcus aureus* mixed with *Streptococcus pneumoniae* and *Burkholderia cepacia* in one patient aged <3 years.

^c*Burkholderia cepacia* co-infected with *Enterobacter cloacae* in one patient aged <3 years.

^d*Staphylococcus aureus*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* grew in the blood culture in five, three and two patients, respectively.

that children with empyema usually had a normal underlying lung. However, in our study, seven of the 63 children (11.1%) had congenital pulmonary airway malformations. Also, several children in our study had underlying conditions, including intellectual disability, immunodeficiency, and immunosuppression. The role of underlying conditions such as these in increasing the risk of empyema requires further research.

Most of the children in our study were aged <3 years. The children in our study were younger than those in a previous study by Eastham et al.¹¹ conducted in 2004 (median age 1 year versus 5.6 years, respectively). In keeping with the previous research⁷, the incidence of empyema was higher in the winter and the spring than in the summer and autumn, probably due to their infective origin.

Table IV. Medical outcomes of the patients.

Outcome	n, %
Serious adverse events	
Pneumothorax	31 (49)
Multiple organ failure	1 (1.6)
Septic shock	1 (1.6)
Bronchopleural fistula	1 (1.6)
Hemolytic uremic syndrome	1 (1.6)
Purulent meningitis	1 (1.6)
Subcutaneous emphysema	6 (9.5)
Pericardial effusion	1 (1.6)
Duration of total hospital stay, mean (SD), day	33 (12)
Outcome	
Clinically improved	60 (95.2)
Ongoing	0
Death	0
Unknown	3 (4.8)
Hospital readmissions	1 (1.6)

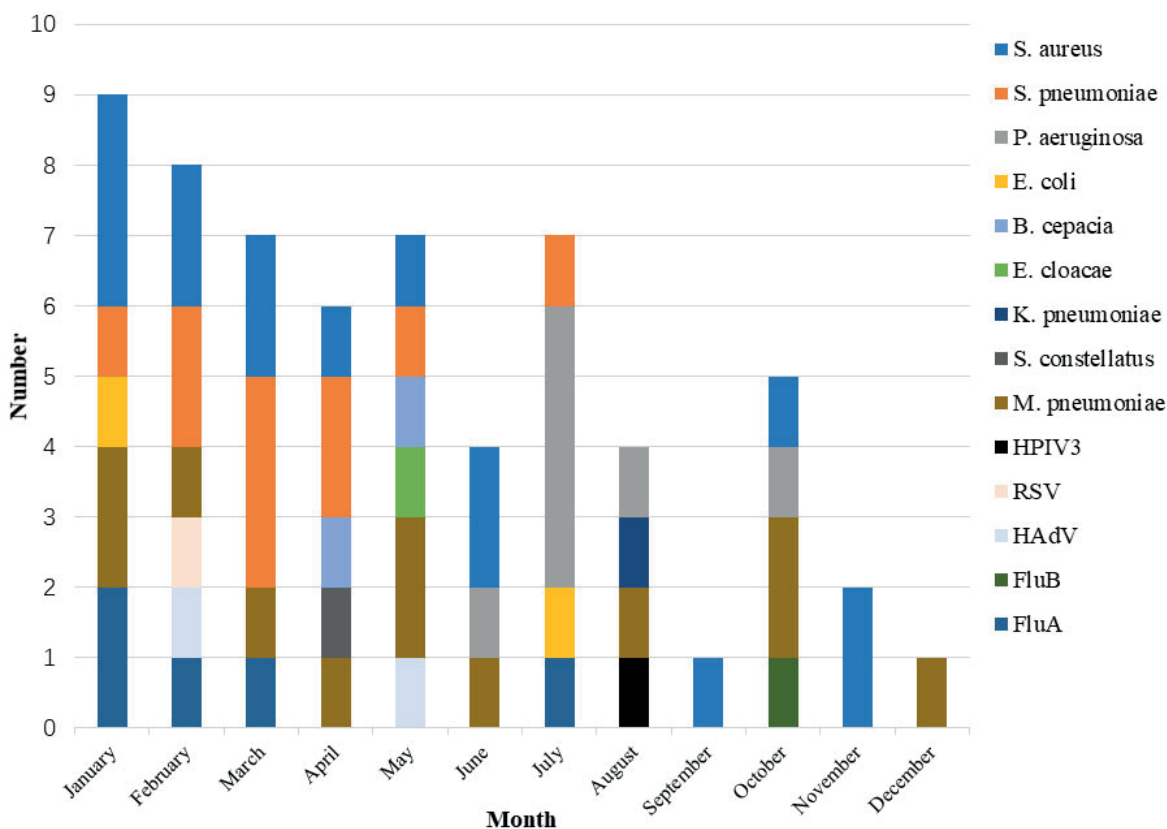


Fig. 2. Causes of pleura empyema according to month. *Staphylococcus aureus*: *S. aureus*; *Streptococcus pneumoniae*: *S. pneumoniae*; *Pseudomonas aeruginosa*: *P. aeruginosa*; *Escherichia coli*: *E. coli*; *Burkholderia cepacia*: *B. cepacia*; *Enterobacter cloacae*: *E. cloacae*; *Klebsiella pneumoniae*: *K. pneumoniae*; *Streptococcus constellatus*: *S. constellatus*; *Mycoplasma pneumoniae*: *M. pneumoniae*; Influenza A virus: FluA; Influenza B virus: FluB; Human adenovirus: HAdV; Respiratory syncytial virus: RSV; Human parainfluenza virus type 3: HPIV3.

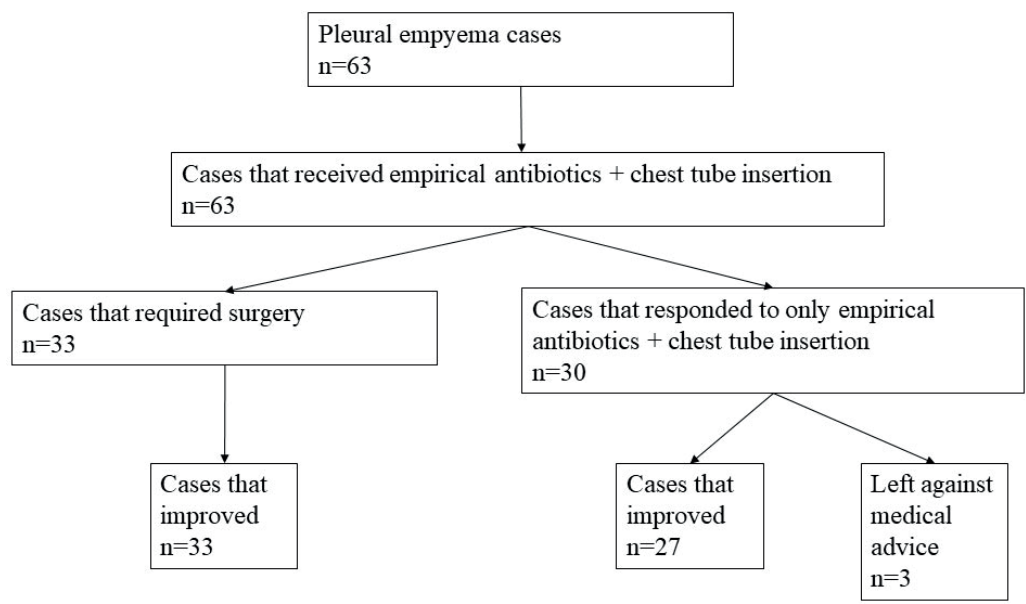


Fig. 3. Study flow chart

In our study, *Staphylococcus aureus* was the most common cause of empyema. This finding is similar to that of previous studies conducted on children in India and New Zealand.¹²⁻¹⁴ However, in other studies, the proportion of cases of empyema caused by *Staphylococcus aureus* infection has varied.¹⁵⁻¹⁶ This can be attributed to regional variations in the epidemiology of community acquired *Staphylococcus aureus* infection.⁷ The study conducted in New Zealand¹¹ revealed that the prevalence of MRSA was 26% among 38 children with *Staphylococcus aureus* empyema. In our study, ten of the 15 isolates of *Staphylococcus aureus* (66.7%) were methicillin resistant (MRSA). The high incidence of MRSA could be due to the injudicious use of antibiotics.

Streptococcus pneumoniae was the second most common cause of empyema in our study and 50% were resistant to penicillin. The proportion of cases of empyema caused by *Streptococcus pneumoniae* was relatively low compared to previous studies.¹⁷⁻¹⁹ Lin et al.²⁰ analyzed the causes of infection among 89 children with empyema thoracic and parapneumonic pleural effusion in Taiwan, confirmed that *Streptococcus pneumoniae* was the most common pathogen. In this study, the number of patients with empyema caused by *Streptococcus pneumoniae* may have been underestimated because we did not use polymerase chain reaction (PCR) to test for *Streptococcus pneumoniae*. Blaschke et al.²¹ confirmed that most patients with culture negative empyema were positive for *Streptococcus pneumoniae*.

Pseudomonas aeruginosa was the third most common cause of empyema in this study. This is similar to the findings of a recent study conducted in Iran, which found a prevalence of *Pseudomonas aeruginosa* of 18.1% among 105 children with empyema.²² According to a previous study, *Pseudomonas aeruginosa* infections occur mainly as a complication of hospital-acquired pneumonia and in patients with chronic lung disease.²³ In contrast to their study, we found that empyema caused by *Pseudomonas aeruginosa* infections occurred

as an outcome of community-onset infections; and ceftazidime sustained activity against all *Pseudomonas aeruginosa* isolates. All children with *Pseudomonas aeruginosa* infection did not have underlying lung disease. We hypothesize that the predisposing factors for *Pseudomonas aeruginosa* infections in children differ from those of adults. Of note is that six of the seven children with *Pseudomonas aeruginosa* aged <3 years were diagnosed with empyema in the summer. Therefore, if children under 3 years are diagnosed with empyema in the summer, *Pseudomonas aeruginosa* should be considered as the main cause. The incidence of *Pseudomonas aeruginosa* infection should be continuously monitored but as there were only two cases of *Pseudomonas aeruginosa* infection in the last 5 years of the study, the incidence is too low to determine risk factors for *Pseudomonas aeruginosa* infection in children.

In our study, the most commonly detected coinfection pathogen was *Mycoplasma pneumoniae*, which was significantly more common in children aged ≥ 3 years. In addition, Influenza A virus was the most common virus detected in patients. However, Krenke et al.¹⁹ reported that *Chlamydia pneumoniae* was the most common pathogen (8.6%), and that adenovirus was the most common virus found in patients with empyema (13.8%). In our study, children aged <3 years were significantly less likely to have a coinfection with a virus or *Mycoplasma pneumoniae* than those aged ≥ 3 years. The observed differences might have been due to age-related differences in immune function and environmental exposures.

In the current study, the duration of total hospital stay was longer than that in previous studies.^{11,13,24} One reason for this difference could be the higher rate of *Staphylococcus aureus* infections in our study and the fact that patients required a longer duration of treatment as compared to those with *Streptococcus pneumoniae* infections. Another reason is presumably the occurrence of serious complications. Most of the children with pleural empyema improved, while three of the children who did not complete

their treatment, left the hospital against medical advice. Thus far, the data has shown that prognoses are good after appropriate treatment, a finding that is consistent with previous studies.²⁵ In addition, children with empyema often have a lower rate of mortality compared to adults, and their long-term prognoses appear to be much better than those for adults.²⁶

There are limitations to this study. Firstly, it is a retrospective study with a limited sample size. Thus, there may have been biases in data selection and analysis. Secondly, we did not conduct PCR testing of samples from the children with empyema when the pleural fluid culture was negative. This may have led the prevalence of bacterial infection in children with empyema to be underestimated.

This study described the microbiological characteristics and outcomes of Chinese children with empyema over the past 10 years and confirmed that *Staphylococcus aureus* and *Streptococcus pneumoniae* were the leading cause of empyema in the study setting. Antimicrobial susceptibility testing revealed a high percentage of resistance against penicillin while vancomycin provided 100% coverage for these pathogens. *Pseudomonas aeruginosa* isolates are the third most common pathogens mainly detected in those under 3 years old in the summer and have shown to be susceptible to ceftazidime. The prognosis is good after appropriate therapy.

Author contribution

Author contributions have been stated as follows: study conception and design: HZ; data collection: XZ; analysis and interpretation of results: HZ; draft manuscript preparation: XZ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Institutional Review Board of The Second Affiliated Hospital

of Wenzhou Medical University (Protocol LCKY2019-199).

Source of funding

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Conflict of interest

The authors declare no conflict of interest.

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