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# Bacterial Pleural Effusion and Antimicrobial Resistance at the Children's Medical Center, Iran between 2012 and 2019

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## Abstract

**Background:** Bacterial pleuritis is a rare disease with high mortality rate in untreated patients, but effective antimicrobial treatment reduces its frequency. Drug resistance is rising to seriously high levels and is an emerging threat to public health systems. We aimed at evaluating antimicrobial resistance in pediatrics with bacterial pleural effusion.

**Methods:** This retrospective study was carried out at the Children's medical center between 2012 and 2019. Samples obtained with thoracocentesis from 487 hospitalized pediatric patients with pleural effusion with different etiologies. In addition to routine culture and disk diffusion method, to achieve quantification and standardization, in some cases E-test MICs was performed. BACTECT culture system was used for some critical patients. All microbiology data were used in this study was reported to the WHONET as software for the microbiology laboratory database.

**Results:** Positive bacterial cultures were found in 22 (4.5%) cases. The most common isolated microorganisms were *Streptococcus pneumonia* 40/90% (9/22), *Acinetobacter baumani* 18/18% (4/22) and *Staphylococcus aureus* 13.63% (3/22). Other less prevalent organisms include *Pseudomonas aeruginosa*, *Staphylococcus epidermis*, *Klebsiella pneumonia*, and *Serratia marcescens*. 88% of *S. pneumonia* isolates were resistance to Erythromycin. A. baumannii expressed 100% resistance to Cefotaxime. S. aureus had the highest resistance rates to Penicillin (100%). The rate of MRSA and MRSE were 33/3% and 50% respectively.

**Conclusion:** Our findings revealed the antibacterial resistance rate is expanding. Surveillance on antimicrobial susceptibility patterns and hospital antibiotic formulary are essential to find bacterial resistance and establishing guidelines for monitoring antibiotic therapy.

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## Introduction

The prevalence of pleural effusion has been reported to range from 5.4% to 6% [1,2] and it has increased in children in recent decades. Pleural effusion is a common manifestation of pulmonary and respiratory diseases and is usually associated with underlying diseases. In developed countries, the most common reason of the pleural effusion is bacterial *pneumonia* [3,4]. It is reported that 50-60% of the causes of pediatrics pleural effusion are infectious agents [5]. Despite vaccination, it is associated with complications, but fewer deaths occur [6] Treatment of pleural effusion includes intravenous antibiotic therapy (as the main method), the drainage through thoracocentesis and thoracic tube replacement, finally thoracoscopy and open thoracic surgery [7].

In recent years, the prevalence of community- resistant bacterial strains has increased [8,9] It leads to death in children and infants, especially in low incomes countries [10]. However, little is known about the antimicrobial-resistant with focus on pediatric infections in under developing and developing countries [11,12]. This study was conducted to identify resistant bacterial species in samples collected from children with pleural effusion.

## Methods

This retrospective study was carried out at the Children's medical center, as one of the largest pediatric hospital in Iran, between 2012 and 2019. Samples obtained with thoracocentesis from 487 pediatric patients who were hospitalized with pleural effusion with different etiologies.

All specimens were carried out by a pediatrician or pediatric surgeon, and a volume of 1 to 5 ml in sterile containers deliver to the laboratory promptly. Also, in some critical cases, pleural fluid directly inoculated into blood culture bottles (BACTECT) at the patient's bedside. Specimens were cultured on blood agar, chocolate agar, and thioglycolate broth, according to guidelines for the selection of media providing the optimal conditions for pathogens growth.

Positive cultures after incubation, arranged for standard antimicrobial susceptibility testing by inoculum preparation with a turbidity equivalent to a 0.5 antibiotic disk selection and qualified Mueller-Hinton agar as testing media.

The Kirby-Bauer disk diffusion method was used for antimicrobial susceptibility testing that followed the Clinical and Laboratory Standards Institute (CLSI) rules [13]. To achieve a better level of accuracy and sensitivity, in some cases the Epsilometer (E-test) MICs accompaniment with the disk diffusion method was obtained.

Minimum Inhibitory Concentration (MIC) is a standard method for quantitative determining antimicrobial susceptibility of bacteria. The 'E test' is a method that is based on diffusion of an antibiotic gradient from a strip. WHONET software enable microbiology laboratory across one country or multiple countries to share data with others, so surveillance of Antimicrobial Resistance (AMR) and monitor all the reports of all the world's microbiology laboratories is achieved [14]. It is noteworthy, that the entire laboratory data were used in this study was reported to the WHONET as software for the microbiology laboratory database and they are accessible in whonet.org.

## Results

We studied a total of 487 consecutive patients with pleural effusion hospitalized in Children Medical Center. Positive bacterial growth cultures were found in 22 (4.5%) cases.

The most common isolated microorganisms were *Streptococcus pneumonia* 40/90% (9/22), *Acinetobacter baumani* 18/18% (4/22) and *Staphylococcus aureus* 13.63% (3/22) respectively, other less prevalent organisms include *Pseudomonas aeruginosa, Staphylococcus epidermis, Klebsiella pneumonia and Serratia marcescens*, briefly illustrated in **Table 1**.

**Table 1**: Percentage of positive culture of growth of each bacterium.

| Positive bacterial growth cultures | Total number |
|---|---|
| *Streptococcus pneumonia* | 9/22 (40/99%) |
| *Acinetobacter baumani* | 4/22 (18/18%) |
| *Staphylococus aureus* | 3/22 (13/63%) |
| *Pseudomonas aeroginosa* | 2/22 (9/09%) |
| *Staphylococus epidemis* | 2/22 (9/09%) |
| *Klebsiella pneumonia* | 1/22 (4/5%) |
| *Serratia marcescens* | 1/22 (4/5%) |

**Table 2:** Antimicrobial susceptibility of *Streptococcus pneumonia, Acinetobacter baumani* and *Staphylococus aureus* isolated from pleural fluid cultures between 2012 and 2019.

| Microorganism | Antibiotics | Susceptible | Intermediate | Resistance |
|---|---|---|---|---|
| *Streptococcus pneumonia* | Cotrimoxazole | 7/9 (77/77%) | 1/9 (11/1%) | 1/9 (11/1%) |
| | Clindamycin | 3/9 (33/3%) | 0 (0%) | 6/9 (66/6%) |
| | Erythromycine | 1/9 (11/1%) | 0 (0%) | 8/9 (88/8%) |
| | Penicillin | 7/9 (77/77%) | * | * |
| | Vancomycin | 9/9 (100%) | 0 (0%) | 0 (0%) |
| | Ceftriaxone | 7/9 (77/77%) | * | * |
| | Ampicillin | 9/9 (100%) | 0 (0%) | 0 (0%) |
| *Acinetobacter baumani* | Gentamycin | 0/4 (0%) | 0/4 (0%) | 4/4 (100%) |
| | Amikacin | 2/4 (50%) | 0/4 (0%) | 2/4 (50%) |
| | Piperacillin Tazobactam | 2/4 (50%) | 0/4 (0%) | 2/4 (50%) |
| | Cefepime | 2/4 (50%) | 0/4 (0%) | 2/4 (50%) |
| | Cefotaxime | 0/4 (0%) | 0/4 (0%) | 4/4 (100%) |
| | Ceftazidime | 1/4 (25%) | 0/4 (0%) | 2/4 (50%)* |
| | Imipeneme | * | 1/4 (25%) | 2/4 (50%) |
| | Ampicillin Sulbactam | * | * | 2/4 (50%) |
| | Ciprofloxacin | * | * | 2/4 (50%) |
| | Colistin | 2/4 (50%) | 0/4 (0%) | 2/4 (50%) |
| *Staphylococus aureus* | Cotrimoxazole | 2/3 (66/6%) | 1/3 (33/33%) | 0/3 (0%) |
| | Oxacillin | 2/3 (66/6%) | 0/3 (0%) | 1/3 (33/33%) |
| | Clindamycin | 3/3 (100%) | 0/3 (0%) | 0/3 (0%) |
| | Erythromycin | 2/3 (66/6%) | 0/3 (0%) | 1/3 (33/33%) |
| | Penicillin | 0/3 (0%) | 0/3 (0%) | 3/3 (100%) |
| | Vancomycin | 3/3 (100%) | 0/3 (0%) | 0/3 (0%) |

*Streptococcus pneumonia* isolated were susceptible to Ampicillin (100%,9/9), Vancomycin (100%, 9/9), Ceftriaxone (77/8%, 7/9), Penicillin (77/8%, 7/9), Cotrimoxazole (77/8%, 7/9), The great resistance were observed with Erythromycin (88/8%,8/9) and Clindamycin (66/6%,6/9) that demonstrated in **Table 2**.

In *Acinetobacter Baumani* infections, Amikacin (50%, 2/4), Tazobactam (50%, 2/4), Colistin (50%, 2/4) and Cefepime (50%, 2/4) were the most effective antibiotics. The highest resistance rate was seen with Gentamycin (100%, 4/4) and Cefotaxime (100%, 4/4) listed in **Table 2**.

*Staphylococcus aureus* had the highest resistance rates to Penicillin 100% (3/3) but Vancomycin and Clindamycin had 100 %( 3/3) sensitivity, which are listed in **Table 2**.

*Pseudomonas aeroginosa* was resistant to Gentamycin, Amikacin, Tazobactam, Cefepime, Ceftazidime Imipeneme. It was susceptible to Colistin.

*Staphylococcus epidermis* showed susceptibility to Vancomycin (100%, 2/2), Erythromycin, Cilindamycin, Oxacillin, Cotrimoxazole and was resistant to Penicillin(100%, 2/2), Erythromycin, Cilindamycin, Oxacillin, Cotrimoxazole.

*Klebsiella pneumonia* was susceptible to Imipenem and resistant to Gentamycin, Amikacin, Cefepime, Ceftazidime, and Cefotaxime.

*Serratia marcescens* was resistant to Gentamycin, Amikacin, Cefepime, and Cefotaxime and susceptible to Imipenem.

The rate of methicillin-resistant *S. aureus* (MRSA) was 33/33 % (1/3), and that of methicillin-resistant *S. epidermis* (MRSE) was 50% (1/2).

Most positive cultures were found in the Cardiac ICU (23%, 6/22) including two positive cultures for *Pseudomonas aeruginosa*, two *Acinetobacter baumani*, one culture *Klebsiella pneumonia* and one *Serratia marcescens* cultures. The second step is for pediatric ICU (15%, 4/22) including two cases of *Acinetobacter baumani* and two *Streptococcus pneumonia.* cultures Emergency, Urology, Rheumatology, and Emergency ICU with two positive cultures are the third level.

# Discussion

Antimicrobial resistance is one of the causes of rising global mortality and economic burden to countries [15]. Integrated multilevel surveillance of resistance to antimicrobial agents is the major requirement of the public health community [14]. In this study, we focused on positive culture bacterial isolates from pediatric pleural fluid samples.

*Streptococcus pneumonia* is one of the potential sources of community-acquired pneumonia (CAP) in children under five [16]. The prevalence of CAP related Para pneumonic effusion is rising and was demonstrated from 5.4% to 18.8% between 2002 and 2013 in Krenke K et al study. They found that *Streptococcus pneumonia* was the main organism in 66.7% of cases of known causes. Only 22.6% of cases were treated with antibiotics and the rest required invasive procedures [17]. In Zhanel et al study, most of the samples with antimicrobial resistance were *Streptococcus pneumonia*. The methods of macrolide resistance include three categories: target site change, changes in antibiotic transmission and modification of the antibiotic [18] In the United States, the frequency of macrolide and clindamycin resistance to *S. pneumonia* is reported 20%-40% and 4.9 % respectively [19-21] In our study, High level resistance of *S. pneumonia* was observed in Erythromycin (88/8%, 8/9) and Clindamycin (66/6%, 6/9) susceptibility testing.

At present, multidrug resistant *acinetobacter* strains are becoming more common and the rate of resistance to Carbapenems are expanding in Europe and is evolving worldwide [22-24] An integrated systematic review of 101 pediatrics on *Acinetobacter* Species infection including 28 studies up to 1970, 13 from 1971 to 1990, and 70 from 1991 to 2008 showed that *Acinetobacter* was found in three cases from the pleural fluid, pulmonary lymph node and lung at autopsy [25]. In the present study, about 18% of cultures were positive for *Acinetobacter baumani*, with 50% resistance to imipenem in samples with available antimicrobial disk.

According to surveillance data from 2004 to 2006 reported the prevalence rates of imipenem-resistant A. baumannii were 14.1%, 39.4%, 11.4%, and 30.8% in Europe, Latin America, North America, and the Asia-Pacific region, respectively [26].

*Staphylococcus aureus* is one of the most common causes of infections associated with surgical site, catheter-associated bloodstream and ventilator-associated *pneumonia* [27] a large body of literature has focused on different prevalence of MRSA in different geographical areas [28]. Lyall et al. study in India on different clinical samples have been presented a high rate of MRSA (91.5%) [29]. In contrast, Kourtis study reported the rate of hospital-acquired MRSA during 2005–2012 declined 17.1% annually, but community-based infections declined less 6.9% annually during 2005–2016 [30].

The MRSA-related deaths impose huge costs on governments and limit therapeutic options, and may now colonize more than 53 million of the world's population with MRSA, which is a threat for themselves and others [31-33].

Similar to *S. aureus*, MRSE has become a concern with considerable variation in its prevalence. In some parts of Europe, 60-70% of *S. epidermis* are methicillin-resistant [34,35].

In the present study, *Staphylococcus aureus* expressed as the third cause of positive cultures with highest resistance rates to Penicillin (100%).The most effective antimicrobial agents were Vancomycin and Clindamycin with 100 % sensitivity. The rate of methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermis* (MRSE) were 33/3% and 50 % respectively.

There are few published literatures about *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Klebsiella pneumonia* and *Serratia marcescens* in pediatric pleural fluids and their antibiotic resistance behavior that limits comparison. In one study in Korea, Prevalence of Ceftazidime-Resistant *Klebsiella* *pneumonia* reported 32% and imipenem-resistant *Pseudomonas aeruginosa* was 24% [36].

## Conclusion

There are limited data concerning bacterial resistance patterns, especially in effusions and mainly in pediatric population, and prospectively evaluation of bacterial species isolated and their susceptibility patterns is crucial. It seems that our data as a tertiary center, associate with comprehensive research data from other regions of Iran, will further increase the consistency of global stewardship programs in developed countries and decline the spread of bacterial resistance worldwide.

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