http:// ijp.mums.ac.ir
Original Article (Pages: 7421-7432)

The Survey of Pediatric Pleural Empyema in North of Iran (from 2004 to 2016)

Gohar Eslami[1], Azade Panji[2], Hosein Firoozi[3], Fatemeh Hosseinzadeh[4], Siavash Moradi[5], Ali Mohammadpour-Mir[6], *Mohammad Sadegh Rezai[7]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Cardiovascular Research Center, Mazandaran University of Medical Sciences, Sari, Iran. [2]Pharmacologist, Student Research Center, Mazandaran University of Medical Sciences, Sari, Iran. [3]Neonatologist, Department of Pediatrics, Ramsar Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. [4]Midwife, Pediatric Infectious Diseases Research Center, Mazandaran University of Medical Sciences, Sari, Iran. [5]Gastrointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran. [6]Pediatric Infectious Diseases subspecialist, Non-communicable Pediatric Diseases Research Center, Babol University of Medical Sciences, Babol, Iran. [7]Pediatric Infectious Diseases Subspecialist, Pediatric Infectious Diseases Research Center, Mazandaran University of Medical Sciences, Sari, Iran.

Abstract

Background: Pleural empyema is a collection of purulent exudate between the lungs and the chest wall. Despite the importance of the disease in children, no study has investigated it in Mazandaran province, Iran. The aim of this study was to evaluate the prevalence, clinical manifestations, diagnosis, treatment and its outcome in children referring to hospitals of Mazandaran during 12 years.

Materials and Methods: In this cross-sectional study, medical records of all children aged 0 to 18 years admitted to 5 educational hospitals of Mazandaran province, Iran, with Tenth Revision, Clinical Modification (ICD-10-CM) codes confirming pleural empyema or effusion from March 2004 to 2016 were identified retrospectively. The clinical records were reviewed for demographic information, hospitalization information, medications, symptoms; laboratory and medical imaging results and the patient's condition on discharge were recorded. Statistical analysis was performed by SPSS version 20.0 software.

Results: Of 50 patients with the mean age of 7.08±5.6 years, 31(62%) were boys and empyema incidence was higher (58%) in 5-18 year-old children. The mortality rate was 12% (6 patients). The most common microorganisms were Escherichia coli and Klebsiella (33.3%). In 17(34%) patients, antipyretics were prescribed prior to admission and pre-admission treatment regimen included beta-lactams with or without macrolides. The most commonly prescribed drug regimens were vancomycin and beta-lactam (50%), and the most common drug resistance of microorganisms was to ampicillin, cephalexin and ceftazidime.

Conclusion: Since most of the gram-negative organisms in Mazandaran hospitals were Extended-Spectrum Beta-Lactamases (ESBL) and all the microorganisms of this study were susceptible to gentamicin, it is suggested to consider it in empiric therapy of pediatric pleural empyema in Mazandaran province. Also, lower rate of surgical intervention in children who received pre-admission antibiotics highlights the importance of antibiotic intervention before admission.

Key Words: Anti-Bacterial Agents; Children, Empyema, Chest tubes, Pleural, Pediatrics.

*Please cite this article as: Eslami G, Panji A, Firoozi H, Hosseinzadeh F, Moradi S, Mohammadpour-Mir A, et al. The Survey of Pediatric Pleural Empyema in North of Iran (2004 to 2016). Int J Pediatr 2018; 6(3): 7421-32. DOI: **10.22038/ijp.2018.29138.2545**

Corresponding Author:

Mohammad Sadegh Rezai, MD. Address: Pediatric Infectious Diseases Research Center, BouAli Hospital, Pasdaran Boulevard, Sari, Iran. Postal code: 48158-38477.
Email: drmsrezaii49@gmail.com
Received date: Dec.12, 2017; Accepted date: Jan.22, 2018

1- INTRODUCTION

Pleural infection is an ancient disease that remains an important clinical problem (1). Despite being recognized for over two millennia, pleural infection is one of the oldest and severest diseases with an increasing incidence in many countries (2). Pleural empyema is a collection of purulent exudate between the lungs and the chest wall (3). Pediatrics pleural effusion is an abnormality that frequently develops from collection of fluids in the pleural space and commonly caused by a primary phenomenon or secondary to variety of disorders such as infections (4).

The incidence of this disease decreased rapidly after antibiotic use, representing 5% of pneumonias in the pre-antibiotic era, and 2% in the post-antibiotic era (5). However, the incidence of pleural infection has increased in recent years (1, 6). Causes for the increase in incidence remain uncertain, but changes in primary care antibiotic prescribing and bacterial virulence and antibiotic susceptibility, the use of a wide range of pneumococcal vaccines in children, and delayed hospital presentation have been suggested (5, 7, 8).

The etiological mechanisms of pleural effusion is considerably different in childhood and the effusion secondary to pleural infections is the most common cause of this abnormality in children (4). The development of pleural empyema is determined by a balance between host resistance, bacterial virulence, and timing of presentation for medical treatment. Management of empyema includes antibiotics and procedural interventions to drain the pleural space (9). Chest x-ray (CXR) is the first simplest imaging strategy to etiological assesses of pleural empyema in children (4). Next step is ultrasonography that easily permits characteristics of empyema (10). In those conditions with sufficient effusion size thoracentesis is recommended. The initial diagnostic test for the aim of diagnosis is analysis of the pleural fluid (7). Prompt treatment with appropriate systemic antibiotics and chest tube drainage are the key to success (1). A variety of procedural interventions are used for the management of empyema including Video-assisted thoracoscopic surgery (VATS), early thoracotomy or chest tube placement with instillation of fibrinolytics (9). According to studies conducted in Iran and other countries, the incidence of pleural effusion and resistant cases is increasing (2, 3, 5-7, 11-19). Despite the importance of the occurrence of pleural empyema in children, yet no study have been performed to investigate the prevalence, clinical manifestations, diagnosis, treatment and the outcomes of children with pleural empyema in Mazandaran province, Iran. Having such information will be effective by identifying the current state of the pleural empyema and identifying problems in reducing the incidence, diagnosing the disease faster, timely and appropriate treatment, and improving the prognosis of the patients (20).

2- MATERIALS AND METHODS

2-1. Study design and population

In this cross-sectional census study, medical records of all children aged 0 to 18 years admitted to educational hospitals of Bouali Sina (Sari), Imam Khomeini (Sari), Shahid Zare (Sari), Razi (Ghaemshahr), and Shafizadehn (Babol) in Mazandaran province with ICD-10-CM (J86.9 and J90) discharge codes for the study period March 2004 to 2016 were identified, retrospectively.

2-2. Methods

For each patient, a checklist including demographic information, hospitalization information, history of treatment, underlying diseases, presenting symptoms, date of fever from symptoms onset, laboratory results, ultrasound, presence of

loculations, the duration and output of chest drain placement, medical decisions and the patient's condition on discharge were recorded. Validity of the checklist was confirmed by 5 infectious diseases subspecialists. Also, medical records were reviewed for days of post-operative intubation, post-operative complications, and length of hospitalization and children who died at the end of the hospitalization due to complications of empyema were recorded as mortality.

2-3. Ethical consideration

This study was reviewed and approved by the Mazandaran University of Medical Sciences' Ethics Committee (Ethics number: IR.MAZUMS.REC.96.2340).

2-4. Inclusion and exclusion criteria

The clinical records were reviewed and cases of pleural empyema or effusion were identified. Patients with fever, clinical signs of pneumonia (cough and shortness of breath), the presence of consolidation in chest X-ray, positive bacterial smear and culture, pH<7.2, Lactate dehydrogenase (LDH)> 1000 IU/L, glucose>40 mg/dL in pleural fluid, presence of leukocytosis with shift to left, were included. Cases of incomplete medical records, suspicious diagnosis and referral patients from other provinces were excluded.

2-5. Data Analyses

All data were statistically compared and statistical and descriptive analyses were performed using IBM SPSS software, version 21.0. Determining the distribution of data was performed by plotting the histogram and Kolmogorov-Smirnov test. Quantitative data was presented as mean ± standard deviation (SD) qualitative data was presented with frequency and percentage. To analyze the data, correlation analysis, Pearson coefficient, ANOVA and appropriate follow-up tests such as Tukey and Scheffe tests were used. The time-to-event analysis was performed to investigate the incidence of death in various drug regimens, and the results were analyzed by performing log rank test. In all cases, the p value less than 0.05 was considered statistically significant.

3- RESULTS

In this study investigating the prevalence, clinical manifestations, diagnosis, treatment and outcomes of pleural empyema children in Mazandaran province, a total of 50 patients were admitted with the diagnosis of empyema during the study period and fulfilled the study definition for empyema. Of them, 31(62%) were boys and the mean age of the patients was 7.08±5.6 years (range 0 months-18 years). Two cases aged less than one month, 10 in the age group of 1-12 months, 9 in the age group of 1-5 years and 29 cases were in the age group of 5-18 years. Empyema incidence (58%) was highest in children aged 5-18 years.

Figure.1 shows the annual distribution of patients with pleural empyema in Mazandaran province during 2004 to 2016.

In terms of admitted hospital, 2 patients were admitted to Razi Hospital of Ghaemshahr, 13 were admitted to Shafizade Hospital of Babol and 35 at Bouali Hospital of Sari. No medical records for pediatric empyema were found in Imam Khomeini and Shahid Zare hospitals of Sari. The most common bacterial isolates were Escherichia coli (E. coli), and Klebsiella equally in 33.3%, Enterobacter species in 22.2%, and Staphylococcus saprophyticus, Staphylococcus aureus and Serratia equally in 11.1%. The mean duration of hospitalization was 15±9.33 days and the duration of symptoms before admission was 12.0±7.7 days. Twelve patients had a history of admission to other centers (9.0±10.56 days), and 52% of the patients received medication for 9.0±6.66 days

prior to admission. The most common primary diagnosis was pneumonia (14%), thoracic mass (6%), and pleural effusion (4%). The medication used before admission was antipyretic in 34%, beta-lactams in 30%, macrolide in 10% and 4% used other drugs. Thirty patients (60%) had complaint of fever, chills, nausea and shortness of breath, chest pain, loss of appetite and weight, and lethargy (**Table.1**). Blood culture was requested in 40% (20 cases) of the patients, of which 10% (2 ones) had positive results and in both patients, Klebsiella was detected to be resistant to gentamicin, ampicillin, cephalexin, ceftazidime, ceftriaxone, and ampicillin (50%). Pleural fluid smear and culture were performed in 62% (31 patients), of which 14% (7 cases) were positive and all patients had pleural empyema. In diagnosis of pleural effusion with CXR, 2% (1 patient) was less than Hemithorax, 72% (36 patients) had unilateral effusion and 16% (8 subjects) had bilateral pleural effusion. In 16% (8 cases) pneumothorax was unilateral and in 2% (1 case) bilateral pneumothorax was found. Ultrasound finding in 6% (3 patients) showed cardiac and tracheal tube deviation, in 4% (2 cases) cardiomegaly and in 4% (2 cases) lobar pneumonia (**Tables 2, 3**).

The most commonly prescribed medications prior to admission were antipyretics (34%) and beta-lactams (30%). Among antipyretics, acetaminophen (28%) was administered more than ibuprofen (10%) and other drug (4%) prior to admission. 26% of patients who received antipyretic agents and 26% had pleural effusion and 8% suffered from pleural empyema, but this finding was not statistically significant (p=0.367). For 56% (28 people) of the patients, chest tube was inserted for an average of 11.0±10.02 days. The number of thoracotomies was 8(16%), decortication in 8(16%) and 5(10%) were treated with lobectomy.

Complications during treatment were found in 20% (10 patients) of the patients, of which 5 were pneumothorax and 5 were bronchopleural fistula complications. The time to resolve fever after antibiotic treatment was 6.74±8.0 days. The mean hospitalization period for patients with chest tube was 19.8±10.8 days and in those without chest tube, it was 10.8±5.8 days (r= -0.46 and p=0.001). The length of hospitalization period for patients undergoing surgery was 15.8±8.1 days and 15.6±10.8 days for patients who did not undergo surgery and this difference was not statistically significant (p=0.9).

From 19 patients who had surgery, only 1 patient had received antibiotics prior to admission (p=0.0001). Of the patients who presented with pneumonia, ultimately, 15 patients were diagnosed with pleural effusion and 4 were diagnosed with pleural empyema and this difference was not statistically significant (p=0.220). Among the different treatments used for patients, only surgical treatment was correlated with prognosis of the disease (r=0.3 and p=0.046). There was no significant difference between the mean fever time in four groups of drug regimens (p=0.95). Also, 30% of the patients had underlying disease and no significant correlation was found between plural empyema and underlying disease (p=0.80).

Chest tubing increased the hospitalization duration (19.8±10.8 days vs 10.8±5.8 days), and the correlation between chest tube placement and hospitalization duration was statistically significant (r= -0.46, p=0.001). There was only one positive blood culture in both effusion and empyema patients and it was not statistically significant (p=0.332). There was no positive culture in patients with pleural effusion but 7 cases (14%) of empyema were positive for pleural fluid culture (p= 0.3). The length of hospitalization period was not statistically significant for patients undergoing surgery

and patients who did not undergo surgery (15.8±8.1 vs. 15.6±10.8 days, p=0.9). Of the 19 patients who had surgery, only 1 patient had received antibiotics prior to admission (p=0.0001).

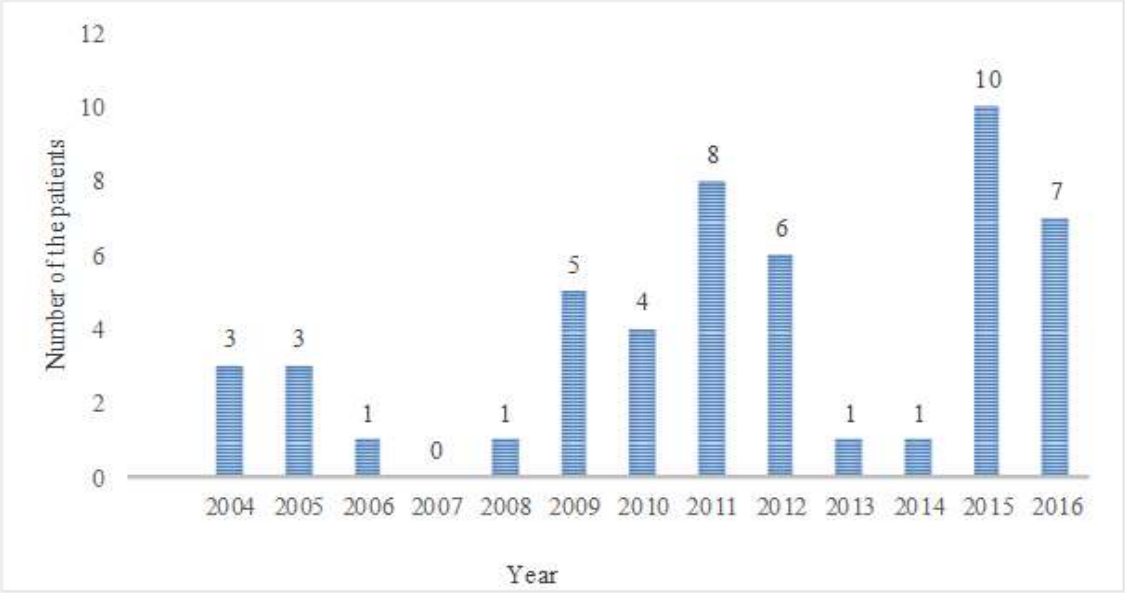

Fig.1: The annual distribution of children with pleural empyema in Mazandaran province, Iran.

Table-1: The frequency of clinical findings during examination in patients with pleural empyema

Clinical finding	Frequency	Percent
Fever	39	78
Cough	28	56
Respiratory distress	24	48
Vomiting	9	18
Abdominal pain	13	26
Diarrhea	4	8
Chest pain	18	36
Tachypnea	14	28
Reduced respiratory sound	32	64
Abnormal pulmonary auscultation	5	10
Tachycardia	11	22
Hepatomegaly	3	6

Table-2: The ultrasound findings in children with pleural effusion

Ultrasound finding	Frequency	Percent
Pleural thickness	2	7.14
Loculation	4	14.28
Air-liquid	2	7.14
Free liquid	2	7.14
Debris and remaining particles	1	3.57
Bilateral effusion	3	10.71
Debris along with free fluid	2	7.14
Pleural thickness along with free fluid	1	3.57
Unilateral pleural effusion	11	39.28
Total	28	100

Table-3: CT scan findings for children with pleural empyema

CT scan findings	Frequency	Percent
Pleural thickness	4	25.0
Loculation	4	25.0
Air-liquid	1	6.25
Pleural effusion	7	43.75
Total	16	100

CT scan: Computed Tomography.

Table-4: Success report of the most commonly prescribed drug regimen in admission

The most commonly prescribed drug regimen	Discharge with continuing antibiotic treatment	Discharge without continuing antibiotic treatment	Death
Beta-lactam	5	2	2
Vancomycin + beta-lactam	12	2	3
Clindamycin + beta-lactam	4	3	1
Clindamycin + Vancomycin + beta-lactam	4	1	0

4- DISCUSSION

Empyema in children usually develops as a complication in 0.6% of bacterial pneumonias (21, 22). Empyema is a known complication of pneumonia yet the frequency of this complication is not well documented in Mazandaran province. This study investigated the clinical features and outcomes of empyema in 0-18 year-old children presenting to Hospitals in North of Iran. In this study incidence of empyema was highest in children aged 5-18 years and in boys higher than girls. In accordance with our study, in some studies the prevalence of pleural effusion in boys was higher than girls (6, 15, 19, 23). Contrary to us, Burton et al., and Hailu reported higher prevalence in children aged less than 5 years (15, 23). In this study, the incidence of empyema during 12 years increased from 6 to 14% (average prevalence = 7.5 years). In the study of Krenke et al., the prevalence of pleural effusion increased from 5.4% to 18.8% during ten years (19). Mahon et al. reported a ten-fold increase in pleural effusion during 15 years (6), and Munoz-Almagro et al. reported 2.4 times increase (7). It is probable that the number of cases of pediatric empyema was underestimated in our study due to lack of access to medical records or incomplete records and use of a pneumococcal vaccines in their children. Additionally, it is possible that the some patients had empyema based on Polymerase chain reaction (PCR) or pleural fluid criteria but were not identified because these tests were not performed in these centers. The most common bacterial isolate in our study were Escherichia coli, Klebsiella, and Enterobacter species. Some studies have reported increased Staphylococcus aureus empyema incidence over the previous decade (23-25). In Krenke et al. and Hardie et al.'s study, the most commonly identified bacteria detected by PCR method was Streptococcus pneumonia (19, 26).

In Mahon et al.'s study 63% of the cases of empyema and Staphylococcus aureus was most frequently isolated organisms and 26% of Staphylococcus aureus isolates were Methicillin-resistant Staphylococcus aureus (MRSA). Streptococcus pneumonia was the causative organism in 41% and Streptococcus pyogenes in 9% of cases (6). The reason why Streptococcus pneumonia and Haemophilus influenza

have not been found in our study can be the difficulty to growth of Haemophilus influenza. Another reason is applying PCR detection method in other studies which enables growth of many organisms. Also, most of the studies evaluated pneumonia patients and in our study, some patients had previous history of antibiotic use and this negatively impacted the culture results (27). In this study, chest tube placement and antibiotic therapy were the most prevalent procedures while in Mahon et al.'s study, surgery was the preferred procedure (6). Antibiotics remain a key component in medical management of empyema (9, 28, 29).

In the present study, the success rate of thoracotomy was higher than that of decortication, and 20% of the patients had bronchopleural and pneumothorax fistula complications. Lau et al.'s study demonstrated a strong association between delay in operation and prolonged hospitalization. Timely surgery is recommended as it promotes early recovery and shorter hospitalization (30). Goldschlager et al. found that thoracoscopic drainage is an effective procedure for treating empyema in children. It is less invasive than open thoracotomy and is associated with less patient discomfort and less severe pain as measured by objective pain scores (31).

Of 28 patients (56%) who underwent chest tube placement, 4 had bronchopleural fistula and 4 had pneumothorax complications. Therefore, of 8 patients with thoracotomy, 1 person suffered from pneumothorax. After decontamination of the 8 patients, 2 patients had pneumothorax and 4 patients had bronchopleural fistula. In this study, the most commonly prescribed medications prior to admission were antipyretics and betalactams. Also, 26% of patients who received antipyretic agents had pleural effusion and 8% suffered from pleural empyema, but this finding was not statistically significant. In Elemraid et al.'s study, ibuprofen prescription more than other medications was an independent risk factor associated with empyema (32). According to Zampoli et al., cumulative doses of more than 78 mg/kg of Ibuprofen are associated with a 2.5-fold increase in the risk of pneumonia (2). The reason for insignificant finding in our study can be due to the lower number of patients in our study than other studies, which needs further studies. Also, in our study Acetaminophen was prescribed more than Ibuprofen. It can also be due to the higher administration of acetaminophen than other antipyretics in our study. In the present study, 38% of the patients received antibiotics before admission and of 17 patients who underwent surgery, only one patient received antibiotics before admission. In Grant et al.'s study, 40% of children received antibiotics before admission (33).

In Krenke et al.'s study, 61% of children received antibiotics before admission, and the first line antibiotic treatment included ampicillin or amoxicillin/Clavulanic acid with or without macrolides (19). The potential choice of antibiotics should be guided by local antimicrobial policies that consider susceptibility patterns, specifically the prevalence of MRSA (9). In our study, the pre-admission treatment regimen included beta-lactams such as Penicillins with or without macrolides. In a study by Mahon et al., 35% of children with pleural empyema had preadmission antibiotics and these children needed 40% less surgical intervention than untreated people (6). In Grant et al.'s study, 61% of children received no antibiotics prior to admission (33). Crocker et al.'s study showed the association between primary care antibiotic prescribing and increased pneumonia and empyema hospitalization rates in children (16). Antibiotics for lower respiratory tract infection in primary care have been shown at a population level to

reduce respiratory morbidity and mortality in children (34-37). According to the findings of the present study, the higher need to surgical intervention in children who did not receive antibiotics prior to admission showed the importance of antibiotic intervention before admission. Also, antibiotics prescribed for a respiratory tract infection may protect against subsequent hospital presentation for pneumonia or empyema in some children (16). In this study, the most common microorganisms were Enterobacteriaceae which were more resistant to cephalosporins, ampicillin and cotrimoxazole and most sensitive to gentamicin and imipenem. The results of Fried et al.'s study was consistent with our findings (38). In Nakhaei and Moshrefi's study in Mashhad, the most common resistance was to Cotrimoxazole and the most sensitivity to Imipenem (39). In the study of Goodarzi et al. in Iran, the highest resistance was to ampicillin (40).

Srisangkaew and Vorachit's study showed high resistance to third-generation cephalosporins in Thailand (41). Chibuk et al. stated that initial empirical antibiotic choice, in the absence of a confirmed organism, would be cefotaxime or ceftriaxone, with some experts adding clindamycin to better cover MRSA (9). Adding vancomycin (or linezolid) instead of clindamycin is another option, and is usually reserved for culture-proven or severe suspected MRSA pneumonia (9). It is advisable to pay more attention to antibiotic test results in order to prevent the occurrence of drug resistance with minimal complications (42). In this study, the mortality rate was 12%, among which the highest mortality was in the age group of children under 12 months. In the study of Mahon et al. mortality rate was 2.88% in three 6 month-old children (6). In Hailu et al.'s study in Ethiopia, the case fatality rate was 16% (23). In de Britto et al.'s study, the lethality of pleural empyema was 7.8% (17). The higher mortality rate in our study compared to some studies may be attributed to earlier diagnosis and advanced diagnostic equipment like PCR which was not performed in our centers previously. There is great variation worldwide in the management of patients with pleural infection, and approaches differ between physicians especially in developing countries due to the absence of facilities (2). Early diagnosis and proper treatment of pneumonia prevents the development of empyema (23).

The process of rapid evaluation and therapeutic intervention appears to reduce morbidity and mortality, as well as healthcare costs (43). Moreover, the type of employed treatment regimens can also affect the prognosis of pleural effusion in children so that a higher mortality rate for children treated with antibiotics and chest tubes compared with those treated with fibrinolytic therapy, VATS or thoracotomy has been reported (44). Patients who undergo primary operative therapy may have a lower mortality rate, length of stay, and duration of antibiotic therapy (21).

5- CONCLUSION

All the microorganism found in this study were susceptible to gentamicin, therefore it is suggested to consider it as an empirical therapy of children with pleural empyema in this region because in our previous studies (20, 45-52), gram-negative organisms in educational centers of Mazandaran hospitals, as well as Neonatal Intensive Care Units (NICUs), and the Paediatric Intensive Cares (PICUs) of Mazandaran province were Extended-Spectrum Beta-Lactamases (ESBL), and empirical treatment with third generation cephalosporins has a strong resistance. Also, multi-antibiotic resistance was observed among the patients (53,54). Therefore, gentamicin should be added to the third generation cephalosporins or other classes of antibiotics such as

imipenem and meropenem should be administered in this region (55, 56). We suggest that linzolid or Teicoplanin, which are indicated for the treatment of vancomycin resistant staphylococcus aureus infection, should be prescribed instead of vancomycin. Concerning the fact that antibiotic treatment with early surgical approach was associated with lower mortality rate, it is recommended to apply early surgery with antibiotic prescription in management of pediatric pleural empyema. It is believed that early VATS (or thoracotomy if VATS is not possible) leads to shorter hospitalization (21). So, early antibiotic prescribing for children with respiratory tract infection in primary care is recommended to prevent empyema and its complications.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

This study was part of a pharmacology thesis of Ramsar Pardis and was supported by a grant of Mazandaran University of Medical Sciences, Research Council, Sari, Iran. The authors thank all those who helped us in this study.

8- REFERENCES

1.Kwon YS. Pleural infection and empyema. Tubercul & Resp Dis. 2014;76(4):160-2.

2.Zampoli M, Kappos A, Wolter N, von Gottberg A, Verwey C, Mamathuba R, et al. Etiology and incidence of pleural empyema in South African children. Ped Infect Dis J. 2015;34(12):1305-10.

3.Simbi KA, Kazadi V, Aissi L-M, Katsuva FM, Luboya NO, Tshilolo L, et al. Pediatric pleural empyema: one of the management challenges in children of Democratic Republic of Congo. La Pediatria Medica e Chirurgica. 2017;39(2):131 .

4.Izadi M, Ajudani R, Khosravi MH. Pleural Effusion in Children: A Review Article and Literature Review. Int J Med Rev. 2016;3(1):365-70.

5.Burgos J, Falcó V, Pahissa A. The increasing incidence of empyema. Curr Opin Pulm Med. 2013;19(4):350-6.

6.Mahon C, Walker W, Drage A, Best E. Incidence, aetiology and outcome of pleural empyema and parapneumonic effusion from 1998 to 2012 in a population of New Zealand children. J Paed & Child Health. 2016;52(6):662-8.

7.Munoz-Almagro C, Selva L, Pallares R. Influence of pneumococcal vaccine on the incidence of empyema. Curr Opin Pulm Med. 2010;16(4):394-8.

8.Rezai MS, Ghaffari J, Mahdavi M, Bahari A, Ala S. Conjugate and 23-valent pneumococcal polysaccharide booster vaccination in asplenic patients with thalassemia major: A randomized clinical trial study. Casp J Internal Med. 2017;8(1):16.

9.Chibuk T, Cohen E, Robinson J, Mahant S, Hartfield D. Paediatric complicated pneumonia: diagnosis and management of empyema. Paediatr Child Health. 2011;16(7):425-9.

10. Givan DC, Eigen H. Common pleural effusions in children. Clin Chest Med. 1998 Jun;19(2):363-71.

11. GBD 2015 Eastern Mediterranean Region LRI Collaborators, Mokdad AH. Burden of lower respiratory infections in the Eastern Mediterranean Region between 1990 and 2015: findings from the Global Burden of Disease 2015 study. I Int J Public Health. 2017 Aug 3. 1-12. doi: 10.1007/s00038-017-1007-10.

12. Kargar Maher MH, Rahkar Farshi M, Bilan N, Jalilzadeh-Binazar M, Teimouri-Dereshki A, Abdinia B. Evaluation and outcomes of pediatric pleural effusions in over 10 years in Northwest, Iran. Int J Ped. 2014;2(3.2):41-6.

13. Saffar MJ, Rezai MS. Management of lower respiratory tract illnesses in developing countries: A narrative review. J Ped Rev. 2014;2(2):47-56.

14. Saffar M, Enayti A, Abdolla I, Razai M, Saffar H. Antibacterial susceptibility of uropathogens in 3 hospitals, Sari, Islamic

Republic of Iran, 2002-2003. East Mediterr Health J. 2008;14(3):556-63.

15. Burton C, Walls T, Price N, Glasgow T, Walker C, Beasley S, et al. Paediatric empyema in New Zealand: a tale of two cities. 4 2015;128(1415):25-33.

16. Crocker JC, Powell CV, Evans MR, Hood K, Butler CC. Paediatric pneumonia or empyema and prior antibiotic use in primary care: a case–control study. J Antimicrob Chemotherapy. 2011;67(2):478-87.

17. de Britto MCA, da Conceicao Silvestre SMM, do Carmo Menezes Duarte M, de Matos Bezerra PG. Clinical profile of pleural empyema and associated factors with prolonged hospitalization in paediatric tertiary centre in Angola, Luanda. Tropic Doc. 2008;38(2):118-20.

18. Fletcher MA, Schmitt H-J, Syrochkina M, Sylvester G. Pneumococcal empyema and complicated pneumonias: global trends in incidence, prevalence, and serotype epidemiology. Eur J Clin Microbiol Infect Dis. 2014;33(6):879-910.

19. Krenke K, Sadowy E, Podsiadły E, Hryniewicz W, Demkow U, Kulus M. Etiology of parapneumonic effusion and pleural empyema in children. The role of conventional and molecular microbiological tests. Resp Med. 2016;116:28-33.

20. Rezai MS, Bagheri–Nesami M, Nikkhah A, Bayg AHA. Incidence, risk factors, and outcome of ventilator-associated Pneumonia in 18 hospitals of Iran. Running title: ventilator-associated pneumonia in Iran. Int J Adv Biotechnol & Res. 2016;7(3):936-46.

21. Scarci M, Zahid I, Billé A, Routledge T. Is video-assisted thoracoscopic surgery the best treatment for paediatric pleural empyema? Interact Cardiovasc Thorac Surg. 2011;13(1):70-6.

22. Rezai MS, Shahmohammadi S. Nosocomial Infections in Iranian Pediatric Patients With Burn Injuries: A Review. J Ped Rev. 2015;3(2): e680.

23. Hailu S. Paediatric thoracic empyema in an Ethiopian referral hospital. East Afr Med J. 2000;77(11):618-21.

24. Strachan RE, Cornelius A, Gilbert GL, Gulliver T, Martin A, McDonald T, et al. Bacterial causes of empyema in children, Australia, 2007–2009. Emerg Infect Dis. 2011;17(10):1839-45.

25. Wright N, Hammond P, Morreau P, Hamill J. Increased incidence of empyema in Polynesian children. Surgery. 2011;3:2-6.

26. Hardie W, Bokulic R, Garcia VF, Reising SF, Christie CD. Pneumococcal pleural empyemas in children. Clin Inf Dis. 1996;22(6):1057-63.

27. Behzadnia S, Davoudi A, Rezai MS, Ahangarkani F. Nosocomial infections in pediatric population and antibiotic resistance of the causative organisms in north of iran. Iran Red Cres Med J. 2014;16(2): e14562..

28. Navaeifar MR, Rezai MS. Device associated nosocomial infection in children. J Ped Rev. 2013;1(2):25-41.

29. Fahimzad A, Eydian Z, Karimi A, Shiva F, Sayyahfar S, Rahbarimanesh AA, et al. Surveillance of Antibiotic Consumption Point Prevalence Survey 2014: Antimicrobial Prescribing in Pediatrics Wards of 16 Iranian Hospitals. Arch Iran Med. 2016;19(3):204.

30. Lau C, Fung C, Wong K, Tam P. Timely thoracoscopic decortication promotes the recovery of paediatric parapneumonic empyema. Ped Surg Int. 2015;31(7):665-70.

31. Goldschlager T, Frawley G, Crameri J, Taylor R, Auldist A, Stokes K. Comparison of thoracoscopic drainage with open thoracotomy for treatment of paediatric parapneumonic empyema. Ped Surg Int. 2005;21(8):599-603.

32. Elemraid MA, Sails AD, Eltringham GJ, Perry JD, Rushton SP, Spencer DA, et al. Aetiology of paediatric pneumonia after the introduction of pneumococcal conjugate vaccine. Eur Resp J. 2013;42(6):1595-603.

33. Grant C, Harnden A, Mant D, Emery D, Coster G. Why do children hospitalised with pneumonia not receive antibiotics in primary care? Arch Dis Child. 2012;97(1):21-7.

34. Petersen I, Johnson A, Islam A, Duckworth G, Livermore D, Hayward A. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the

UK General Practice Research Database. BMJ. 2007;335(7627):982.

35. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.

36. GBD 2016 Mortality Collaborators. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet (London, England). 2017;390(10100):1084-150.

37. GBD 2015 Eastern Mediterranean Region Neonatal, Infant, and under-5 Mortality Collaborators, Mokdad AH. Neonatal, infant, and under-5 mortality and morbidity burden in the Eastern Mediterranean region: findings from the Global Burden of Disease 2015 study. Int J Public Health. 2017:1-15. doi: 10.1007/s00038-017-0998-x. [Epub ahead of print]

38. Farid S, Peeri Dogaheh H, Ghiami Rad M. Prevalence of SHV-1 Type Extended-Spectrum β-Lactamases in Enterobacteriaceae Isolated from Urinary Samples in Ardabil, Iran. J Ardabil Univ Med Sci. 2015;15(3):311-9. [Fulltext in persian].

39. Nakhaei M, Moshrefi S. Determining the antibiotic resistance pattern of urinary isolates od escherichia coli and prevalence of extended spectrum ß-lactamases (ESBLS) among them. J Sabzevar Univ Med Sci. 2010;16(4):228-33. [Fulltext in persian].

Infection in Children: A Narrative Review. J Pediatr Rev. 2017 (In Press): e11562. doi: 10.5812/jpr.11562..

47. Rezai S, Peyravii Ghadikolaii F, Ahanjan M, Valadan R, Ahangarkani F, Ghara N. Prevalence of Nasal Carriage Methicillin-Resistant Staphylococcus aureus with mecA Gene among Healthy Primary School Boys in North of Iran; A Cross-Sectional Study. Int j Ped. 2017;5(12):6515-25.

48. Bagheri-Nesami M, Rezai MS, Ahangarkani F, Rafiei A, Nikkhah A, Eslami G, et al. Multidrug and co-resistance patterns of non-fermenting Gram-negative bacilli

40. Goudarzi G, Momeni Mofrad S, Shakib P. The prevalence of extended-spectrum betalactamases among uropathogenic Escherichia coli isolates from Ibn Sina hospital of Delfan, Lorestan. Yafte. 2014;16(2):17-23. [Fulltext in persian].

41. Srisangkaew S, Vorachit M. The optimum agent for screening and confirmatory tests for extended-spectrum beta-lactamases in Escherichia coli and Klebsiella pneumoniae in Ramathibodi Hospital, Thailand. J Infect Dis Antimicrob Agents. 2004;21:1-5.

42. Eslami G, Salehifar E, Behbudi M, Rezai MS. Rational Use of Amikacin in Buali-Sina Hospital in Sari 2011. J Maz Univ Med Sci. 2013;23(100):2-9. [Fulltext in persian].

43. Sommerburg O, Schenk J, Mall M. Lung diseases in children. Der Radiologe. 2015;55(7):545-53.

44. Byington CL, Spencer LY, Johnson TA, Pavia AT, Allen D, Mason EO, et al. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations. Clin Infect Dis. 2002 Feb 15;34(4):434-40.

45. Rahimzadeh G, Gill P, Rezai M S. Characterization of Methicillin-Resistant Staphylococcus aureus (MRSA) Phages From Sewage at a Tertiary Pediatric Hospital. Arch Pediatr Infect Dis. 2017 ;5(1):e39615. doi: 10.5812/pedinfect.39615.

46. Rahimzadeh G, Gill P, Rezai MS. Endolysins of Bacteriophages as an Anti-Methicillin Resistant Staphylococcus Aureus

involved in ventilator-associated pneumonia carrying class 1 integron in the North of Iran. Germs. 2017;7(3):123.

49. Pourmousa R, Dadashzadeh R, Ahangarkani F, Rezai MS. Frequency of Bacterial Agents Isolated From Patients With Chronic Sinusitis in Northern Iran. Glob J Health Sci. 2015;8(5):239-46.

50. Eslami G, Rezaie MS, Salehifar E, Rafiei A, Langaie T, Rafati MR, et al. Epidemiology of extended spectrum beta lactamases producing E. coli genes in strains isolated from children with urinary tract infection in north of

Iran. J Maz Univ Med Sci. 2016;25(132):270-9. [Fulltext in persian]

51. Rezai MS, Salehifar E, Rafiei A, Langaee T, Rafati M, Shafahi K, et al. Characterization of multidrug resistant extended-spectrum beta-lactamase-producing Escherichia coli among uropathogens of pediatrics in North of Iran. Biomed Res Int. 2015;2015:309478.

52. Rahimzadeh G, Gill P, Rezai MS. Characterization and lytic activity of methicillin-resistant Staphylococcus aureus (MRSA) phages isolated from NICU. Australasian Med J. 2016;9(6):169-75.

53. Rezai MS, Rafiei A, Ahangarkani F, Bagheri-Nesami M, Nikkhah A, Shafahi K, et al. Emergence of extensively drug resistant acinetobacter baumannii-encoding integrons and extended-spectrum beta-lactamase genes isolated from ventilator-associated pneumonia patients. Jundishapur J Microb. 2017;10(7): e14377.

54. Rezai MS, Pourmousa R, Dadashzadeh R, Ahangarkani F. Multidrug resistance pattern of bacterial agents isolated from patient with chronic sinusitis. Caspian J Intern Med. 2016 Spring;7(2):114-9.

55. Rezai MS, Bagheri-nesami M, Hajalibeig A, Ahangarkani F. Multidrug and Cross-resistance Pattern of ESBL-producing Enterobacteriaceae Agents of Nosocomial Infections in Intensive Care Units. J Maz Univ Med Sci. 2017;26(144):39-49. [Fulltext in persian]

56. Bagheri-Nesami M, Rafiei A, Eslami G, Ahangarkani F, Rezai MS, Nikkhah A, et al. Assessment of extended-spectrum β-lactamases and integrons among Enterobacteriaceae in device-associated infections: multicenter study in north of Iran. Antimicrob Resist Infect Control. 2016;5(1):52.