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Analysis of Antibiotic Treatment and Microbiological Findings and Its Implication on Outcome in Patients with Parapneumonic Effusions

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Abstract

BACKGROUND: Parapneumonic effusion (PPE), as a complication of community-acquired pneumonia, sometimes progresses into complicated PPE (CPPE) and empyema, thus becoming a significant clinical problem. There is a lack of guidelines for antibiotic therapy and reports on local microbiological status and resistance of microorganisms.

AIM: The paper is focused on the analysis of antibiotic therapy and microbiological findings that are affecting patient outcomes and length of treatment.

METHODS: We analyzed 94 patients, 50 with uncomplicated PPE (UCPPE) and 44 with CPPEs.

RESULTS: More patients (59.57%) were male, average age 53.82 ± 17.5 years. Alcoholism was the most common comorbidity in patients with CPPE registered in 25% of patients. A positive pleural punctate culture was present in 31.82% of patients with CPPE. *Peptostreptococcus* was most often isolated in 28.57%. Blood culture was positive in 12.76% of patients. Most of the patients were treated with combined therapy that also covered anerobes (64.89%). Statistical differences existed in terms of days of hospital treatment with a longer hospital stay for patients with CPPE ($p < 0.0001$). The average time of hospital treatment in patients with UCPPE was 15 days, and in patients with CPPE, it was 21 days.

CONCLUSION: As soon as a pleural infection is noted, patients should receive antibiotic therapy, which should be based on pleural fluid culture. Anerobic coverage is required. In this way, the development of CPPE and empyema will be prevented, and thus, mortality and long hospital stays will be reduced.

Introduction

Pleural infection is a centuries-old serious respiratory illness, first described by Hippocrates of Kos (460–377 BC) who recognized that "pneumonia coming on pleurisy is bad" [1]. Parapneumonic effusions (PPEs) occur in 20–40% of patients who are hospitalized with community-acquired pneumonia (CAP) like most common complication [2]. The mortality rate in patients with PPE is higher than that in patients with pneumonia without PPE [2]. In one study, the morality risk was 6.5 times higher if the effusions were bilateral, whereas the mortality risk was 3.7 times higher if the effusions were unilateral [3]. Some of the excess mortality has resulted to inadequate antibiotic treatment of patients with pneumonia or PPE [2], [4]. In patients with comorbidities, there is a greater possibility of developing PPE [2].

The evolution of a PPE can be divided into three stages that represent a continuous spectrum [4], [5]. There is uncomplicated PPE (UCPPE), which is sterile exudative pleural effusion, resolves following treatment with antibiotics [2], [6]. A minority becomes secondarily infected complicated PPE (CPPE), and sometimes, drainage is required for resolution [6]. CPPE occurs in 10% of all patients hospitalized with effusion [7]. Ongoing infection eventually leads to the accumulation of pus in the pleural space (empyema). Epidemiological studies describe an increasing incidence of this problem [8]. Empyema requires pleural drainage and may also require surgical treatment [7], [8], [9], [10]. There is a considerable variation in the course and aggressiveness of PPEs; therefore, an understanding of its progression is important [11].

The American College of Chest Physicians developed a consensus statement on the medical and surgical treatment of PPEs using evidence-based methods [12]. This document defines 4 risk categories: (a) category 1 (very low risk): effusion of <1 cm on ipsilateral decubitus film, with negative Gram stain and culture and unknown pH; (b) category

2 (low risk): effusion >1 cm, with negative Gram stain and culture and a pH value above 7.20; (c) category 3 (moderate risk): free-flowing effusion occupying more than half the hemithorax, loculated, or with thickened parietal pleura, positive Gram stain or culture, or pH <7.20; and (d) category 4 (high risk): purulent pleural fluid. The consensus statement makes the following recommendations, which should be interpreted with caution because of the methodological problems affecting the articles analyzed:

1. Patients with category 1 and 2 PPE may not require pleural drainage (D).
2. Pleural drainage is recommended in category 3 and 4 effusions (C).
3. Therapeutic thoracentesis or drainage tube alone appears to be inadequate for the treatment of many patients with category 3 and 4 effusions (C). Nevertheless, in some cases, these measures may be effective and result in complete resolution. Careful monitoring is recommended during the initial stage of the disease, and further measures are unnecessary when the effusion resolves completely (D).
4. Fibrinolytics, VAT, and surgery are acceptable additional treatments for patients with category 3 and 4 parapneumonic infusions (C).

If adequate antibiotic therapy is started at an appropriate time, the process of complication and the progression of the effusion to the higher categories of division, 3 or 4 can be stopped [12]. In this way, the progression of the PPE to empyema, which requires surgical procedures and results in longer hospitalization and higher mortality, can be prevented [12], [13], [14].

Antibiotic therapy creates the basis of the treatment of all PPEs, but there is still debate about the indication and timing of other pleural treatments [13]. There is no prevailing consensus on the appropriate antibiotic choice, route, and duration of the treatment of bacterial pleural effusion after appropriate source control. Professional guidelines note the lack of comparative studies that influence the creation of guideline recommendations [13]. As with any infection, source control with prompt initiation of antibiotics is paramount for infection control and patients' recovery, and pleural infections are no different. Specific factors that should be considered are the clinical history of the patient (and any risk factors for resistant or hospital-acquired organisms), local antibiotic resistance pattern, pharmacologic characteristics of the potential antibiotics, ability to penetrate the pleural space, and local antibiotic institutional stewardship [14]. Specifically, penicillin, ceftriaxone, metronidazole, and clindamycin have all shown good penetration into the pleural space [15].

For patients with community-acquired pleural empyema with a low risk of methicillin-resistant organisms or other resistant Gram-negative organisms, reasonable empiric antibiotic regimens include a non-pseudomonal second-generation cephalosporin, a third-generation cephalosporin, or an aminopenicillin with a B-lactamase inhibitor [16], [17]. Consideration of anerobic coverage is also somewhat unique when treating pleural space infections in that the addition of anerobic coverage with metronidazole or clindamycin is generally advisable [16], [17]. This is in contrast with the American Thoracic Society and Infectious Disease Society of America guidelines that this does not recommend routine anerobic coverage [18]. Coverage for atypical organisms with macrolide therapy is also generally not required and is not routinely advised; however, PPE or empyema secondary to legionella, which has rarely been reported, should be treated with a macrolide antibiotic [16]. Aminoglycosides have no role in the treatment of PPE as they penetrate poorly into the pleural space and may be inactive in the generally acidic environment of infected pleural fluid [16], [17], [18], [19].

The most appropriate is to start antibiotic treatment quickly based on the microbiological findings. Despite the relationship with pneumonia, studies suggest that the bacteriology of pleural infections differs from that of pneumonia and has been significantly altered by the introduction of antibiotic treatment [7]. The most common causes of community-acquired pleural infection in some studies are *Streptococcus milleri* (28%), *Streptococcus pneumoniae* (14%), Staphylococci (12%), and anerobes (19%). Other less common organisms responsible for community-acquired infection include other Streptococci, *Enterobacteria*, *Haemophilus influenzae*, *Pseudomonas* spp, tuberculosis, and *Nocardia* [19].

Hospital-acquired pleural space infections raise different considerations for antibiotic selection and may result from nosocomial pneumonia or surgery. Specifically, antibiotic therapy for patients with these risk factors should be expanded to cover methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas*. Specifically, *S. aureus* will comprise approximately 50% of positive pleural fluid cultures in patients with hospital-acquired pleural infections, with MRSA representing about two-thirds of these cases and the remainder being Gram-negative organisms (predominantly *Escherichia coli*, Enterobacter, and *Pseudomonas*) [16]. Intrapleural antibiotics are not recommended [8]. The timely initiation of appropriate antibiotic therapy leads to a possible delay in the development of UCPPE in CPPE or empyema, which treatment requires a longer hospital stay, combined longer-term antibiotic therapy, and increases mortality in patients [6], [7], [8].

De-escalation of antibiotic therapy is recommended when there is recorded improvement in the objective clinical picture and biomarkers in patients [16], [17], [18], [19], [20]. After discharge from the hospital, the need of a prolonged course of antibiotics

is often necessary [16], [17]. With our study, we want to see the benefit of timely antibiotic treatment and thus prevent PPE from progressing to empyema.

Materials and Methods

This was a prospective observational study. The patients were diagnosed and treated in the University Infectious Diseases Clinic, Faculty of Medicine, Skopje in the Department of Respiratory Diseases. Of 755 patients with CAP, 175 (23.18%) had PPE. Of those 175 patients with PPE, 81 (46.28%) patients were not analyzed, due to effusions smaller than 1 cm, refusal to perform thoracentesis as a diagnostic procedure, or obtained a small amount of fluid that could not be completely analyzed. Primary empyemas were not included in the study.

Thoracentesis was performed in 94 (53.71%) patients, 50 patients with UCPPE and 44 with CPPE. Thirty-three patients were excluded from the study because of cancer and malignant effusion, transudative effusion, vasculitis, pulmonary embolism, tuberculosis, and age <18 years. The suspected diagnosis of PPE was made in all cases through clinical manifestations, biochemical findings, and a chest radiograph (posteroanterior and lateral, showing pleural-based opacity obscuring the diaphragm). The diagnosis was confirmed by thoracocentesis with biochemical and/or microbiological analysis of the pleural fluid. According to Light's criteria, effusions are divided into transudative and exudative. Satisfying any one criterium means that it is exudative:

1. Pleural Total Protein/Serum Total Protein ratio >0.5
2. Pleural lactate dehydrogenase/Serum lactate dehydrogenase ratio >0.6
3. Pleural lactate dehydrogenase level >2/3 upper limit of the laboratory's reference range of serum lactate dehydrogenase.

Further exudative pleural effusions are divided according to their evolution and on the basis of pH, glucose and lactate dehydrogenase (LDH) values in the pleural fluid:

- UCPPEs: pH > 7.2, glucose >60 mg/dL, LDH <1000 UI/mL
- CPPEs: pH < 7.2, glucose <60 mg/dL, LDH >1000 UI/mL.

Pleural fluid obtained by thoracentesis has been sent for a series of biochemical, cytological, histopatological, and microbiological tests for determination of the nature of effusion. Following test of pleural fluid had been performed:

1. Physical characteristics - Color, turbidity, viscosity
2. Biochemical findings - Glucose, Protein, Albumin, Lactate dehydrogenase (LDH), and pH are done in the biochemical laboratory of the "Infectious Diseases Clinic"
3. Cytological examination of pleural fluid - done in "Institute of Oncology"
4. Microbiological examination of pleural fluid - done in "Institute for Microbiology and Parasitology"
5. Tuberculosis tests - adenosine deaminase, lysozyme, culture for acid-resistant bacilli or Lewenstain – done in "Institute for Lung Diseases and Tuberculosis".

Statistical analysis

Statistical analysis was conducted using SPSS 17 for Windows. Categorical traits are displayed by absolute and relative representation with quantitative traits mean, SD, median, minimum, maximum, 25–75 percentiles. To compare the groups with uncomplicated and CPPEs were used non-parametric and parametric methods (Chi-square test). *Post hoc* analysis was done with the Mann–Whitney U test. For the level of significance, the value of $p < 0.05$ was used, and $p < 0.01$ for an even more significant value.

Results

Demographic characteristics of respondents

The gender structure of patients with PPE comprised 59.57% male and 40.43% female respondents, and their average age was 53.82 ± 17.5 years. The oldest participant had 93 years, and the youngest was 18 years. Previously had pneumonia in 37 (39.36%) of participants and antibiotics before hospitalization received 61 (64.89%) patients. The results are shown in Table 1.

Table 1: Demographic characteristics of the patients with parapneumonic effusion

Age	
Mean ± SD (53.82 ± 17.5); min-max (18–93)	
Sex	
Male	56 (59.57%)
Female	38 (40.43%)
Smoke	68 (72.34%)
Contact with similar patients	32 (34.04%)
Previous pneumonia	37 (39.36%)
Antibiotics before hospitalization	61 (64.89%)

Accompanying chronic conditions were significantly less common in patients with UCPPE compared to CPPE patients (56% versus 77.27%, $p = 0.029$).

Alcoholism, as the most common comorbidity condition, was registered in 25% of patients with CPPE. In the group with UPPE, diabetes mellitus and chronic heart

diseases were the most common comorbidities verified in 14% of patients. Two or three comorbidities were noted in 5 (11.36%) in the group with CPPE (Table 2).

Table 2: Comorbidity of the patients

Comorbidity	UCPPE (n = 50) n (%)	CPPE (n = 44) n (%)	p-value*
Total comorbidity			
No	22 (44.00)	10 (22.73)	0.0299
Yes	28 (56.00)	34 (77.27)	0.0488*
Type of Comorbidity			
Chronic lung disease	2 (4.00)	2 (4.55)	>0.9999
Chronic heart disease	7 (14.00)	2 (4.55)	0.1665
Diabetes mellitus	7 (14.00)	3 (6.82)	0.1665
Chronic liver disease	1 (2.00)	1 (2.27)	>0.9999
Chronic renal failure	1 (2.00)	0	>0.9999
Alcoholism	1 (2.00)	11 (25.00)	0.0011*
Malignancy	4 (8.00)	2 (4.55)	0.6812
Chronic systemic disease	1 (2.00)	2 (4.55)	0.5979
Poor dental hygiene	0	2 (4.55)	0.2164
Drug addiction	0	2 (4.55)	0.2164
Neurological disease	0	2 (4.55)	0.2164
Two or three comorbidities	3 (6.00)	5 (11.36)	0.4671
Other diseases	1 (2.00)	0	>0.9999

*p (Chi-square test), *p<0.05.

Microbiological findings

In patients with UCPPE, we had 5 positive sputums for *S. pneumoniae*. We also obtained positivity for *Klebsiella pneumoniae* in 1 patient each with UPPE and CPPE. Blood cultures also remained negative in the highest percentage (Table 3).

Table 3: Serological and microbiological findings in patients with PPE

Variable	UCPPE (n = 50) n (%)	CPPE (n = 44) n (%)	p-value
Pneumoslide IIF IgM			
Negative	37 (74)	32 (72.73)	>0.9999
Positive	13 (26)	12 (27.27)	
PCR influenza			
Not done	47 (94)	39 (88.64)	
Influenza A	1 (2)	0	
Influenza AH3N2	0	0	
Influenza AH1N1	2 (4)	2 (4.55)	
Influenza B	0	3 (6.82)	
Throat swab			
Negative	50 (100)	43 (97.73)	0.4681
Streptococcus pyogenes	0	1 (2.27)	
Streptococcus pneumoniae	0	0	
Nasal swab			
Negative	50 (100)	44 (100)	
Staphylococcus aureus	0	0	
Streptococcus pneumoniae	0	0	
Sputum			
Negative	42 (84)	36 (81.82)	0.7908
Streptococcus pneumoniae	5 (10)	0	0.0584
Haemophilus influenzae	0	0	
Staphylococcus aureus	0	3 (6.82)	0.0988
Streptococcus pyogenes	1 (2)	3 (6.82)	0.3372
Pseudomonas spp.	0	0	
Klebsiella pneumoniae	1 (2)	1 (2.27)	>0.9999
Candida sp.	1 (2)	1 (2.27)	>0.9999
Blood culture			
Negative	47 (94)	3535 (79.55)	0.0604
Staphylococcus aureus	0	2 (4.55)	0.2164
Methicillin-resistant *Staphylococcus aureus*	0	1 (2.27)	0.4681
Streptococcus pneumoniae	3 (6)	3 (6.82)	>0.9999
Streptococcus pyogenes	0	1 (2.27)	0.4681
Haemophilus influenza	0	0	
Anerobic (*Peptostreptococcus*)	0	0	
Enterococcus sp.	0	0	
Escherichia coli	0	2 (4.55)	0.2164

Cultures of pleural punctate were positive in 14 (31.82%) patients with CPPE, 4 (28.57%) of them were with *Peptostreptococcus*, then *S. aureus* and MRSA in 3 (21.43%) patients. *S. pneumoniae* was isolated in 2 (14.29%) patients (Table 4).

There was a statistically significant difference in the days of hospitalization between the two groups ($p < 0.0001$). The mean value of the length of hospitalization and treatment in patients with CPPE was 20.75 ± 18 days and in those with UCPPE 15.78 ± 4.3 days. The shortest hospitalization in patients with UCPPE was 13 days, and the longest was 16, and in patients with CPPE, the shortest hospitalization was 18, and the longest was 23 days (Table 5).

Table 4: Culture of pleural fluid in patients with CPPE (n = 44)

Variable	n (%)
Culture of pleural fluid	14 (31.82)
Staphylococcus aureus	3 (21.43)
Methicillin-resistant *Staphylococcus aureus*	3 (21.43)
Streptococcus pneumoniae	2 (14.29)
Streptococcus pyogenes	1 (7.14)
Anaerobes (Peptostreptococcus)	4 (28.57)
Escherichia coli	1 (7.14)

Table 5: Characteristics of patients with PPE

Variable	UCPPE n = 50	CPPE n = 44	p-value
Previous treatment in another hospital n (%)			
Yes	10 (20)	12 (27.27)	^{ap} = 0.48
No	40 (80)	32 (72.73)	
Treatment with antibiotic therapy in days n (%)			
7–10 days	4 (8)	3 (6.82)	
11–14 days	23 (46)	2 (4.55)	
15–21 days	19 (38)	26 (59.09)	
>21 days	4 (8)	13 (29.55)	
Treatment by number of days			
Mean ± SD	15.42 ± 3.9	20.59 ± 3.9	^{b}p < 0.0001**
Median (25-75th quartiles)	14.5 (13–16)	20 (18–23)	
Intensive care stay n (%)			
Yes	3 (6)	8 (18.18)	^{a}p = 0.2
No	47 (94)	36 (81.82)	

^{a}p (Chi-square test); ^{b}p (Mann–Whitney test); *p < 0.05; **p < 0.01.

A certain number of patients with PPE were previously treated with antibiotic therapy prescribed by the family physician. However, some of the patients were hospitalized in different hospital institutions where they were treated with antibiotic therapy. There was no significant difference between the patients of the two groups.

According to the recommendations for the treatment of patients with CAP and PPEs, most patients with CPPE were treated with cephalosporin 3rd generation and clindamycin. In patients who had no good answer and the effusion complicated it, we used cephalosporin in combination with vancomycin and metronidazole (Table 6).

Table 6: Antibiotic treatment of patients with parapneumonic effusions and length of hospitalization

Variable	n (%)
Antibiotic treatment after hospitalization	
Cephalosporin, 3rd Gen + Quinolones	18 (19.15)
Cephalosporins, 3rd gen + Clindamycin	28 (29.79)
Cephalosporins, 3rd gen + Vancomycin + Metronidazole	26 (27.66)
Cephalosporins, 3rd gen + Vancomycin	10 (10.63)
Imipenem + Vancomicin	7 (7.4)
Cephalosporins, 3rd gen	2 (2.13)
Cephalosporins, 4rd gen + Aminoglycosides	1 (1.06)
Other therapy	2 (2.13)

Discussion

In our study, PPE is verified in 23.18% of patients hospitalized with CAP. PPEs occur in 20–40%

of patients who are hospitalized with pneumonia [2], [3]. This information correlated with our study where PPE is verified in 23.18% of patients hospitalized with CAP.

In our research, 59.57% were male patients, which correlates with the Dzurik study where from 130 patients with PPE, 60% were men [21]. Ozol *et al*. [22] and Tsang *et al*. [23] in their studies even indicate that the male population has more inclination to develop CPPE. The average age among our respondents was 53.82 ± 17.5 years, the oldest was 93 years old, and the youngest 18 years. Age correlates with the age of patients in several studies for adult patients [23], [24].

We mentioned that there are comorbidities as risk factors for the development of CPPEs, especially empyema. Accompanying, chronic diseases had 65.96% of the participants. Comorbidities were significantly less common in patients with UCPPE compared to CPPE patients (56% versus 77.27%, p = 0.029). Alcoholism as the most common comorbidity condition, was registered in 25% of patients with CPPE. In the group with UCPPE diabetes mellitus and heart diseases were the most common comorbidity noticed in 14% of patients. In the group with CPPE, 5 (11.36%) patients had two or three comorbidities. In Chalmer's study from 2011, alcoholism was the most common comorbidities noted in patients with CPPE, followed by diabetes mellitus, same as in our study [24]. This study demonstrates that the presence of more than one comorbidity is a requirement for the development of a CPPE in a patient with CAP [24]. Patients with alcohol use disorder (AUD) are at higher risk of pneumonia and poor outcomes [25]. This article reviews the etiology of pneumonia in patients with AUD, its impact on mortality and resource utilization, and implications for treatment. So, the presence of comorbidity affects our approach to antibiotic treatment [25].

The bacteriology implicated in pleural space infection is distinct from that of pneumonia and serves as further evidence of the two separate clinical entities. This also indicates that mechanisms of transmission are different (e.g. hematogenous route from oropharyngeal sources [26], [27]. UCPPE are sterile exudates microbiologically negative. Positive cultures of pleural punctate in our study were found in 14 (31.81%) patients with CPPE. In 4 (28.57%) cases *Peptostreptococcus* was isolated, then *S. aureus* and *MRSA* in 3 (21.43%) patients. *S. pneumoniae* was isolated in 2 (14.29%) patients. In the same studies higher numbers of positive pleural punctate were reported which is 32–50% of cases [28], [29]. A recent systematic review has shown that pleural fluid culture is positive in only about 56% of cases and is polymicrobial in 12.9% [30]. In addition to *S. pneumoniae* as a less common isolate in CPPE and empyema's, the *Streptococcus viridans* group is also found as a more common isolate than methicillin-susceptible *S. aureus* [31]. Isolates also vary by region and climate [31]. However, community-acquired infections were often caused by a Gram-positive aerobe (65%), whereas within hospital-acquired settings, Gram-negative aerobes had the larger share (38%) [26], [31]. However, recently, new techniques for detecting microorganisms (by sequencing the genetic material) in the pleural puncture have been increasingly introduced, so it is detected that the causative agents are polymicrobial [15]. Perhaps the lower percentage of isolates in our study is the results of the previous antibiotic treatment of the patients that are analyzed in our study and the inappropriate way of transport of the material. All this imposes the need to introduce new molecular techniques.

The initial antibiotic coverage of patients with PPE is generally dictated by treatment guidelines for pneumonia and is altered according to blood and pleural fluid microbial sensitivity [9]. Empirical anerobic antibiotic treatment is generally advised [6]. Choices in community-acquired CPPE/empyema include intravenous (IV) amoxicillin with clavulanic acid or a combination of a second-generation cephalosporin and metronidazole [9], [32]. Clindamycin monotherapy is effective for patients with beta-lactam allergy and is a suitable alternative to metronidazole for anerobic cover [9], [30] [31], [32]. Possible choices include carbapenems, antipseudomonal penicillin, or third or fourth-generation cephalosporins with metronidazole in patients with community-acquired CCPE/empyema or nosocomial empyema. Vancomycin, linezolid, or alternatives may have to be added for suspected or proven MRSA infection [9], [26]. Aminoglycosides demonstrate poor pleural penetration and reduced efficacy in acidic environments and should be avoided [9], [31], [32]. However, in the recommendation of the Spanish Society of Pulmonology and Thoracic Surgery, cephalosporin is recommended through the penetration into pleural space is slow, but the concentration is stable and persistent [32]. The penetration of quinolones is better than that of penicillin [32]. Until now recommendations indicated that it is necessary always to cover anerobes with antibiotic treatment [9], [26], [31], [32]. American Thoracic Society and Infectious Disease Society of America guidelines do not recommend routine anerobic coverage [18]. Opposite to this the results of the review of Corcoran *et al*. demonstrate that anerobes to the pleurae were isolated relatively more commonly in community-acquired infections, which may be related to poor dental hygiene [27].

Additional MRSA coverage is recommended in the setting of hospital-acquired infections [33]. Coverage for atypical organisms with macrolide therapy is generally also not required since the prevalence of atypical organisms in pleural infection is low. According to these recommendations, it was summarized that in all cases, empiric antibiotic treatment must be started as early as possible and subsequently adjusted in correlation with the results of cultures. It is also significant the comorbidity characteristics of the patients, the microbiological peculiarities of the local geographical

area, and the activity of the chosen antibiotic in pleural fluid [26], [30], [31], [32].

In our study, 18 (19.15%) patients with UCPPE, according to the recommendations for the treatment of patients with CAP and PPE, were treated with cephalosporin 3rd gen combined with quinolone. Most patients, 28 (29.79%) are treated with cephalosporin 3rd gen. and clindamycin. In patients with no good answer, we used cephalosporin in combination with vancomycin and metronidazole. Polymicrobial causes of the CPPE or empyema, occur very often, which requires covering the patient with double or triple antibiotic therapy [30], [34]. Most of the patients were treated with combined therapy that also covered anerobes (64.89%). In our experience by covering the anerobes, the clinical picture was improved, and the markers of inflammation decreased. Avner *et al*., 2022 in a retrospective study of 355 adults suspected of empyema found that patients who received anti-anerobic therapy had less hospital readmissions [34].

Part of the patients in our study is treated according to the positive microbiological findings. Most of the patients with pleural infection previously received an antibiotic [19]. In our study, 64.89% of patients had received an antibiotic before hospitalization. This significantly complicates the treatment and leads to the development of resistance [19], [32], [34]. Another problem in our country, which is also a problem in many other countries, is the lack of reports on resistance and microbial peculiarity [32], [33].

Blood cultures also remained negative in the highest percentage in the research we conducted. In both groups of patients, only 12.76% of the blood cultures were positive. Moreover, in patients with sepsis, and a septic condition is usually a large part of the effusions, especially CPPE, positive blood cultures are found on average in about 30% of patients [34]. This low number of positive blood cultures is certainly the result of previous treatment with antibiotics [22], [34], [35].

The length of hospitalization, and therefore the length of antibiotic treatment, differed significantly between subjects ($p < 0.0001$). The median, that is the average time of hospital days, shows that half of the patients with CPPE were in the hospital for more than 21 days and half of patients with UCPPE for more than 15 days. A significant difference in hospitalization between the two groups of patients is found in several studies [1], [16], [24]. It indicates that the presence of pleural effusion is associated with longer hospitalization, especially if it is complicated [24], [36]. CPPE is the result of omissions made in the management of pneumonia as well as UCPPE. If the effusion is associated with failure of initial antibiotic treatment [22], [24], systemic disease-sepsis develops and hospital stay is prolonged [22], [37], costs of the treatment is increased [22], co-morbidity from invasive procedures [37], [38], resulting in increased patient mortality [22], [24], [32]. Ozol's study from 2004 indicated that the approach to treatment is significant and closely related to the length of hospital treatment. In this study, he divides complicated effusions (according to the method of treatment) into three groups: patients who are treated with therapeutic thoracocentesis, with the application of a drain, and with intrapleural fibrinolytics [37]. Average hospitalization in the three groups is 18.6 ± 13.2 days; in the first group it was 14.8 ± 10.1, the second 21.8 ± 15.2, and in the third group 20.2 ± 13.7 days, which shows that timely therapeutic thoracocentesis in patients with PPE requires a shorter hospital stay and less mortality in patients [37]. However, verification of pleural fluid and the need to perform only diagnostic thoracocentesis require a longer hospital stay [24]. It provides additional costs in the treatment of patients and the use of additional healing techniques with increased morbidity and mortality in patients [9], [34].

The American Association for Thoracic Surgery, in their 2017 guidelines, identifies a range of 2–6 weeks in the literature [18]. The mean treatment time of our patients coincides with these recommendations. These guidelines further suggest, without a citation, that oral rather than IV antibiotics are adequate once source control is achieved, and the patient is clinically improved [18].

Conclusions

Patients with PPEs have comorbidities that are a risk for complicating the effusions. Our study demonstrated that even in patients with PPE in whom there is no microbiological evidence, antibiotic coverage for anerobes is required. As soon as a pleural infection is noted, patients should receive antibiotic therapy, which should be based on pleural fluid culture or blood culture results if possible. Use of antibiotic therapy before hospitalization, especially uncontrolled leads to a reduced number of positive microbiological findings and the development of resistance. Polymicrobial causes of the CPPE or empyema occur very often, which requires covering the patient with double antibiotic therapy. More recently, there has been a need to introduce new molecular techniques to detect the causative agent in CPPE or empyema.

Preventing the development of CPPE or empyema will reduce morbidity and mortality in patients with PPE and thus the length of treatment and hospital stay. The identification of these patients and prompt management are important. In today's era of broad-spectrum antibiotics PPEs still present a problem with a multitude of unresolved dilemmas.

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