RATIONAL USE OF ANTIBACTERIALS IN PLEURAL EMPYEMA

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Introduction. *Pleural empyema remains a significant cause of morbidity and mortality globally. The rising incidence of this complex pathology necessitates an evaluation of diagnostic methods, surgical treatment, and antibiotic therapy strategies.*

Material and methods. *We selected and analyzed 50 observation records of patients with pleural empyema admitted to the thoracic surgical ward at Timofei Mosneaga Republican Clinical Hospital. A literature review was conducted to elucidate the rationale behind the administration of antibacterial treatment.*

Results. *Bacteriological examination of the pleural fluid revealed the presence of pathogenic flora, predominantly gram-negative (15 cases) - P. aeruginosa, Acinetobacter, K. pneumoniae, E. aerogenes, S. marcescens, Corrynebacterium, P. mirabilis, and in 5 cases, a polymicrobial etiology was observed. Evaluation of microbial susceptibility allowed for a rational choice of antibacterial treatment. Beta-lactam antibiotics were most frequently administered, either in monotherapy or in combination. Other groups of antibacterials administered included fluoroquinolones, aminoglycosides, macrolides, polymyxins, nitroimidazole derivatives, and glycopeptides.*

Conclusions. *Effective and harmless antibacterial treatment can only be achieved by identifying the causative pathogens and their antimicrobial susceptibility, ensuring adequate concentrations in the pleural space, determining the routes of administration, the duration of therapy, and the rational combination of antimicrobials.*

Cuvinte-cheie: *empiem pleural, antibacteriene, floră patogenă, utilizare rațională.*

UTILIZAREA RAȚIONALĂ A ANTIBACTERIENELOR ÎN EMPIEMUL PLEURAL

Introducere. *Empiemul pleural continuă să fie o cauză importantă de morbiditate și de mortalitate în lume, iar creșterea incidenței acestei patologii complexe necesită o evaluare a metodelor de diagnostic, de tratament chirurgical și a strategiilor de antibioterapie.*

Material și metode. *Au fost selectate și analizate 50 de fișe de observație ale pacienților cu empiem pleural internați în Secția chirurgie toracică a IMSP SCR „Timofei Mosneaga". Pentru elucidarea raționalității administrării tratamentului antibacterian a fost efectuat review-ul literaturii.*

Rezultate. *Examenul bacteriologic al lichidului pleural a permis depistarea florei patogene, preponderent floră gramnegativă (15 cazuri) - P. aeruginosa, Acinetobacter spp., K. pneumoniae, E. aerogenes-, S. marcescens, Corrynebacterium spp., P. mirabilis, iar în cinci cazuri – de etiologie polimicrobiană. Evaluarea sensibilității microorganismelor la antimicrobiene a permis alegerea rațională a tratamentului antibacterian. Cel mai frecvent, în monoterapie sau în combinație, au fost administrate antibioticele beta-lactamice. De asemenea au fost administrate antibacteriene din următoarele grupe: fluorochinolone, aminoglicozide, macrolide, polimixine, derivați de nitroimidazol, glicopeptide.*

Concluzii. *Tratamentul antibacterian eficient și inofensiv în emfizemul pleural poate fi realizat doar prin stabilirea agenților patogeni etiologici și a sensibilității lor la preparatele antimicrobiene, asigurarea unor concentrații adecvate în spațiul pleural, determinarea căilor de administrare, duratei curei de tratament, asocierea rațională de antimicrobiene.*

INTRODUCTION

Pleural infections present a significant challenge for medical practice and public health, with a mortality rate of 10-20%, and even 35% in elderly and immunocompromised patients. Recent epidemiological data has indicated a global increase in the incidence of pleural infections, attributed to factors such as the growing elderly population with multiple chronic comorbidities, frequent use of immunosuppressive medications, evolution of pathogenic microbial flora and bacterial resistance, and improved accessibility of diagnostic methods, including in outpatient settings. The treatment of pleural infections is considered one of the most expensive among all lung infections. Various causes of pleural infections have been identified, including community-acquired and hospital-acquired pneumonia, lung abscess, chest injuries and trauma, bronchopleural fistula, esophageal perforation, post-surgical complications, bronchogenic cancer, immunocompromised conditions, post-operative infections, patients on hemodialysis, and those undergoing antitumor therapy. The subacute onset of the pathology leads to delayed admission of patients to specialized medical services and thus the therapeutic management of pleural empyema is associated with long duration of hospitalization, significant use of healthcare resources, long-term antibiotic therapy, chest tube drainage, and/or surgery. While mortality from pleural infections has decreased considerably in the antibiotic era, the increased use of antimicrobial preparations, including irrational use, has led to a rise in bacterial resistance, as evidenced by the epidemics and pandemics of the early 21st century (SARS CoV, MRES, Ebola, SARS CoV-2, etc.). In this context, it is imperative to adjust the antibacterial therapy of pleural infections by addressing several key questions, such as the selection of antibacterial preparations for empirical therapy, improvement of methods for detecting pathogens and their susceptibility to antimicrobial preparations, determination of optimal routes of antibiotic administration and duration of antibacterial treatment, rationality of stepwise antibacterial therapy, pharmacokinetic studies on drug penetration into the site of infection, ensuring sufficient inhibitory concentrations to combat pathogens, and advocating for combinations of antimicrobial preparations (1 - 4).

The aim of the study was to analyze the spectrum of pathogens causing pleural empyema and their susceptibility to antimicrobial preparations, to characterize the groups of antibacterial preparations used, the duration of antibacterial treatment, and to justify the prescription of antimicrobial preparations based on pharmacokinetic data.

MATERIAL AND METHODS

The study was retrospective, involving the selection and analysis of 50 medical records of patients with pleural empyema as the primary (46 cases) or secondary (4 cases) clinical diagnosis, with or without fistulas, who were admitted to the thoracic surgery ward at the *Timofei Mosneaga* Republican Clinical Hospital. Bacteriological results from the medical records were analyzed to identify pathogens and their sensitivity to antibacterial preparations, and the prescription records were examined to analyze the antibiotics and synthetic chemotherapeutic agents used in the treatment. Additionally, relevant literature on antibacterial treatment for pleural infections was selected and analyzed in the PubMed database using keywords such as pleural infection, pleural empyema, pathogens, antibiotics, and bacterial resistance.

RESULTS

Based on the analysis of the medical records, it was found that the average age of the patients was 58 years (ranging from 31 to 77 years), with a predominance of male patients (41 males and 9 females). The duration of hospitalization ranged from 4 to 35 days, with an average of 12 days, and 8 patients required transfer to other wards, including intensive care. The causes of pleural empyema included pneumonia (29 cases), chest trauma (7 cases), pulmonary gangrene (4 cases), post-surgical infection (4 cases), lung abscess (2 cases), healthcare-associated empyema (2 cases), mesothelioma (1 case), and sepsis (1 case). The study was retrospective, and as a result, the data from observation records were not sufficient to differentiate between hospital-acquired and community-acquired etiologies.

The bacteriological examination of pleural fluid was conducted in all patients included in the study to identify the pathogen and antibacterial susceptibility. Our results indicate that bacterial growth was present in the pleural fluid in only

28 cases (56%). Among these, a single pathogen was identified in 23 cases (82.2%), while the etiology was polymicrobial in 5 cases (17.8%). Gram-positive flora (including *Staphylococcus aureus-5, Staphylococcus hominis-1, Staphylococcus epidermidis-1, Actinomyces odontolyticus-1*) was identified in 8 patients, and gram-negative flora (including *Pseudomonas aeruginosa-8, Acinetobacter-1, Klebsiella pneumoniae-2, Enterobacter-1, Serratia marcescens-1, Corrynebacterium-1, Proteus mirabilis-1*) was found in 15 patients. The predominance of gram-negative agents and Staphylococcus aureus suggests that the pathogenic flora of the pleural infection was most likely acquired in a hospital setting.

The analysis of bacterial susceptibility results to antibacterial preparations revealed a high resistance of the identified agents. Specifically, *Staphylococcus aureus* MRSA was found to be pandrug-resistant, *Pseudomonas aeruginosa* exhibited polyresistance, with sensitivity only to colistin or amikacin, *Enterococcus faecium* showed sensitivity to vancomycin, and *Corrynebacterium* was sensitive to linezolid.

Antibacterial treatment was administered to 45 patients, with 17 receiving a single antimicrobial preparation and 28 receiving a combination of two or more antibacterials. Among these patients, bacterial growth was not observed in the pleural fluid of 3 individuals, and following surgery, their clinical condition improved, leading to a recommendation for continued antibacterial treatment at home. In 2 patients with detected pathogenic flora, no antibacterials were prescribed as the condition improved after pleural cavity drainage. The results of the bacteriological examination of pleural fluid prompted a modification of the drug regimen. The absence of bacterial growth in the pleural fluid may be attributed to the administered antibacterial treatment or to the presence of anaerobic agents, the identification of which is challenging using standard tests. Considering the advantageous nature of anaerobic infection growth in pleural fluid, the use of an antibacterial drug with a spectrum of action against anaerobic agents is essential. The study identified the use of metronidazole, meropenem, cefoperazone, ceftazidime, and piperacillin as monotherapy or combination therapy, providing coverage against anaerobic agents in 29 cases.

Based on the analysis of the prescription records, the following medications were prescribed to patients with pleural empyema: beta-lactams (49); fluoroquinolones (9); aminoglycosides (11); polymyxins (4); macrolides (2); glycopeptides (1); and nitroimidazole derivatives (12). Among the beta-lactams, penicillins with beta-lactamase inhibitors were used in 16 cases (amoxicillin+clavulanic acid-9, piperacillin+tazobactam-7), second-generation cephalosporins (cefuroxime-4), and third-generation cephalosporins alone (ceftriaxone-4, cefotaxime-5) or in combination with beta-lactamase inhibitors (cefoperazone+sulbactam-14, ceftazidime+avibactam-5), as well as carbapenems (meropenem-3). Fluoroquinolones such as ciprofloxacin (7), levofloxacin (1), and moxifloxacin (1) were also used. Additionally, aminoglycosides like gentamicin (4) and amikacin (7), polymyxins specifically colistin (4), macrolides such as azithromycin (2), glycopeptides like vancomycin (1), and nitroimidazole derivatives like metronidazole (12) were prescribed.

In our study, the third generation of cephalosporins was the most frequently used beta-lactams (56% of cases). Their broad spectrum of action, which covers aerobic gram-positive, gram-negative (including anti-pseudomonas preparations such as cefoperazone and ceftazidime), and anaerobic bacteria, allows for effective coverage of the pathogenic flora commonly associated with pleural infections. Penicillins with beta-lactamase inhibitors were used in 15 cases either as monotherapy or in combination with other antibacterials. Amoxicillin+clavulanic acid, with its broad spectrum of action against predominantly aerobic bacteria, was frequently administered concomitantly with metronidazole to provide anti-anaerobic action. Patients showed negative bacteriological results, and the average duration of intravenous administration was 7 days. Piperacillin+tazobactam was used in 7 patients, either alone or in combination, for its anti-pseudomonas action as well as its anaerobic spectrum. An important issue is the increased resistance of Pseudomonas aeruginosa, Enterobacteriaceae, Acinetobacter spp, and Klebsiella spp, as detected in the bacteriological examination of pleural fluid in patients treated with beta-lactam antibiotics. Combining them with beta-lactamase inhibitors extends their spectrum and increases efficacy. Meropenem, with its ultra broad spectrum of action against both gram-positive and gram-negati-

ve aerobic and anaerobic bacteria, can therefore be used in polymicrobial pleural infections.

According to the results of the bacteriological examination of pleural fluid, aminoglycoside-sensitive pathogens were identified, including Staphylococcus hominis, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Klebsiella pneumoniae, leading to the intravenous use of gentamicin or amikacin in 13 patients diagnosed with pyothorax. Gentamicin and particularly amikacin demonstrate activity against gram-negative aerobic flora and less activity against gram-positive flora, although this may be enhanced when combined with beta-lactams. Amikacin is considered to be an aminoglycoside with higher efficacy against Pseudomonas aeruginosa, attributed to its resistance to enzymes produced by microbes.

Vancomycin was administered in combination with amoxicillin/clavulanic acid to a patient whose pleural fluid showed growth of both *Enterococcus faecalis* (susceptible to amoxicillin/clavulanic acid, ampicillin, nitrofurantoin, ofloxacin, piperacillin/tazobactam, and vancomycin) and *Enterococcus faecium* (susceptible to linezolid, nitrofurantoin, and vancomycin). Creatinine values were monitored during treatment and showed insignificant variations. The patient was discharged with clinical improvement and recommended internal administration of ampicillin 500 mg twice daily (sources recommend administration every 6 hours-4 times daily).

Colistin was administered to 2 patients with polymicrobial pyothorax (*P. aeruginosa* with *Acinetobacter* and *P. aeruginosa, K. pneumoniae, P. mirabilis, S. saprophyticus*) and to 2 patients with P. aeruginosa in pleural fluid, susceptible to colistin. The disease progression in these patients was severe, requiring an average hospitalization period of 30 days, repeated surgical interventions for diagnostic and therapeutic purposes, and stays in 2 or 3 hospital wards during their hospitalization. Combined antibacterial therapies were ineffective, and colistin administration was the final treatment option. One patient received both inhaled and intravenous administration. The optimal dosing regimen is the administration of 9 million units per day, considering the severity of the pleural pathology.

Due to the diversity of causative pathogens and the presence of mixed flora (aerobic, anaerobic, fungal) in the treatment of pyothorax, it is recommended to administer antibiotics with a spectrum of action against anaerobic agents, such as metronidazole. Metronidazole-resistant anaerobic bacteria (Actinomyces odontolyticus) and facultatively anaerobic bacteria (Proteus mirabilis, Serratia marcescens), which are not covered by the spectrum of action of metronidazole, were identified in the study. The dosing regimen, to ensure efficacy, involves administration of 500 mg internally or intravenously every 8 hours. In the study, metronidazole was administered intravenously in 10 cases, with a 100 ml of 5% solution twice daily, and internally in 2 cases, with 500 mg administered twice daily at 12-hour intervals.

DISCUSSIONS

The agents of community-acquired pleural infection included *Streptococcus viridans, Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Enterobacteriaceae, Klebsiella*, and *Pseudomonas*. Hospital-acquired infections involved methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacteriaceae, Enterococcus, Streptococcus viridans, Pseudomonas*, and *Klebsiella*. Additionally, atypical flora (*Mycoplasma* spp., *Legionella* spp.) and fungal flora (*Candida, Aspergillus*) were rarely found, especially in immunocompromised patients. Anaerobic infections, which are difficult to detect, were thought to accompany pleural infection in about 25% of cases (1-5).

Pleural infection caused by resistant pathogens was found in 37% of isolates from community-acquired infections and 77% of isolates from hospital-acquired infections, which were resistant to at least one of the prescribed antibiotics for respiratory infections. The high rate of resistant bacteria limits therapeutic options, and in *vitro* susceptibility of pathogens does not always correlate with the therapeutic efficacy of antibacterials, given the importance of pharmacokinetic features (1, 2).

Prompt initiation of antimicrobial therapy is crucial for the treatment of pleural infection. The initial selection of antibacterials is empirical, based on the etiology of the pathology (community-acquired, hospital-acquired), the patient's condition, and clinical manifestations (2, 6).

For the selection of antibacterial therapy in a patient with pleural empyema, it is necessary to evaluate patient -dependent factors, pathology-

dependent factors, and the characteristics of the drug, which may influence the disease's progression and response to treatment. Among patient-dependent factors, it is essential to consider age, comorbidities, previous antibacterial treatment, and so on. Among pleural pathology-dependent factors, the stage of empyema, pleural effusion size, pleural thickening, degree of pleural inflammation, and duration of symptom onset to hospital admission are important. Significant characteristics of the antimicrobial preparation include its spectrum and mechanism of action, dose- and time-dependent antibacterial effect, duration of action and dosing regimen, pharmacokinetic properties, ability to penetrate pleural fluid, availability of parenteral and enteral forms, and adverse reactions (4).

In pleural infections, pleural effusions can rapidly progress from uncomplicated parapneumonic effusions to empyema. During the exudative stage of empyema, pleural fluid accumulates due to increased permeability of the visceral pleura. As the infection progresses, fibrin accumulation on the pleural membranes leads to pleural thickening and septum formation. When pyothorax develops, the pleural fluid becomes more acidic and purulent due to inflammation, and there is an increased flow of protein into the pleural space. Consequently, the penetration of antibiotics may be difficult due to the thickened pleura, with pleural fluid characteristics varying depending on the stage of pleural empyema. Mesothelial cells, which line the pleural cavity, play a crucial role in the filtration of pleural fluid, as it results from differences in hydrostatic and colloid-osmotic pressure between the pleural fluid and capillary blood. Furthermore, it has been suggested that mesothelial cells have the ability to reabsorb antibiotics (6, 7).

Cephalosporins are commonly prescribed and administered as first-line therapy for respiratory, urinary, and CNS infections, spanning from mild to severe, due to their broad spectrum of action, bactericidal effect, and low risk of adverse reactions. However, widespread use has led to the development of resistance to these drugs. The microorganisms mainly involved in conferring resistance to this antibiotic can be identified by the acronym *ESCKAPE*, which stands for *Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*, and *Enterobacteriaceae*. The rapid emergence of this resistance poses a serious threat to the continuous relevance of the antibiotic (8).

First-generation fluoroquinolones (such as ciprofloxacin) exhibit greater activity against gram-negative flora and moderate activity against atypical agents and gram-positive cocci. They also possess advantageous pharmacokinetic properties, allowing for effective penetration into body fluids and tissues, and maintenance of bactericidal concentrations for 12-24 hours. Moxifloxacin, on the other hand, demonstrates activity against both Gram-positive and Gram-negative bacilli, including anaerobes. In both animal and human studies, moxifloxacin has shown favorable pleural penetration and could be considered as a de-escalation option, particularly for internal administration (3, 9).

Polymyxins demonstrate significant activity against aerobic Gram-negative bacteria, including most pathogens of the *Enterobacteriaceae* family, such as *E. coli, Enterobacter, Klebsiella, Citrobacter, Salmonella*, and *Shigella*. They are also effective against common Gram-negative non-fermentative pathogens, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Gram-negative bacteria that are naturally resistant to polymyxins include *Pseudomonas mallei, Morganella morganii, Vibrio cholerae, Serratia marcescens, Proteus spp., Providencia spp., Burkholderia cepacia, Chromobacterium spp., Edwardsiella spp., Legionella, Brucella*, and *Campylobacter*. Polymyxins are not active against gram-negative cocci (*Neisseria spp*.), Gram-positive and anaerobic bacteria, parasites, or fungi. Orally administered polymyxins are used only for disinfection of the digestive tract due to poor absorption when taken internally. Additionally, polymyxins do not efficiently diffuse into tissues or penetrate the cerebrospinal fluid, pleural and peritoneal cavities. However, they are used systemically by intravenous administration for serious infections caused by pathogens resistant to other therapies. Carbapenem-resistant Enterobacteriaceae, *Pseudomonas aeruginosa*, and multidrug-resistant or pan-drug-resistant *Acinetobacter baumannii* pose major problems for antimicrobial therapy due to extremely limited treatment options. Polymyxins, along with fosfomycin, ceftazidime/avibactam, and the recently approved meropenem-vaborbactam, are among the last-resort antibiotics that are still effective against such pathogens (10, 11).

Along with aminoglycosides, polymyxins can be administered by inhalation. In ICU patients, pneumonia caused by carbapenem-resistant gram-negative bacteria is a frequent and serious complication. When treating lower respiratory tract infections, the pulmonary penetration of antimicrobials is considered an important factor that can affect their efficacy. For patients with pneumonia caused by multidrug-resistant bacteria, the intravenous administration of colistin combined with nebulized inhalation is more effective than intravenous infusion alone. However, the utility of polymyxins is currently facing increasing resistance worldwide, mainly due to the plasmid-encoded colistin resistance gene present in pathogens such as *Escherichia coli* and *Klebsiella pneumoniae* (10, 11).

Macrolides, including azithromycin, may be recommended for coverage of atypical microorganisms. They have a minor role in the etiology of pleural empyema, which is why they are rarely recommended as empirical therapy (4).

In community-acquired pleural infection, antibiotic regimens typically include either parenteral second or third-generation cephalosporins (e.g., ceftriaxone) combined with metronidazole for anaerobic coverage, or a β-lactam/β-lactamase inhibitor combination (e.g., amoxicillin-clavulanic acid) in monotherapy. For patients with penicillin allergy, moxifloxacin used alone or a combination of levofloxacin and metronidazole are optimal therapeutic alternatives. In hospital-acquired pleural infection, antipseudomonal and anti-anaerobic antibiotics are required. Appropriate combinations include cefepime-metronidazole, piperacillin-tazobactam, or carbapenem. Additionally, coverage of S. aureus with vancomycin or linezolid should be considered (12, 13).

The therapeutic efficacy of antibacterials administered to patients with pleural empyema is determined by their ability to penetrate the pleural space and provide a concentration that reaches or exceeds the minimum inhibitory concentration (MIC) at the site of infection. Penetration of antibiotics into the lung follows various mechanisms, such as passive diffusion (beta-lactams), permeation (macrolides), and active transport (quinolones, clindamycin). The differences in these mechanisms lead to variations in antimicrobial concentration between pulmonary sites and serum. For example, aminoglycosides are hydrophilic, so they can enter cells very slowly via endocytosis and accumulate almost entirely in lysosomes. Macrolides enter the lungs through membrane penetration, and the rate is limited by the degree of lipid solubility. Quinolones and clindamycin penetrate cell membranes by active, energy-dependent transport and therefore can be saturated, leading to differences between serum and tissue levels. Another important pharmacokinetic parameter is the ability of antibiotics to penetrate pleural fluid. Studies recommend the use of beta-lactams in the treatment of pleural empyema, demonstrating efficacy due to high penetration into pleural fluid (1, 3, 4, 14, 15).

It has been suggested that antibiotic levels in pleural fluid are lower than those in serum in patients with empyema, due to the lower permeability of the thickened pleura and the more acidic local environment. However, during acute infection characterized by inflammation, vasodilation, edema, and increased membrane permeability, the penetration of antimicrobial agents may be enhanced. In this context, for the assessment of antibiotic penetration into the pleural space, special and careful consideration should be given to the underlying pathophysiology and mechanisms of fluid formation. In empyema, during the exudative stage, pleural fluid accumulates in the pleural space due to inflammation and increased permeability of the visceral pleura. Progression of infection, bacterial invasion of the pleural space, fibrin deposition on pleural membranes, and the formation of septations cause thickening of the pleura and loss of elasticity. Regarding malignant effusions, an exudate predominantly forms due to the deregulation of pleural space drainage caused by the obstruction of blood and lymphatic vessels in the lungs and pleura. These features would determine the penetration of antimicrobial agents into the pleural fluid depending on the etiology and pathophysiological mechanisms. Based on the reported results, it was concluded that there is very little difference between chemically different antimicrobial agents in their degree of pleural penetration (16).

Most antibiotics exhibit good lung penetration. Blood concentrations of ampicillin and penicillin G were higher than those in lung sites. The pulmonary and blood concentration ratios of orally and intravenously administered amoxicillin and cefotaxime were greater than 1 at 5-6 hours after the last dose. Oral administration or intravenous in

fusion of linezolid and levofloxacin resulted in higher concentrations in pleural fluid than in serum. The higher concentration of the drug at the sites of infection compared to that in the blood may be associated with changes arising from the inflammatory process. Inflammatory conditions cause vasodilation of capillaries and loss of selectivity of penetration of large molecules through membrane cells. Increased membrane permeability facilitates the ability of antibiotics to penetrate the lung. The degree of expression of inflammation and the stage of empyema may influence lung penetration capacity, as demonstrated by the use of β-lactams, clindamycin, oleandomycin, and erythromycin. Lung penetration decreases with a reduction in the expression of the inflammatory process (14).

In pharmacokinetic studies, the penetration of antibiotics into the pleura is assessed by calculating the ratio of the total area under the curve (AUC) for the concentration of a given antibiotic in the pleural fluid to the serum concentration. In an experimental pleural empyema model in animals, penicillin exhibited the highest pleural fluid to serum AUC ratio (AUCLP/S), followed by metronidazole, ceftriaxone, and clindamycin. Most studies have indicated that aminoglycosides have poor pleural penetration and are inactivated by the acidic environment of the infected pleural space. Gentamicin had the lowest ratio in this study. Therefore, due to the low pleural penetration and the tendency of aminoglycosides to be inactivated in the acidic environment of the infected pleural space, this group is not recommended for the management of pleural infections. In a study of humans with parapneumonic effusions, ceftriaxone concentration remained above the minimum inhibitory concentration level for most susceptible organisms for 53 hours after a single parenteral dose. In patients with *Staphylococcus aureus* MRSA mediastinitis given linezolid, the drug had an AUCLP/S of 1.64, suggesting that it is a rational therapeutic option in resistant pleural infections (2, 4, 5, 13).

Fluoroquinolones, antimicrobial preparations with a large volume of distribution, exhibit extensive tissue penetration. The respiratory fluoroquinolones, moxifloxacin or levofloxacin, are recommended as initial empirical antibiotic therapy for patients with respiratory infections, including pleural effusion, due to their high activity against gram-positive and gram-negative bacteria, including anaerobes. Several studies have investigated ciprofloxacin penetration into pleural fluid. Analysis of the structure of moxifloxacin, specifically the absence of the piperazinyl ring, revealed that the antimicrobial activity is not affected by acidic conditions. Thus, novel fluoroquinolones, including moxifloxacin, may be an attractive treatment option for pleural infections. The study determined inter-individual variability in moxifloxacin pharmacokinetics due to patient condition, concomitant drug administration, and competition for the same metabolic pathways. Examination of similar pharmacokinetic parameters (Cmax, AUC) confirmed moxifloxacin's ability to penetrate tissue compartments independent of the degree of inflammation or pH reduction. Therefore, the empirical use of moxifloxacin in the treatment of parapneumonic effusion and empyema is supported by its sufficient penetration into the pleural space and a favorable pharmacokinetic profile, regardless of the origin of pleural fluid (15).

There are few reports describing vancomycin penetration into the pleural cavity, and the available data are inconclusive. In pleural empyema, the parietal pleura, which consists of the mesothelial cells lining the pleural cavity, may already be thickened, and the minimum inhibitory concentration (MIC) of vancomycin may not be sufficient for a bactericidal effect. However, other studies report the efficacy of vancomycin administration in patients with pleural empyema caused by sensitive gram-positive bacteria. In some countries, increasing cases of resistance have been observed, especially in enterococci, including multiresistant strains of *Enterococcus faecium* (7).

An important clinical issue is the duration of antibacterial treatment. The duration of antimicrobial therapy in pleural infection is an area lacking in evidence and is largely based on expert opinion and extrapolation from recommendations for the treatment of lung abscess. The recommended duration ranges from 2 to 6 weeks, and the authors suggest a minimum of 4 weeks (including both intravenous and oral treatment). Discontinuation of treatment (less than 2 weeks) increases the risk of recurrence. However, the duration should be guided by the response to therapy, improvement in clinical symptoms, positive dynamics and/or radiographic resolution, and improvement in laboratory markers of infection (2-4, 6, 13).

Another issue that needs to be assessed is the optimal time to switch from intravenous to oral antibiotics or to perform de-escalation therapy (stepwise). This could be done in the context of analyzing the clinical response and biochemical parameters and could coincide with the time of chest tube removal. Current guidelines recommend switching from intravenous to oral antibiotics when there has been clinical improvement with normal body temperature, resolution of inflammation, and radiological improvement. A retrospective study showed that 3 weeks of antimicrobial therapy was usually adequate to prevent treatment failure. Treatment options with intrapleural enzyme therapies and surgery could serve as additional arguments for reducing the duration of antibiotic regimens (5, 13).

CONCLUSIONS

1. In patients with pleural empyema, gram-negative pathogens, commonly associated with hospital-acquired infections, were detected. Most of the bacterial isolates exhibited a high level of resistance to commonly prescribed empirical therapies.
2. Antibacterial preparations (beta-lactams, fluoroquinolones, polymyxins, glycopeptides, nitroimidazole derivatives) were carefully selected, taking into account their beneficial pharmacokinetic properties for penetration into pleural fluid and their activity against anaerobic flora.
3. The dosing regimen needs to be reviewed based on pharmacokinetic properties and the ability to penetrate the pleural space for patients with pleural infection.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

ETHICAL APPROVAL

Since the article does not involve ethical risks, no research approval was required from the Ethics Committee.

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There is no information.

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