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Research Article

Modern approaches to pharmacotherapy of Community-Acquired Pneumonia

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Abstract

Introduction: The study presents current views on the pharmacotherapy of community-acquired pneumonia (CAP). This study also describes in general terms the current pharmacoepidemiological situation of the CAP in Russia and abroad, which can both help medical professionals make an informed choice when choosing a pharmacotherapy, and inspire them to follow-up research and observations.

The aim of the study is to conduct an analysis of the available research on the pharmacotherapy of CAP in order to accelerate the accumulation and assimilation of knowledge in the field of this pathology.

Materials and methods: The following databases of medical publications and electronic libraries were used to search for the relevant sources of information: PubMed, Medline, Google Scholar, Crossref, and eLIBRARY.RU.

Results and discussion: The choice of a rational antimicrobial therapy (AMT) for CAP is of high relevance due to the widespread of the pathology. The article highlights modern approaches to the pharmacotherapy of CAP in adults, including a review of promising new drugs, and presents the main problematic issues related to the emergence of antibiotic resistance of pathogens, as well as methods to combat it.

Conclusion: The analyzed and generalized results of the conducted research allow the authors to make a conclusion about the feasibility of a more detailed study and raising the level of awareness of medical professionals in this pathology.

Keywords

clinical recommendations, antibiotics, antimicrobial therapy, COVID19, SARS-COV2, community-acquired, pneumonia.

Introduction

CAP is an acute infectious disease characterized by focal lung lesions with intra-alveolar exudation, detected by objective and x-ray examination, and is accompanied by fever and intoxication. The paradox of pneumonia is that, on the one hand, significant results have been achieved in understanding the pathogenesis of this pathology and in increasing the effectiveness of antibiotic therapy (Cillóniz et al. 2018), but, on the other hand, the number

of patients with a severe disease increases annually; therefore, mortality increases.

Studies in this area are actively conducted in almost all countries of the world (Ambaras Khan and Aziz 2018; ERRATUM 2019b). Therefore, CAP is a modern medical challenge, covering a number of epidemiological, clinical, pharmacological and social aspects. In the Asian multicenter surveillance study (Poulakou et al 2017; Bjarnason et al. 2018), the annual incidence of CAP in adults was 16.9 cases per 1,000 people per year; the incidence of CAP in men was higher. The incidence of CAP in Europe is lower – 1.07–1.2 cases per 1,000 people per year, with an even higher rate in men. Annually, 5.6 million patients with CAP are registered in the United States, with 1.1 million of them hospitalized, with 10 000 of those patients later dying during hospitalization, and one in three adults dying within one year after being hospitalized with pneumonia. In general, the mortality rate of outpatients with CAP in the USA varies from 1 to 5%, and that of inpatients – 12%, and the mortality rate among those treated in intensive care units reaches 40% (Mikasa et al. 2016; Uyeki et al. 2018). In South America, there is limited data on the prevalence of CAP: according to the 2010 data, the annual incidence rates in Argentina, Chile and Brazil were 120,000, 170,000 and 920,000 cases, respectively. The improved care of patients with CAP in South Africa is especially important due to the high incidence rate and the need to improve antibiotic prescribing standards in the face of increasing antibiotic resistance. According to the statistical report on the state of mortality in South Africa, influenza and CAP together were ranked sixth among the leading causes of death in 2015 (Athlin et al. 2018; Skinner et al. 2018).

More than 2 million people have CAP every year in Russia, which is 3.86 per 1,000 cases of the disease. The highest risk group includes people under 5 years old and over 75 years old (Escobar et al. 2019; Weinberger 2019). The CAP mortality rate is 5%, but it reaches 21.9% among patients requiring hospitalization and among the elderly – 46% (Metersky and Kalil 2017; Frantzeskaki and Orfanos 2018).

Economic losses associated with the management of patients with CAP are significant. For example, in the United States, CAP treatment expenses amount to about 20 billion dollars annually, with a considerable part of the costs spent on CAP inpatients (Lyons and Kollef 2018, Almansa et al. 2017). In Australia, CAP costs are estimated at over 300 million annually; and the number of CAP hospitalizations is more than that in any other disease – 61 000 hospitalizations per year (Sweeney 2019). Significant economic costs are often caused by adverse outcomes for hospitalized patients, such as loss of respiratory function and, as a result, the need for artificial pulmonary ventilation, high incidence of nosocomial adverse events (risk of developing nosocomial infections, vascular complications) (Torres-García et al. 2019).

CAP in the elderly is another challenge. According to the demographic forecast of the Russian Federal State Statistics Service, the share of people over working age in the total population will increase from 22.7% to 28.9% by 2031. Many of risk factors are especially relevant for the elderly, determining higher mortality rates for them. The risk of protracted pneumonia also increases, which contributes to the development of antibiotic resistance. The presence of comorbidity plays a great role in the development of pneumonia in the elderly. In Russia, the frequency of comorbidity is 94.2% (Sweeney 2019). According to Y. NanZhu based on an analysis of 980 case histories, the number of chronic diseases varies from 2.8% in young patients to 6.4% in elderly people (NanZhu et al. 2019) Not only the diseases but also their supportive therapy are important. For example, the use of statins, the most significant tool to reduce hyperlipidemia, has very mixed results (Turchinovich et al. 2019). Along with materials concerning reducing CAP mortality, the obtained data did not exclude a possible increase in pneumonia incidence while taking statins. Currently, there is some evidence that the use of proton pump inhibitors (PPIs) increases the risk of CAP developing. PPIs and H2 receptor blockers, reducing the acidity of gastric juice, leads to gastric and oral bacterial overgrowth, causing microaspiration pneumonia.

Environmental effects in CAP development should be highlighted. A number of studies reported that traffic-related air pollution through a massive release of nitric oxide (NO) and particulate matter with an aerodynamic diameter of ≤10 mcm is associated with the development of pneumonia in children (Torres-García et al. 2019). The European Study of Cohorts for Air Pollution Effects (ESCAPE) found that pneumonia diagnosed by a doctor in early childhood was largely associated with environmental exposure. A prospective cohort study of 3,677 children in Southern California showed that compared to the children living more than 1,500 m away from the highway, the children living within 500 m of the highway had a deficit in forced expiratory volume per 1 s (FEV1) and peak expiratory flow (PEF). Another systematic review also showed a positive relationship between the daily level of environmental pollutants and hospitalizations of children with pneumonia.

So, all the leading medical communities are involved in the issues of diagnosis and rational pharmacotherapy of CAP, in view of its high relevance and medical significance (ICPIC 2019a).

The aim

To organize and conduct an analysis of the available relevant research on CAP to accelerate the accumulation and assimilation of knowledge in the field of this pathology.

Materials and methods

The organization and analysis of the available data on the pharmacotherapy of CAP was performed using the method of document retrieval. The following databases of

medical publications and electronic libraries were used to search for the relevant sources of information: PubMed, Medline, Google Scholar, Crossref, eLIBRARY.RU.

Results and discussions

The etiological and pathogenetic similarities among patients with CAP make it possible to determine the general features for the management of patients with this pathology. Most pulmonary societies claim that patients with mild and moderate forms of CAP can be treated by oral drugs, either at hospital or on an outpatient basis, and if tablets cannot be taken, parenteral pharmacotherapy is recommended. The average therapy duration for uncomplicated CAP is 5 days (Akagi et al. 2019). However, the pharmacotherapy duration should be increased if the initial empirical therapy has no effect against a specific pathogen or if pneumonia is complicated by an extrapulmonary infection. The antibiotic therapy can be stopped if patients have normothermia for 48–72 hours and positive clinical dynamics. Unfortunately, a large number of doctors make mistakes when choosing a pharmacotherapy. Thus, according to the results of a survey of 588 general physician from 14 centers in Russia, the Ukraine and Kyrgyzstan; the rate of correct answers to the questions about pharmacotherapy for non-severe community-acquired pneumonia in patients with risk factors and/or comorbidities was 24.2% (ranging from 1.3% to 62.9% among the centers, $p < 0.01$); the treatment regimen for the patients with neither risk factors nor comorbidities was 27.0% (ranging from 2.5% to 74.5%, $p < 0.01$) (Bontsevich et al. 2018; Bontsevich et al. 2019; Bontsevich et al. 2020).

Despite the similarities in the etiology and pathogenesis of CAP, there are some differences in the approaches to the pharmacotherapy over the world. For example, the guidelines for management of CAP patients, developed by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) and revised in 2019 (Kamat et al. 2018; Wan et al. 2019), offer the following guidelines for managing patients with CAP:

1. The use of the pneumonia severity index (PSI) to determine the severity of CAP and to decide on the a place of treatment for the a patient;
2. The earliest possible start of an antibiotic therapy with an established diagnosis of CAP;
3. Fast removal of fluid and electrolytes and treatment of hypoxia in patients with CAP;
4. Early activation of patients;
5. Prevention of thromboembolism and cardiovascular complications.

The American Society for Infectious Diseases (IDSA) and the American Thoracic Society (ATS) offer the following antibiotic regimen for patients on outpatient treatment without either concomitant diseases or risk factors: 1 g of amoxicillin three times a day or macrolide (500 mg of azithromycin once a day and then 250 mg per day or 500 mg of clarithromycin twice a day) or 100 mg of doxycycline twice a day. In this case, the use of macrolides is possible only with their resistance to pneumococcus less than 25%. During the influenza season, it is also advisable to start treatment with oseltamivir, zanamivir, or baloxavir in outpatients with CAP.

Treatment of patients with a concomitant pathology (chronic cardiovascular diseases, diseases of the lungs, liver or kidneys; diabetes; alcoholism; malignant tumors; asplenia; immunosuppressive conditions; previous antibiotic therapy for 90 days or other risk factors for the development of drug-resistant infection) includes combined beta-lactam antibiotic therapy (1 g of high-dose amoxicillin 3 times a day, 2 g/125 mg of amoxicillin/clavulanate 2 times a day or 500 mg/125 mg –3 times a day, or 875 mg/125 mg – 2 times day, 200 mg of cefpodoxime 2 times a day or 500 mg of cefuroxime 2 times a day) with a macrolide or doxycycline; or monotherapy with respiratory fluoroquinolone (400 mg of moxifloxacin per day, 750 mg of levofloxacin per day).

According to the recommendations of the Canadian Infectious Disease Society and the Canadian Thoracic Society, macrolides are the drugs of choice for CAP therapy in patients without any concomitant diseases and risk factors (for COPD (Chronic obstructive pulmonary disease) – clarithromycin, azithromycin); doxycycline is considered as an alternative; in the presence of the class ”modifying” factors the drugs of choice are respiratory fluoroquinolone or amoxicillin/clavulanate, second-generation cephalosporins in combination with macrolides.

The Japanese Respiratory Society recommends starting treatment of CAP with high doses of penicillin (in patients with neither risk factors nor concomitant diseases) (Lee et al. 2018). In the case of atypical pneumonia, macrolide or tetracycline is the first choice. Respiratory fluoroquinolones should be reserved as alternative drugs (Waites et al. 2017). Pharmacotherapy of CAP in elderly patients has a special place in the recommendations (according to some data, it reaches 30% in Japan); the probability of an atypical pathogen increases in this cohort of patients, and therefore an initial therapy of respiratory fluoroquinolones for these patients can be considered positive (Yamazaki and Kenri 2016).

As noted earlier, there are a number of important international guidelines, including recommendations from IDSA/ATS), the Japanese Respiratory Society, etc. However, South Africa is a unique environment with a high prevalence of both HIV infection and a high level of antibiotic resistance, so the principles of CAP treatment should be developed at the local level. Societies interested in rational pharmacotherapy for CAP in South Africa include the South African Thoracic Society and the Federation of Infectious Diseases Societies of Southern Africa. Their recommendations for managing patients with CAP include the following rules: outpatients ≥65 years of age who have received antibiotics for the previous 90 days or have concomitant diseases should receive oral

amoxicillin/clavulanate or second-generation oral cephalosporin. An alternative is the use of oral respiratory fluoroquinolone in the presence of severe beta-lactam allergy. Patients with severe CAP should be treated with a combination of amoxicillin/clavulanate, cefuroxime or third-generation cephalosporin (ceftriaxone, cefotaxime) + macrolide/azalide antibiotic. An alternative regimen for severe CAP is respiratory fluoroquinolone, which should be combined with another antibacterial drug, most often a beta-lactam one.

New pharmacotherapy options for CAP include: omadacycline, lefamulin, solithromycin, ceftaroline, nemonoxacin, and delafloxacin (Voelker 2019). Omadacycline is a new tetracycline that bypasses the previous mechanisms of bacterial resistance; it turned out to be an equivalent drug during the second three-phase randomized study in the treatment of CAP. Nevertheless, the results of the study published in The New England Journal of Medicine (Katsurada et al. 2017; Barber et al. 2018) leave open the question of whether an antibiotic approved in the USA (and soon to be approved in Europe) can help with the treatment of complicated infections (Maravi-Poma et al. 2011; LaPensee et al. 2019). Lefamulin is a semi-synthetic antibiotic of the pleuromutilin class, which was found to be non-toxic compared to moxifloxacin in the third phase of the study in 2019, and was approved for use in the United States in the same year (Alexander et al. 2019). Lefamulin is indicated for the treatment of bacterial infections caused by *S. pneumoniae*, *S. aureus*, *H. influenzae*, *Legionella pneumophila*, *M. pneumoniae* or *Cl. Pneumoniae* in adults (Lefamulin 2019c). Ceftaroline is the 5th generation cephalosporin, which when compared with other cephalosporins is superior in activity against gram-positive bacteria, including multi-resistant strains of *S. pneumoniae* and MRSA (*methicillin*-resistant *Staphylococcus aureus*). Clinical trials of FOCUS 1 and FOCUS 2 have proven the efficacy and good tolerance of ceftaroline in the treatment of CAP in hospitalized patients. The main indications for the use of this drug are CAP and complicated infections of the skin and soft tissues (Rosanova et al. 2018; Sader et al. 2018). Nemonoxacin is an antibiotic from the group of non-fluorinated quinolones; its studies have demonstrated safety and efficacy compared to levofloxacin in 3 trials, mainly in Asia and Russia. During clinical studies of nemonoxacin, a high activity of the drug was observed in relation to MRSA, to pneumococci and staphylococci, resistant to respiratory fluoroquinolones, and to other gram-positive, gram-negative and atypical microorganisms (Chang et al. 2019). Delafloxacin, a new respiratory fluoroquinolone, has an advantage in activity against both MRSA and pseudomonads; in October 2019, it was approved for the treatment of bacterial CAP in adults in the USA (File Jr et al. 2016; Hoover et al. 2017).

In the past decade, there has been an increase in the incidence of viral pneumonia. About 500 million people get the flu every year, with 2 million of them later dying from various complications. This disease is a significant medical and social problem, primarily due to the magnitude of the incidence rate, a large number of complications and the economic losses associated with these factors: about 20 billion dollars is spent annually on the treatment of influenza and its complications (primarily CAP). Another unpleasant and very dangerous feature of this "ordinary" disease is its unpredictability (Kim et al. 2019; McLaren et al. 2019). Depending on the pathogen's virulence, the presence of concomitant diseases, as well as the age of a patient, viral pneumonia can vary from mild-severity to life-threatening disease (Dugan et al. 2017). In men, viral CAP develops more frequently than in women.

Complications of influenza can be divided into those that are caused directly by influenza infection, and those that are caused by secondary bacterial microflora. The most dangerous among influenza complications are lung lesions. According to the mechanism of development, severity of the course and consequences, scientists distinguish primary influenza pneumonia, which develops on the 2nd–3rd day of the disease, and secondary influenza-bacterial pneumonia, which develops at the end of the 1st or the beginning of the 2nd week from the onset of the disease.

Earlier, viruses were believed to cause only 8% of CAP cases resulting in hospitalization, but current studies have shown that viruses are responsible for approximately from 13% to 50% of viral CAP cases and from 8% to 27% of cases of mixed (bacterial-viral) etiology. Among all cases of community-acquired viral pneumonia in adults, type A and B influenza viruses account for more than 50% of cases. The available studies have shown a different role in the etiology played by other viruses that cause CAP: respiratory syncytial virus (RSV) – from 1% to 4% of cases, adenovirus – 1–4%, parainfluenza virus – 2–3%, human metapneumovirus – 0–4% and, relevant to date, coronavirus – 1–14% of CAP cases (CDC Home 2014; Huijts et al. 2017).

Influenza A and B viruses have a particularly significant effect on elderly patients already suffering from various chronic diseases. It has been estimated that at least 63% of the 300,000 hospital admissions associated with influenza and 85% of the 36,000 deaths from influenza occur in patients 65 years old and older, although this group makes up only 10% of the population (Fathima et al. 2018). Human respiratory syncytial virus (HRSV) is becoming an increasingly important etiological factor in the occurrence of viral pneumonia in infants, children and elderly patients, causing 2–9% of the annual 687,000 hospital admissions and 74,000 deaths from pneumonia in these populations (Petarra-Del Río et al. 2017).

In healthy adults, as well as in children, most viral CAP cases proceed as a mild course of the disease. The main exception to this rule was the 2009–2010 H1N1 pandemic, when the infection was more common among the middle-aged population than among the elderly. It was considered that this was due to the lack of contact and immunity to the 1957 (and ealier) H1N1 influenza strain (s).

The etiological role of acute viral pneumonia is often underestimated in pregnant women, but unlike bacterial pneumonia, a viral one can have a serious and rapid clinical evolution. Pregnant women with viral pneumonia are believed to have a higher risk of developing serious diseases than other women. Pregnant women have a disproportionate risk of severe H1N1 infection since 2009 (Mehta et al. 2015).

At the end of 2019, a new coronavirus (2019-nCoV) was identified as the cause of the accumulation of cases of viral pneumonia in Wuhan, Hubei Province, China. Between December 31, 2019 and February 24, 2020, 79,360 cases of COVID-19 infection and 2,618 deaths were recorded (Cadell and Stanway 2020). Two cases of infected tourists were reported: one in Japan, the other in Thailand. One case wasreported in Washington State, United States of America.

Pharmacotherapy of viral pneumonia differs from that of pneumonia of bacterial etiology; however, in both cases, the earliest initiation of treatment leads to a decrease in the frequency of complications. USA centers have approved two drugs for the treatment and prevention of influenza A virus: amantadine hydrochloride and its synthetic counterpart – rimantadine hydrochloride. The mechanism of action of these drugs is by blocking the M2 protein in the viral ion channel, which inhibits the further spread of the virus. Both drugs are well absorbed orally. However, neither of the drugs are active against influenza B virus; many of the existing viral strains have now lost their sensitivity to amantadine/rimantadine (including the H1N1 influenza virus) (CDC Home 2014). Thus, during the 2009–2010 H1N1 flu epidemic, the Centers for Disease Control and Prevention of the United States recommended oseltamivir or zanamivir (neuraminidase inhibitors) for the treatment of all hospitalized patients with suspected or confirmed disease and for outpatients with an increased risk of complications of H1N1 infection. The mechanism of action of this pharmacological group is the following: they block the surface protein of neuraminidase, as a result of which the virus is retained inside the infected cells of the respiratory epithelium, thereby preventing the spread of infection and the occurrence of further bacterial superinfection. Neuraminidase inhibitors are active against both type A and type B influenza viruses (Fathima et al. 2018). The results of studies of zanamivir and oseltamivir confirmed their effectiveness only if a therapy was started within 24–48 hours from the onset of symptoms in febrile patients. In severe influenza CAP cases, antiviral drugs should be prescribed even after 48 hours.

Conclusion

Thus, the rational pharmacotherapy of CAP is of high interest among the leading medical communities all over the world. The following problems of pharmacotherapy of CAP should be highlighted: arbitrary use of antibiotics, such as macrolides or β-lactams, without any recommendation from a physician, which leads to the development of further drug resistance; potential underestimation of the role of viral etiology in the development of CAP; increased population's susceptibility to pneumococcal and influenza vaccination, especially among children and people 65 years old and older. A correct assessment of a patient's condition, along with an immediately started and rationally selected pharmacotherapy, will both reduce morbidity and mortality in each age group, and reduce enormous economic damages caused by acute respiratory diseases, including CAP. Therefore, raising the level of senior medical students' and physicians' awareness in the management of patients with CAP, their high-quality professional training are a priority in practical medicine. The essence of this study is to describe in general the current pharmacoepidemiological situation with CAP in Russia, which may both help medical practitioners and future doctors to make an informed choice of therapy administration and inspire them to further research and observations.

Conflict of interests

The authors have no conflict of interest to declare. The study was conducted without the participation of any sponsors.

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