Original Article

Current aspects of antibacterial drug administration when treating nosocomial Pneumonia

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ABSTRACT

The article presents a literature review on the current aspects of antibacterial drug administration when treating nosocomial pneumonia. Current data are presented regarding the most important scientific and practical issues of development, justification, and clinical use of modern antibacterial therapy for nosocomial pneumonia.

Keywords: antibiotic drugs, nosocomial pneumonia, antibacterial therapy, antibiotic, carbapenem

Introduction

Despite continuously developing medical technologies and improving approaches to prevent, diagnose, and treat nosocomial pneumonia (NP). This nosological form is still one of the most common infectious diseases development of which is associated with medical care provision. According to relevant data, NP dominates in the structure of nosocomial infectious complications in the most severe category of patients treated in intensive care units (ICU) [1, 2]. NP development is not only associated with a significant deterioration in treatment outcomes but also leads to a significant increase in patients' staying duration and cost in ICU and in-hospital [3, 4].

More than 50% of all antibiotic drugs (AD) administered in ICU are related to the need to treat NP. This condition is inevitably associated with an increase in pathogenic strain resistance to antibacterial therapy, which further aggravates the problem of AD administration, reducing their effectiveness [5]. All these conditions are the reason for the rational use of antibacterial drugs when treating nosocomial pneumonia.

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Materials and Methods

When writing the article, the following methods were used: general scientific (dialectical, analysis and synthesis of literary data available, comparisons and analogies, annotating, note-taking and referencing of data obtained from contemporary scientific sources) and special (systematic, comparative analysis, etc.).

Results and Discussion

Currently, two NP antibacterial therapy modes are distinguished: empirical and targeted (etiotropic). Empirical antibacterial therapy is a starting point for the majority of patients [6-10]. When conducting it, specific drugs are selected based on their potential efficacy in a particular clinical situation. At the same time, in the majority of cases, information on the assumed infectious pathogens, local monitoring of nosocomial microflora spectrum, and their antibiotic resistance are relied on. Subsequently, when bacteriological examination results are

obtained, AD is changed, if required, switching to their targeted administration [4].

The basic principles of effective empirical antibacterial therapy include timeliness of its start and reduced AD administration [11]. Several clinical studies have shown a significant deterioration of treatment outcomes in cases of inadequate AD choice for initial empirical NP therapy [12, 13].

Most contemporary authors point out that when forming the empirical antibacterial therapy strategy, it is required to consider risk factors that involve poly-resistant pathogenic strains [5, 14]. Thus, in case of high risk for antipseudomonal infection to develop, treatment should include AD with antipseudomonal activity. Such drugs include cephalosporins (cefepime, ceftazidime, cefoperazone/sulbactam), carbapenems (meropenem, imipenem, doripenem), fluoroquinolones (levofloxacin, ciprofloxacin), piperacillin/tazobactam. When identifying risk factors for staphylococcal infection, having methicillin resistance (MRSA) in particular, it is recommended that antibacterial therapy include AD having high potency against resistant gram-positive strains. The most effective of these drugs are vancomycin, linezolid, and telavancin [11, 12].

According to contemporary literary sources, AD that has no anti-MRSA or antipseudomonal activity can be considered to be administered in patients with early NP (debuting no later than 4 days from admission to the hospital) with no risk factors for resistant microorganisms. In the cases shown, such drugs as ceftriaxone, cefotaxime, moxifloxacin, ertapenem, ampicillin/sulbactam, amoxicillin/clavulanate can be administered [11, 15].

An important factor is the increased probability of infection with pathogens having resistance to carbapenems: acinetobacter, enterobacteria, and pseudomonades [16, 17]. In recent years, these strains, characterized by the products of various carbapenemase types: NDM, KPC, OXA-48, VIM, etc., have become increasingly common in Russian hospitals [1]. A characteristic feature of pathogens producing carbapenemases is the associated resistance to the AD of different groups. At the same time, sensitivity is often preserved only to polymyxin and tigecycline. Thus, it should be considered that carbapenems are now no longer universal drugs to treat NP, due to the increasing prevalence of strains resistant to them [17]. On the other hand, no effective NP empirical antibacterial therapy caused by carbapenemase-producing bacteria has been developed. Therefore, most contemporary authors point to the need to use carbapenems with antipseudomonal activity (doripenem, meropenem, imipenem) in combination with drugs effective against resistant gram-positive bacteria (vancomycin, linezolid, telavancin) as a starting empirical therapy to treat severe NP forms [15, 18].

One of the most effective broad-spectrum antibiotics used to treat NP is doripenem, which is resistant to most beta-lactamases, including cephalosporinases and penicillinases. Doripenem has a bactericidal effect, which is realized by penicillin-binding protein inactivation, leading to blocking the synthesis of the microorganism cell wall [19]. As a result of several studies, the high efficacy of doripenem when treating NP associated with infectious-inflammatory processes in the urinary abdominal cavity and the urinary system was established [20]. The advantages of doripenem administration, in comparison with other carbapenems, include its higher activity against Pseudomonas aeruginosa, which is 2-4 times higher than that in meropenem and imipenem, as well as a lower probability to develop resistance with these pathogens [19, 21].

Today, the advantages and disadvantages of combination antibacterial therapy over monotherapy are still undetermined entirely. Combination therapy is supported by the results of studies demonstrating a higher probability to achieve the required clinical effectiveness when applying this technique to treat NP caused by multiresistant strains. This is due not only to the higher estimated probability of empirical therapy efficacy but also due to potential AD synergy. At the same time, most researchers generally point to the lack of significant differences between antibacterial combination and monotherapy both in terms of the probability to achieve a clinical effect, and the survival rate [22-25].

An important factor to ensure the NP antibacterial therapy efficacy is a rational choice to administrate AD, which depends on several factors, the major of which are the severity of the patient's condition, as well as antibiotic pharmacokinetic and pharmacodynamic properties [15]. The intravenous way to administer AD is recognized as the most effective way to administer the majority of ADs in NP which provides 100% drug bioavailability. When the condition is stabilized, pathology severity is reduced and no significant gastrointestinal function disorders are observed, there is an opportunity to switch to oral AD administration if this way to administer drugs provides an acceptable level of particular drug bioavailability. Such a strategy is called step-down therapy. Drugs having high oral bioavailability include fluoroquinolones and linezolid [11]. It should also be considered that different ADs have different degrees of affinity for pulmonary tissue. For example, fluoroquinolones and linezolid quickly penetrate the pulmonary tissue and reach effective concentrations there, while vancomycin and daptomycin have this ability to a substantially lesser extent [13].

Effective AD administration when treating NP directly depends on their pharmacokinetic and pharmacodynamic properties. Thus, the antibacterial action intensity of several drugs, which include beta-lactam antibiotics, is determined by concentration duration in the affected area above the minimal inhibitory concentration (MIC), which requires repeated administration during the day. An approach based on extended or continuous beta-lactams infusion is recognized as promising, which, according to several studies, has some advantages in improving pharmacokinetic and perhaps clinical indicators. At the same time, no compelling evidence enabling to expect improved treatment outcomes as a result of such AD administration pattern has not yet been obtained [3, 11, 13].

Another group of drugs having similar pharmacokinetic properties is ADs the effectiveness of which depends on their maximum concentration in the affected area, the increase of which leads to an increase in the probability of pathogen

excretion. Antibiotics of this group include aminoglycosides and fluoroquinolones. Thus, when studying aminoglycosides, it was found that switching to a single drug administration with an appropriately determined daily dose increases antibacterial therapy effectiveness and safety [26].

The challenge of AD clinical administration when treating NP is associated not only with the increasing nosocomial strain resistance but also with the limited ability to penetrate the pulmonary tissue in several modern drugs, which is a significant obstacle to a causative agent eliminated in the lesion. Often, intravenous administration of a potentially toxic AD dose is required to achieve a therapeutic drug concentration in the pulmonary tissue. These conditions determine the necessity to administer drugs using inhalation to ensure antibacterial therapy effectiveness and safety [11]. In the contemporary literature, one can find the results of some clinical and experimental studies that indicate the effectiveness of inhaled AD administration belonging to the group of aminoglycosides (amicacin, tobramycin), polymyxins (sodium colistimethate), cephalosporins with antipseudomonal activity (ceftazidime) [13, 27].

When injected intravenously, aminoglycosides penetrate the pulmonary tissue rather poorly - less than 30%, and have pronounced nephrotoxicity. In case aminoglycosides are injected intravenously, the risk of renal injury development exceeds 25%. At the same time, achieving a sufficiently high concentration of this AD group in the bloodstream does not provide an effective drug concentration in the pulmonary tissue, which not only prevents pathogen eradication but also contributes to an increase in their resistance. This problem can be solved by inhaled aminoglycoside administration, thereby achieving an effective concentration in the pulmonary tissue and avoiding nephrotoxicity [13, 28].

The inhaled form of tobramycin administration is the most widespread in Russia and around the world. When inhaling, this drug remains in the airways, practically not getting into the blood. In this case, drug bioavailability depends on several conditions, which include the degree of airway damage and inhalation technique. It was found that when tobramycin was inhaled at a dose of 300 mg, sputum drug concentration reached 1237 μg/g in 10 minutes. This is more than 10 times higher than tobramycin concentration when administered intravenously. At the same time, 1 hour after the drug is inhaled, its plasma concentration does not exceed 0.9 μg/ml [27].

In the course of a multicenter retrospective study, it was found that tobramycin inhaled administration, being part of an NP empirical antibacterial therapy caused by multiresistant strains and having its clinical inefficiency, ensures an increase in successful infectious treatment by 32% and reduce the duration of the required invasive respiratory support by 3 days. Also, the cases of complete agent eradication increased by 24% [27].

When conducting a multicenter clinical study aimed to study the effectiveness of inhaled amicacin administration to treat NP caused by multiresistant pathogens, it was found that drug concentration in the lungs was 976 μg/ml on average, which exceeded the pathogenic strain MIC by more than 100 times. Against this background, the amicacin plasma concentration was significantly lower than toxic, at 0.9 μg/kg/min [28, 29]. Also, several experimental studies demonstrate higher efficacy of ceftazidime inhaled administration in NP compared to intravenous administration [30, 31].

The efficacy of the inhaled sodium colistimethate administration to treat NP is undisputed today. If the drug is administered intravenously, no significant concentrations are detected in pulmonary tissue [32]. Given the pronounced nephrotoxicity of the current AD, the drug use is recommended only when inhaled. Despite the obvious advantages of antibiotic inhaled administration when treating NP, it should be borne in mind that a significant amount of lung damage is a serious obstacle for Ads to get into the pulmonary tissue, which may be associated with the ineffective antibacterial therapy [12].

An extremely important factor in the clinical use of ABP in the treatment of NP, which is not always taken into account by practitioners, is the use of original or generic drugs. At the same time, it is worth noting that all clinical studies, the results of which formed the basis of modern recommendations on the use of ABP in the treatment of NP, were carried out using original drugs. At the same time, publications devoted to comparing the microbiological and clinical effectiveness of original and generic ABPs are quite rare in the modern literature. However, a number of available studies demonstrate lower antibacterial activity in generics compared to original drugs, even despite comparable pharmacological indicators [17]. Thus, probably in the treatment of the most severe, life-threatening forms of NP, the choice should be made in favor of the original ABPs.

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One of the most significant problems of antibacterial therapy in NP is currently due to the fact that in recent years pathogenic gram-negative strains belonging to the Enterobacteriaceae and Acinetobacter spp family, which have resistance to carbapenems, have become increasingly widespread in hospitals around the world. The stability of these pathogens is based on the production of a number of enzymes - carbapenemases, which include class A serine beta-lactamases (CRS type) and class D (OXA-48), as well as class B metal-beta-lactamases

(NDM and VIM) [2]. As a rule, strains producing carbapenemases have resistance to other ABP groups of beta-lactams, as well as to other types of antibiotics, such as aminoglycosides and fluoroquinolones. Said pathogens in most cases retain sensitivity to polymyxin, tigecycline and phosphomycin [17]. An important circumstance is that the degree of resistance to carbapenems varies among pathogens producing different types of carbapenemases. Carbapenemases producers such as OCA and VIM have relatively low carbapenem MPC values, while significantly large MPC are characteristic of bacteria producing NDM type carbapenemases [2]. Data in the current literature indicate that meropenem retains sufficient activity in IPC at a level of ≤ 8-16 μg/ml. For other carbapenems, such data are not yet available [15].

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An indispensable factor for a successful antibacterial therapy of NP caused by carbapenemase-producing pathogens is to determine an enzyme type. This is because metal-beta-lactamases differ from serine carbapenemases' insensitivity to inhibitors. For example, the latest and the most effective beta-lactamases airbactam inhibitor is inactive concerning metal-beta-lactamases, but at the same time, it suppresses serine carbapenemases [4].

One of the most significant problems associated with antibacterial NP therapy is the lack of well-developed clinical research-based AD administration patterns to treat infections caused by carbapenemase-producing pathogens. There is evidence that when involved in monotherapy, polymyxin, or tigecycline administration, to which these strains are normally sensitive, is effective in no more than 50% of cases [4]. However, most researchers note a significantly higher efficiency of combined AD administration. Several studies show the effectiveness of the following drug combinations: tigecycline with a carbapenem, polymyxin B or E with a carbapenem, polymyxin B or E with tigecycline, polymyxin E with tigecycline and meropenem, tigecycline or polymyxin E with phosphomycin [33-36]. It should be noted that most studies mentioned above-examined treatment outcomes of patients whose NP was caused by carbapenemases-producing pathogens such as CRS. Therefore, it is not clear enough how much data obtained can be used to eradicate other types of carbapenemase producers.

An important factor to predict the effectiveness of a particular antibacterial therapy strategy when treating NP is the carbapenem MIC quantitative estimation. Thus, if the doripenem and meropenem index value is less than or equal to 8 μg/ml, most authors recommend carbapenem administration and administration of tigecycline or polymyxin as a secondary antibiotic, if possible. When the doripenem and meropenem MIC exceeds 8 μg/ml, carbapenem administration is likely to be ineffective [34]. However, it is worth noting that some reports in the contemporary literature showing the effectiveness of carbapenems administration combined with tigecycline or polymyxin in a similar case, which is due to antibacterial drug synergism [4].

Detection of pathogenic strains having high resistance against carbapenems requires administration of at least two active ADs, which are normally tigecycline and polymixins B or E [4]. Further third antibiotic administration, which can include aminoglycosides or phosphomycin, is reported. There are data on the potential effectiveness of combined administration of two carbapenems simultaneously: with antisinegnoic activity (meropenem or doripenem) and without it (ertapenem) [17]. There are also arguments for the effectiveness of the antibacterial therapy strategy, implying a combination of carbapenems with beta-lactamase inhibitors being part of other drugs (cefoperazone/sulbactam, ampicillin/sulbactam), which is due to class A and D serine carbapenemases sensitivity to sulbactam [34].

One of the latest broad-spectrum antibiotics administered to treat NP caused by multiresistant strains is ceftazidime/airbactim, the mode of action of which is to inhibit the extended-spectrum beta-lactamases, OXA-48, CRS, as well as class C chromosomally encoded beta-lactamases due to aviabactam. Thus, there is no ceftazidime activity inhibition, which ultimately effective against the producers of these carbapenemases, including multiresistant strains belonging to the Enterobacteriaceae family, as well as P. Aeruginosa [4].

Conclusion

The issue of a rational AD administration when treating NP has continued its relevance over the years. In contrast, over time, the challenge to choose an effective antibiotic to treat nosocomial infection has become increasingly complex because of the increasing spread of multiresistant strains, which is now ahead of newly developed antibacterial drugs. Some progress to improve treatment outcomes has been made by the clinical use of the latest combination of medicine, including the latest and

most effective beta-lactamase inhibitors. However, currently, many reports are indicating newly developed resistance in pathogenic strains to these drugs as well, which makes the struggle for life for a patient with NP even more severe.

Thus, the solution to improve NP antibacterial therapy is based on the implementation of several scientific and practical aspects, the major of which are: developing further effective antibacterial agent, creating new combinations of antibiotics that can overcome nosocomial strain resistance, as well as preventing excessive antibacterial drug administration in hospitals to prevent an increase in the spread of multiresistant infection. Solving the problems indicated requires close interaction between pharmacologists, representatives of the scientific medical community, and clinicians.

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