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RESEARCH ARTICLE

Antimicrobial Pharmacotherapy of Community-acquired Pneumonia in Liver Cirrhosis Patients: Accent on the Antibiotic Resistance Risk Stratification

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Abstract

There is a proliferation of bacteria that are resistant to many drugs. This has created the need to: identify risk factors for the acquisition of resistant pathogens; stratify patients infected with pathogens. Such pathogens should be considered when choosing the starting antimicrobial therapy for pneumonia associated with cirrhosis. Therefore, the aim of the work is to study the profile of antimicrobial resistance of community-acquired pneumonia (CAP) pathogens that are detected in patients with cirrhosis. While stratifying patients with the risk of infection by pathogens. A retrospective analysis was carried out of 216 patients who were hospitalized in a multidisciplinary hospital in 2016-2018 with CAP. The patients were with a positive result of a respiratory bacterial culture sampling. As a result, the most common microorganisms in patients with CAP and cirrhosis of the liver of alcoholic etiology were E. coli (34.6%), St.aureus (26.9%) and Klebsiella pneumoniae (23.1%). In patients with cirrhosis of the liver of mixed alcohol-viral etiology, the following microorganisms prevailed: St.aureus (36.1%), E.coli (31.2%) and Klebsiella pneumoniae (22.9%). After analyzing all the results, the authors came to the conclusion that the microorganisms (that cause CAP in patients with cirrhosis) differ depending on the etiology of cirrhosis and are mostly gram-negative (K.pneumoniae and E.coli). Besides, S.aureus appears frequency. In general, causative agents of CAP with multidrug resistance in patients with cirrhosis are detected in 28.5% of patients: 24.6% MDR and 3.96% XDR.

Keywords: *Pneumonia; Antimicrobial therapy; Antibiotic resistance; Risk stratification.*

Introduction

Liver cirrhosis is accompanied by a range of immunological disorders with a predominantly intense synthesis of proinflammatory cytokines. This condition is called cirrhosis-associated immune dysfunction syndrome (CAIDS). This syndrome refers to systemic inflammatory and immunodeficiency processes in patients with cirrhosis. The syndrome also depends on the degree of decompensation of hepatic functions and affects both the clinical manifestations and prognosis of cirrhosis, and increases the risk of infection [1, 3].

Infectious complications of cirrhosis are found in almost half of patients and are the cause of deaths in a third of cases [4].Among them, spontaneous bacterial peritonitis is leading; urinary tract infections and pneumonia are also common. Other infectious processes are much less common (bacterial meningitis, endocarditis, pleural empyema, infection of the skin and soft tissues, etc.) [5, 8].According to various authors, pneumonia takes 2-4 places among other infectious diseases in patients with cirrhosis. However, pneumonia (among all other infections) is the main infectious cause of death in patients with cirrhosis [9, 10].

The main principle of successful etiotropic therapy of pneumonia is the timely start of adequate antimicrobial therapy (AMT). The empirical choice of an antimicrobial drug (AMD) should be based on the following:

- The conditions of infection progression (community-acquired or nosocomial), which will allow one to choose a drug with the maximum coverage of all potential pathogens of the infection;

- The pharmacokinetics (antimicrobial spectrum, creation of therapeutically effective concentrations in lung parenchyma).

In addition, for effective pharmacotherapy, it is necessary for the pathogen to be sensitive to the prescribed drug [1].

On April 30, 2014, WHO published the report "Antibiotic resistance - a serious public health threat", which gives the main definitions of antibiotic resistance:

- It is the ability of infectious agents to withstand the effects of antimicrobials, as a result of which standard treatment becomes ineffective.
- It is a natural evolutionary phenomenon-under the influence of drugs, sensitive microorganisms die, and resistant ones can multiply, transmit resistance to their offspring and other microorganisms.

It is noted that antibiotic resistance develops as a result of the following:

- Inappropriate use of AMD;
- The use of low-quality drugs, as a result of which patients receive non-optimal drug concentrations, and the pathogens are not eradicated;
- The use of drugs in animal husbandry to stimulate growth or prevent disease;
- Low level of infection prevention;
- Weak epidemiological surveillance systems.

Along with the above, there has been a decline in the development of tools to combat such resistance [12].The data on antimicrobial resistance of key CAP pathogens are studied during ongoing multicenter monitoring studies, the results of which form the basis for the development of Guidelines for practical use.However, often the design of such studies excludes patients with comorbid pathology, i.e. its effect on the etiological factor is not taken into account. While patients with concomitant chronic diseases, which include cirrhosis, might have some peculiarities in the spectrum of pathogens. In this category of patients, a high level of resistance to AMD is often observed, including multidrug resistance of both nosocomial and community-acquired pneumonia pathogens [13].

In practical terms, the problem of antibiotic resistance is associated with the limitation of the number of potential AMDs that can be used. There are the following microorganisms:

- Multidrug-resistant (MDR) microorganisms - insensitive to 1 or more drugs in 3 or more classes of AMD;
- Extensively drug-resistant ones (XDR) - to 1 or more drugs in all classes (except for 1-2 classes) of AMD;
- Pan drug resistant (PDR) - to all classes of AMD [14].

In 2019, the journal Gastroenterology published the results of a multicenter prospective intercontinental study called "Epidemiology and Effects of Bacterial Infections in Patients with Cirrhosis Worldwide". The study was conducted by Piano S. et al, which evaluated the prevalence and outcomes of bacterial and fungal infections in patients with cirrhosis.

According to the data obtained with the inclusion of 1302 patients:

- 57% of patients obtained positive culture test results (959 microbial strains were detected);
- MDR was detected in 34% of patients with a positive culture, which is significantly higher than in previous studies;
- In 62 patients, 73 XDR bacteria were detected [15].

With general antimicrobial resistance growth trends, the characteristics of the resistance of causative agents of community-acquired infections can differ significantly in different geographical regions, and nosocomial infections - in different medical institutions. For example, the above study showed that the prevalence of infections caused by MDR and XDR with the highest frequency was observed in Indian clinical centers (73% and 33%, respectively), and the lowest - in North American (18% and 2%, respectively). Therefore, when choosing an AMD, it is necessary to be guided by local data on the level of antimicrobial resistance and take into account individual risk factors for infection with resistant pathogens.

The ATCS program (Antimicrobial Therapy Control Strategy, Russian clinical guidelines) [16] involves conducting empirical AMT with stratification of patients by the antimicrobial resistance risk into 4 types or treatment groups (2 community-acquired and 2 nosocomial):

Type I - community-acquired infections in a group of patients without risk factors for multi-resistant pathogens. Who did not seek medical help in the previous 3 months and did not take AMD within the last 90 days, and were without any associated pathology;

Type II - community-acquired infections with risk factors for multidrug-resistant pathogens (ESBL among enterobacteria, multidrug-resistant pneumococci). Patients who sought medical attention or were hospitalized and treated with AMD in the previous 3 months, having severe concomitant pathology, as well as traveling to regions with a high level of multidrug-resistant flora;

Type III a- also patients with risk factors for multidrug-resistant pathogens (ESBL among enterobacteria, multi-resistant pneumococci), but with other risk factors. These are nosocomial infections outside the intensive care unit (ICU), without surgical interventions and the use of AMD for more than 24 hours, the presence of a concomitant pathology do not matter;

Type III b- patients with a risk of infection with ESBL bacteria, and MRSA, CRE, multi-resistant NFGNB - long-term hospitalization (> 7 days) and/or stay in ICU > 3 days and/or previous use of AMD, the progression of infection after surgery, with severe co morbid condition;

Type IV - nosocomial infections with both a risk of multi-resistant bacteria and a risk of developing fungal infections. These are all type III patients who have signs of invasive candidiasis or risk factors for its progression: an intravenous catheter, relaparotomy, complete parenteral nutrition, and the use of immunosuppressors.

The aim of the article is to study the antimicrobial resistance profile of community-acquired pneumonia pathogens that are detected in patients with cirrhosis. Along with stratification of patients at the risk of infection with resistant pathogens (MDR, XDR, PDR).

Materials and Methods

A retrospective analysis was conducted of 216 patients with a previously verified diagnosis of cirrhosis, who was hospitalized in a multidisciplinary hospital in 2016-2018 with CAP. The study included only patients with a positive result of respiratory bacterial culture sampling. The criteria for non-inclusion were the presence of diabetes mellitus and chronic obstructive pulmonary disease (COPD).

For bacteriological examination, it was decided to send a sputum sample obtained by free coughing (with a mandatory microscopic assessment of the quality of sputum) or during diagnostic fiberoptic bronchoscopy. The bacterial titer of $\geq 10^5$ colony-forming units (CFU)/ml in the first case and $>10^4$ CFU/ml in the second were considered to be diagnostically significant.

The antibiotic resistance study was conducted in accordance with:

- The Guidelines 4.2.1890-04 "Determining the sensitivity of microorganisms to antibacterial drugs" (Determination of the sensitivity of microorganisms to antibacterial drugs: guidelines 2004)[17];
- The recommendations of the European Committee on Antimicrobial Susceptibility Testing "EUCASTv5.0" (Determination of the sensitivity of microorganisms to antimicrobial agents. Methodical instructions, 2015) [18].

The study was conducted on an automatic bacteriological analyzer "Sensititre". The latter allows the identification of gram-positive and gram-negative bacteria, including fastidious microorganisms, as well as determines the sensitivity to AMD. Determination of DNA of Mycoplasma pneumoniae and Chlamydia pneumoniae in sputum or lavage fluid was performed by the polymerase chain reaction (PCR) method with real-time detection.

The sensitivity of the following microorganisms was studied:

- Enterobacteriaceae spp. to ticarcillin /clavulanate, cefuroxime, cefotaxime, ceftriaxone, ceftazidime, cefoperazone /sulbactam, cefoxitin, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin,

gentamicin, amikacin, tobramycin, netilmicin;

- Staphylococcus aureus - to oxacillin, amoxicillin/clavulanate, cefuroxime, cefepime, imipenem, ciprofloxacin, moxifloxacin, erythromycin, gentamicin, rifampicin, doxycycline, vancomycin, linezolid, daptomycin.

Statistical processing of the research results was carried out using the methods of descriptive statistics for the normal distribution. In the form of mean (m) and standard deviation (± SD).For comparison of quantitative indicators and determination of differences, the Student criterion and the nonparametric Mann-Whitney criterion were used. Differences were considered significant at a significance level of $p<0.05$.

A multivariate logistic regression analysis was performed to identify antibiotic resistance risk factors.

Results

Patients with alcoholic cirrhosis prevailed (n = 122; 56.4%), alcohol-viral etiology of cirrhosis was observed in 26 patients (12.0%), cardiac etiology in 50 (23.1%), viral etiology in 18 (8.33%), the average age of which and the Child-Pugh cirrhosis score are presented in Table 1. There were no patients with cirrhosis of another etiology in this study. The distribution of patients according to the Child-Pugh cirrhosis classification is presented in Table 1.

Table 1: Patient distribution by Child-Pugh cirrhosis classification, indicating the average age

Etiology/Class	A	B	C
alcoholic	-	n=38 (average age 48±5,2)	n=84 (average age 51±3,9)
alcohol-viral	-	n=8 (average age 36±4,1)	n=18 (average age 37±5,5)
cardiac	-	n=38 (average age 59±2,2)	n=12 (average age 63±0,8)
viral	-	n=12 (average age 38±1,9)	n=6 (average age 43±2,8)

The most common microorganisms detected in patients with CAP during cirrhosis of alcoholic etiology were:

- E. coli (34.6%);
- St. aureus (26.9%);
- Klebsiella pneumoniae (23.1%).

Other microorganisms were less common: S. pneumoniae (13.1%), H. influenzae (9.92%), Enterobacter (6.55%), and P. aeruginosa (3.27%).Almost 1/3 of the patients (31.1%) had a mixed micro flora, represented by an association of 2 pathogens, half of them were a combination of St.aureus + K.pneumoniae. A study of the resistance level of the main detected pathogens to AMD showed that in all cases St.aureus remained sensitive to oxacillin (MSSA). E. coli showed a high level of resistance to amoxicillin/clavulanate, cefuroxime, cefotaxime and ceftriaxone (24.0%; 28.0%; 26.6% and 26.6%, respectively).

A relatively low level of resistance was observed for fluoroquinolones (ciprofloxacin - 10.6% and levofloxacin - 9.33%). Low resistance was noted to cefepime (5.33%), cefoxitin (8.00%), cefoperazone/sulbactam (5.33%), gentamicin (5.33%) and amikacin (4.00%). Meropenem and imipenem (1.33% each) had the highest activity (least resistance). K. pneumoniae was also characterized by a high level of resistance to ß-lactam AMD (amoxicillin/clavulanate - 26.6%; cefuroxime 30.6%, cefotaxime 29.3% and ceftriaxone 38.6%), as well as to ciprofloxacin (17.3 %). A relatively low level of resistance was observed for levofloxacin (8.00%), cefepime (8.00%), cefoxitin (9.37%) and cefoperazone/sulbactam (8.00%). Meropenem (4.00%) and imipenem (2.66%) possessed the highest activity (least resistance).

On the whole, representatives of gram-negative microflora were characterized by high antibiotic resistance, and the interpretation of the data obtained according to the criteria of multiple resistances is reflected in Table 2.

The following can be said about patients in whom MDR pathogens were identified (when comparing to the patients without MDR pathogens):

- They were 3 times more likely to seek inpatient medical care (p = 0, 0003);
- 2.5 times more often they experienced intrusive interventions (laparocentesis, laparoscopy) (p = 0.007);
- 1.5 times more often they were given antibiotic prophylaxis (p = 0.00001);

- The administration of AMD was carried out during the previous 6 months.

In all patients with XDR pathogens, anamnesis includes the following:

- Bleeding from varicose veins of the esophagus;
- Long-term treatment in ICU conditions, in 1 patient - artificial ventilation was provided.

The spectrum of pathogens and the profile of their resistance in patients with cirrhosis of mixed alcohol-viral etiology are as follows:

- St. aureus (36.1%), E.coli (31.2%) and Klebsiella pneumoniae (22.9%) prevailed;
- Less common: S.pneumoniae (10.0%), H.influenzae (10.0%), P.aeruginosa (3.84%), Acinetobacter baumannii (3.84%) and Serratia marcescens (3.84%).

The above is not fundamentally different when comparing to cirrhosis of alcoholic etiology. Risk factors for MDR pathogens were also previous hospitalization, invasive interventions, and AMD. In this category of patients, MRSA was detected in patients with a history of intravenous drug use. In case of cirrhosis of cardiac etiology, S.pneumoniae (44.0%), E.coli (30.0%), St.aureus (18.0%), and H. influenzae (16.0%) were found in sputum cultures. There were no mixed infections. All S.pneumoniae are identified as susceptible to penicillin (SPS), macrolides, and levoflocacin. St. aureus - MSSA. For E. coli, a relatively low level of resistance was detected to amoxicillin/clavulanate, cefuroxime, cefotaxime and ceftriaxone (12.0%; 10.0%; 14.0% and 14.0%, respectively), to fluoroquinolones (ciprofloxacin-10.0% and levofloxacin-6.0%). Low resistance was noted to cefepime (5.00%), cefoxitime (4.00%), cefoperazone/sulbactam (5.00%), gentamicin (5.00%) and amikacin (2.00%). Meropenem and imipenem (1.00% each) had the highest activity (least resistance).

Significantly more often, patients with antibiotic resistance had a history of repeated hospitalizations in the therapeutic and cardiology departments (2.8 times, $p = 0.014$), while AMT was not carried out in half of them. The causative agents of CAP in patients with cirrhosis of viral etiology were S.pneumoniae (55.6%) and H.influenzae (33.3%), which was not characterized by a high level of antimicrobial resistance, and St.aureus (11.1%) - 1 MRSA. A comparison of anamnestic data did not reveal any significant differences between patients with sensitive and resistant pathogens. The latter is most likely due to an insufficient number of observations.

Table 2: Detection of CAP pathogens with multidrug resistance

Cirrhosis etiology	The main pathogens	MDR-microorganisms	XDR-microorganisms	PDR-microorganisms
Alcohol cirrhosis	St.aureus	-	-	-
	E.coli	8 (6.55%)	-	-
	K.pneumoniae	12 (9.83%)	4 (3.27%)	-
Alcohol-viral cirrhosis	E.coli	2 (7.69%)	-	-
	St.aureus	4 (18.1%)	-	-
	K.pneumoniae	3 (11.5%)	1 (3.57%)	-
Cardiac cirrhosis	S.pneumoniae E.coli	-	-	-
	St.aureus H.influenzae	1 (2%)	-	-
		-	-	-
		-	-	-
Viral cirrhosis	S.pneumoniae	-	-	-
	H.influenzae St.aureus	-	-	-
		1 (5.55%)	-	-

In order to identify risk factors for resistant causative agents of CAP in patients with cirrhosis (MDR and XDR microorganisms), a multivariate step-by-step regression analysis was performed. The results of which show that the main risk factors for the development of CAP due to resistant pathogens in patients with cirrhosis are:

- Alcohol intake (odds ratio (OR) 5.2; $p = 0.001$);
- Repeated hospitalizations (OR 4.3; $p = 0.005$);
- Previous administration of AMD, in the previous 6 months (OR 2.0; $p = 0.045$).

With the total presence of all three factors, the risk of detection of resistant pathogens is

9.3 (95% confidence interval (CI) 3.339-26.224, p = 0.001) from the chance in the absence of at least one factor.

Discussion

Timely initiation of empirical antibiotic therapy is the key to successful treatment of pneumonia associated with concomitant diseases. The main task of AMD for empirical therapy is the maximum complete coverage of all potential pathogens of a given infection. Pneumonia caused by multidrug-resistant pathogens has traditionally been considered hospital-acquired. However, the occurrence of CAP caused by bacteria with MDR has created the need for stratification of risk factors for the acquisition of resistant pathogens.

In a bacteriological study of sputum obtained in patients with CAP associated with cirrhosis, microorganisms that were not traditionally considered pathogens of this disease were predominantly detected. A specific feature of the microbial spectrum of CAP pathogens in alcoholic and viral-alcoholic cirrhosis was the predominance of gram-negative microorganisms E.coli and K.pneumoniae. The latter were characterized by a high level of antimicrobial resistance. In cardiac cirrhosis, the main causative agents of CAP were S.pneumoniae (SPS) and E.coli. One of the common microorganisms detected in all etiological groups of cirrhosis was St.aureus, which was not characterized by a high level of methicillin resistance. During cirrhosis of viral etiology, CAP causative agents did not differ from traditionally prevalent ones, although they were characterized by an increased level of antibiotic resistance. However, the insufficient number of patients for analysis did not allow identifying risk factors for the formation of antibiotic resistance. The main reasons for identifying resistant causative agents of CAP in patients with cirrhosis regardless of the etiology are alcohol intake, repeated hospitalizations, and AMT in the previous 3-6 months. Such cases of CAP should be considered as healthcare-associated pneumonia (HCAP), which is considered community-acquired. However, they differ from the latter by the structure of pathogens and antibiotic resistance profile. Besides, such patients should be stratified as having a high risk of infection by hospital multi-resistant microorganisms.

Conclusion

Although the spectrum of key microorganisms causing CAP in patients with cirrhosis differs depending on the etiology of cirrhosis, it is still generally characterized by the predominance of gram-negative microflora (K.pneumonia and E.coli) and a high frequency of occurrence of S.aureus. Given the characteristics of the microbial spectrum of pathogens of CAP in the considered category of patients (cirrhosis) and anamnestic data, such cases of cirrhosis should be considered as pneumonia associated with the provision of medical care (HCAP).In general, pathogens of CAP with multiple antimicrobial resistance were detected in 28.5% of patients with cirrhosis: 24.6% MDR and 3.96% XDR. The risk factors for multiple antimicrobial resistances identified in this study should be considered when choosing a starting AMT in patients with CAP associated with cirrhosis.

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