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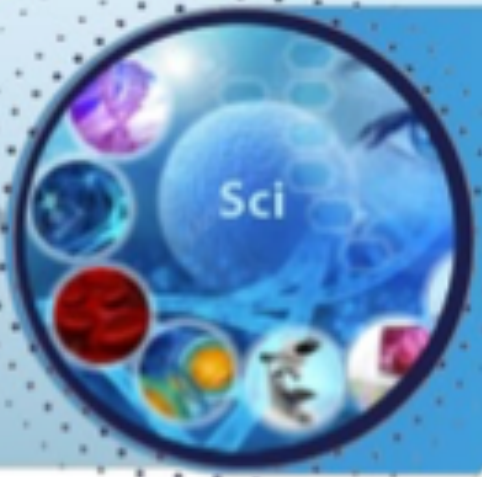

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Research Article

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Microbiological Substantiation of the Choice of Pharmacological Groups of Antibacterial Drugs in the Treatment of Abdominal Sepsis Against the Background of Diabetes Mellitus

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ABSTRACT

Background. The problem of treatment of purulent-septic complications is associated with a steady increase in the resistance of the main pathogens to the antibacterial drugs used, while the profile of antibiotic resistance may have pronounced regional characteristics. In this regard, it is relevant to use clinical and pharmacological approaches to the development of an algorithm for the selection of antibacterial drugs based on the results of studying the etiological structure and local data of pathogen resistance.

Material and methods. A retrospective and prospective analysis of the results of the treatment of 105 patients with abdominal sepsis for the period 2013-2022 was carried out. The main group (n=42) included all patients with abdominal sepsis with diabetes mellitus and the control group (n=63), included all patients with abdominal sepsis without diabetes mellitus who met the principles of inclusion criteria.

Results. Most often, the structure of the causative agents of purulent-septic complications in patients with diabetes mellitus is represented by multidrug-resistant microorganisms: E. coli, Klebsiella spp., fungi of the genus Candida, Proteus spp.

Conclusion. In the schemes of empirical initial therapy of purulent-septic complications against the background of diabetes mellitus, it is advisable to use combinations of 3-4 generation cephalosporins, amoxicillin/clavulanate, 3rd generation fluoroquinolones with metronidazole as first-line agents. With the development of septic shock, carbapenems in combination with Glycopeptide or Oxazolidinone are most effective as first-line antibiotics.

Keywords: Antibacterial drugs, antibiotic resistance of microorganisms, clinical and pharmacological methods, abdominal

INTRODUCTION

The constant increase in the number of patients with abdominal surgical infections complicated by a septic condition against the background of diabetes mellitus remains one of the most difficult and urgent tasks of surgery, resuscitation, and clinical pharmacology [1,3,6,9,39].

Purulent-septic complications in abdominal surgery tend to increase the duration of the disease and the number of deaths that require significant economic costs for treatment, which determines the medical and social relevance of the problem under study [2, 4, 7, 11, 14, 17, 28, 38].

According to the literature, mortality in patients with diabetes mellitus reaches 69-80%. Mortality among patients with sepsis occurring against the background of diabetes mellitus with the appointment of aetiotropic antibiotic therapy is significantly lower than among patients receiving empirical antibiotic therapy, which increases its effectiveness [3, 5, 8, 18, 22, 25, 33, 37].

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In a prospective randomized study of a group of scientists, it was established that it was necessary to maintain a glycemic level of 8-10 mmol/l, to correct secondary immunodeficiency, which statistically significantly reduced the development of purulent-septic complications, reduced the number of repeated surgical debridements of the infectious focus, the mortality rate, and the stay of patients in the intensive care unit [4, 10, 13, 16, 19, 21, 25, 28, 33, 36].

According to Uyttebroek et al. the strategy for the efficacy and safety of antibiotic therapy largely depends on the route of administration of the drug. Intravenous use of antibacterial drugs is preferred since there are no convincing advantages of intra-arterial or endolymphatic administration [5, 7, 17, 26, 33].

The foregoing determines the relevance of the work, and the need to perform retrospective, prospective clinical and pharmacological studies to find and implement optimized, effective, and safe tactics of antibiotic therapy in patients with abdominal surgical infection complicated by a septic condition against the background of diabetes mellitus.

MATERIAL AND METHODS OF RESEARCH

The study was conducted in 2 stages:
Retrospective analysis of the primary medical documentation of patients with abdominal sepsis who were hospitalized in the multidisciplinary clinic of the Tashkent Medical Academy from 2013 to 2017.

The prospective nature of the study aimed at studying the effectiveness of antibiotic therapy and assessing the adequacy of prescribing chemotherapy drugs for abdominal sepsis. Examination of patients to study the structure of pathogens and their indicators of antibiotic resistance was carried out based on a multidisciplinary clinic of the Tashkent Medical Academy from 2018 to 2022.

After inclusion in the study, patients were stratified into 2 groups: the main group (n = 42) included all patients with abdominal sepsis on the background of diabetes mellitus and the control group (n = 63), which included all patients with abdominal sepsis without diabetes mellitus who met the principles of inclusion criteria.

The study included 56 men and 49 women aged 30 to 79 years.

For antibacterial drugs, DDD/100 bed-days in the intensive care unit were calculated. To calculate this indicator, the amount of DDD (antibacterial drugs) consumed during the year was divided by the total bed-day of patients for the year and the result obtained was multiplied by 100. The number of grams of the active substance was used as a unit of measurement.

The microbiological structure of the causative agents of purulent-septic complications in patients with surgical pathology of the abdominal organs was also studied. To identify the pathogen and prescribe aetiotropic therapy, biological material was taken for bacteriological examination during surgery, and then again when diagnosing purulent-septic complications (blood, urine, wound culture) on the third day of treatment.

Patients of both groups were prescribed empirical antibiotic therapy on the first day after surgery, considering the alleged causative agents of abdominal infection according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012.

The effectiveness of the use of antibacterial drugs was assessed by the following indicators: the level of leukocytes in the blood, the erythrocyte sedimentation rate, thermometry, leukocyte index of intoxication, C-reactive protein, procalcitonin, APACHE III and SOFA integral scales.

The results of clinical and biochemical studies were processed using a specialized package of statistical programs Statistica 6.0 (StatSoftlnc., USA) using parametric and nonparametric statistical methods. The measure of the central trend of the data was the sample mean (M), and the measure of scattering was the error of the mean (t). According to the reliability of the differences (p), a conclusion was made about the effect of the trait on the incidence of purulent-septic complications.

The differences between the groups of data obtained were considered statistically significant at $p<0.05$ and highly significant at $p<0.01$.

RESULTS

According to the results of a pharmacoepidemiological study using DDD methodology, it was found that for the entire period of treatment of patients in the intensive care unit, the following antibacterial drugs were used in both groups:

- the first place in terms of consumption is occupied by cephalosporins of III-IV generations (17.92±1.8) DDD.

- the second was divided between a group of nitroimidazoles (Metronidazole) and azoles (Fluconazole), having an equal amount of consumption - (13.54±1.8) and (13.56±1.7) DDD, respectively.

- the third - carbapenems Meropenem (12.4±1.2) and Doripenem (11.8±1.8) DDD.

- the fourth place is occupied by fluoroquinolones of II-III generations Ciprofloxacin (6.58±1.4) and Levofloxacin (b.6±1.2) DDD.

- fifth - III generation aminoglycosides Amikacin (5,3±1,4) DDD.

A smaller volume of consumption is occupied by inhibitor-protected aminopenicillins Amoxicillin/Clavulanate (4.83±1.7) DDD, glycopeptides - Vancomycin (1.79±0.8) DDD, glycylcyclines - Tigecycline (1.8±0.4) DDD, oxazolidinones - Linezolid (1.44±0.2) DDD.

Gram-negative microorganisms among the identified flora accounted for 80.9% of cases, gram-positive microorganisms — 4.8% of cases, and fungi of the genus Candida spp. were detected in 14.3% of studies.

Associations of various pathogens were diagnosed in 33.3% of cases of purulent-septic complications of established aetiology, and in 66.6% of cases, mono-infection was diagnosed. Two-component microbial associations were isolated in 85.7% of cases, and three-component - in 14.3% of cases.

According to the study, the main causative agents of surgical abdominal infection in patients with diabetes mellitus are E. coli (45.2%), Klebsiella spp. (16.6%), fungi of the genus Candida (14.3%), Proteus spp. (11.9%), and in patients without diabetes - E. coli (57.1%), Enterococcus faecalis (14.3%), Streptococcus spp. (11.1%).

In patients of the main group, a high level of resistance of E. coli to antibacterial drugs of the cephalosporin series of the I-IV generation (51-23%), Gentamicin (34%), inhibitor-protected amoxicillin (26%), Metronidazole (24%) was revealed, and in patients of the control group, resistance to antimicrobial drugs of the cephalosporin series of the III-IV generation was 46-14%, inhibitor-protected amoxicillin to gentamicin - 45.8%, 51-54% of strains were insensitive to ciprofloxacin and levofloxacin. Carbapenems (Doripenem and Meropenem) and Amikacin were highly active against E. coli in both groups.

Among the isolated strains of Klebsiella spp. in the main group, the majority formed high resistance to cephalosporins of I-IV generations (85-68%), aminoglycosides: resistance to Gentamicin was 68%, to Amikacin - 50%, Ciprofloxacin - 76%, Amoxicillin / Clavulanate - 46%. Carbapenems are characterized by high activity against Klebsiella (93%).

Resistance to fluconazole fungi of the genus Candida in patients with diabetes mellitus was 15%, and in patients without diabetes - 9%.

Strains of Proteus spp., isolated from patients of the main group, were the most resistant to Amoxicillin/Clavulanate and Cefotaxime - 32% and 22%, respectively. Doripenem and Meropenem showed 100% activity against all strains, high sensitivity was also noted in Ceftazidime and Amikacin.

In patients of the control group, Enterococcus faecalis strains were highly sensitive to carbapenems (Doripenem and Meropenem), and fluoroquinolones of II-III generations (Ciprofloxacin, Levofloxacin). A high level of resistance to aminoglycosides was revealed.

High activity of antibacterial drugs of the group of cephalosporins of the III-IV generation, fluoroquinolones, and carbapenems was detected against strains of Streptococcus spp. seeded in patients without diabetes. The low sensitivity of streptococci to aminoglycosides is explained by their natural resistance to this group of antibacterial drugs.

According to the results of the study, the proportion of nitroimidazoles (Metronidazole) in the treatment of purulent-septic complications was 100%, which is explained by the presence of anaerobic flora in intraabdominal infection.

Among the antibacterial drugs of the cephalosporin group, cephalosporins of the III and IV generations are used, of which Ceftriaxone (39%) and Cefepime (32.4%) occupy a larger proportion, Cefotaxime (20%) was used less often. Appointments of cephalosporins of the I and II generations have not been registered.

The antibacterial drug of the III-generation aminoglycoside group is represented by Amikacin (39%). Aminoglycosides of the I and II generations were not used due to their high resistance to pathogens of intra-abdominal infection.

Among the drugs of the II and III generation fluoroquinolone groups, Ciprofloxacin (61%) and Levofloxacin (26.7%) were used.

When isolating the flora of fungi of the genus Candida, Fluconazole (10.5%) was included in the antibiotic therapy regimen. Voriconazole and caspofungin were not used due to the high cost of treatment.

Penicillin was represented by a single drug - Amoxicillin/Clavulanate (21%), which was used in patients of the main group.

Antibacterial drugs of the carbapenem group are represented by meropenem (66.7%) and Doripenem (33%).

The group of oxazolidinones is represented by linezolid (13%), which was used in patients with diabetes mellitus. The volume of consumption in severe sepsis was 23.8%, and in septic shock - 7.1%.

Glycopeptides were represented by vancomycin (20%), which was used in combination with carbapenems in patients of the main group with severe sepsis.

Monotherapy occurred in 48.5% of cases, and combination therapy - in 71.5% of cases for the entire period of hospitalization.

In patients of the main group, the time spent in the intensive care unit is much longer (331 (in the control group) versus 500.2 hours), which is associated with a tendency to a protracted course of the infectious process, the persistence of inflammatory changes, pronounced and prolonged decompensation of carbohydrate metabolism ($p<0.05$).

Recommendations for the selection of antimicrobial agents for the treatment of abdominal infection are based both on data from systematic reviews and meta-analyses, randomized controlled trials, and on expert opinion.

According to the results of the study, a high level of resistance of E. coli to antibacterial drugs of the cephalosporin series of the I-IV generation (23-51%), Gentamicin (34%), inhibitor-protected amoxicillin (26%), Metronidazole (24%) was revealed. Levofloxacin, carbapenems (Doripenem and Meropenem), Amikacin, Linezolid and Tigecycline were highly active against E. coli. The results obtained, firstly, indicate a high risk in diabetic patients of developing abdominal sepsis caused by resistant strains of E. coli, and secondly, this may indicate a high level of regional antibiotic resistance of the bacillus, which requires additional resistance of E. coli.

Among the isolated strains of Klebsiella spp., the majority formed high resistance to cephalosporins of I-IV generations (68-85%), aminoglycosides: resistance to Gentamicin was 68%, to Amikacin - 50%, Ciprofloxacin - 76%, Amoxicillin/Clavulanate - 46%. Carbapenems are characterized by high activity against Klebsiella (93%).

Strains of Proteus spp. were most resistant to amoxicillin/clavulanate and cefotaxime - 32% and 22%, respectively. Doripenem and Meropenem showed 100% activity against all strains, high sensitivity was also noted in Ceftazidime and Amikacin.

A comparative assessment of the effectiveness of antibiotic therapy in both groups revealed a significant increase in the consumption of antibacterial drugs, as well as the length of hospital stay in patients with diabetes mellitus ($x2 = 9.35$, $df = 1$, $p = 0.0016$).

Based on the results of local monitoring of pathogen resistance, we proposed a list of antibacterial drugs for empirical therapy. Further tactics of prescribing antibacterial drugs depend on the results of the bacteriological examination and determine the structure of aetiotropic antibiotic therapy.

The recommendations of most studies coincide that the main drugs for the treatment of purulent-septic complications in abdominal surgery in patients with diabetes mellitus are carbapenems, fluoroquinolones of the III-IV generation, cephalosporins of the III generation, inhibitory cephalosporins, inhibitory ß-lactams and anti-anaerobic drugs. The widest spectrum, covering almost all etiological significant pathogens, undoubtedly has carbapenems and protected anti-Pseudomonas aeruginosa drugs that can be prescribed in monotherapy. Ideal drugs for monotherapy are carbapenems (Meropenem, Doripenem), inhibitor-protected ß-lactams (Ampicillin/Sulbactam, Amoxicillin/Clavulanate) and inhibitor-protected cephalosporin (Cefoperazone/Sulbactam).

According to the study, initial empirical monotherapy in patients with purulent-septic complications of the abdominal organs against the background of diabetes mellitus was registered in 97.6% of cases and was represented in 47.6% of cases with cephalosporins of the III and IV generation (Cefotaxime and Cefepime), and in 50% of cases with a ß-lactam antibiotic (Amoxicillin/Clavulanate). Combined initial empirical therapy was used in 2.4% of cases and is represented by a penicillin antibacterial drug (Amoxicillin/Clavulanate) with Metronidazole. The choice of drugs was consistent with the sepsis management protocol in 52.4% of cases.

However, the spectrum of the main pathogens and their resistance indicators are crucial in the selection of drugs for empirical therapy of purulent-septic complications of the abdominal organs. According to multicenter clinical trials, the resistance rates of the main causative agents of abdominal sepsis vary significantly in individual regions. This determines the need to use local (regional) data on the resistance of microorganisms to antimicrobial agents when choosing drugs for the treatment of purulent-septic complications.

DISCUSSION

A tetracycline antibacterial drug from the glycylcyclines group - Tigecycline (6.7%) was used in the main group of patients since an important aspect of safety is the possibility of its use in patients with renal insufficiency without dose adjustment and activity against multidrug-resistant pathogens [6, 18, 20].

It has a wide spectrum of activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [7, 27, 37].

Tigecycline is active against multidrug-resistant microorganisms such as MRSA, VRE, extended-spectrum ß-lactamase-producing enterobacteria, and most species of Acinetobacter spp [8, 12, 19].

Tigecycline also has activity against intracellular bacteria and anaerobes. Tigecycline is not active against Pseudomonas aeruginosa [9,1 9].

Also, some members of the Enterobacteriaceae family, such as Proteus spp., have reduced sensitivity to Tigecycline [10, 21, 30].

As a result of the microbiological study in the group of patients with diabetes mellitus, it was revealed that E. coli (45.2%) occupies a leading position in the structure of pathogens of purulent-septic complications. The results obtained are like the literature data, according to which E. coli is the most common (40-45%) causative agent of purulent-septic complications in abdominal surgery [11,28].

According to the study, Candida spp. (14.3%), Klebsiella spp. (16.6%), Proteus spp. (11.9%) were also frequent causative agents of purulent-septic complications in patients with diabetes.

In recent years, antibiotic therapy for abdominal sepsis has been complicated by the rapid increase in the resistance of pathogens of purulent-septic complications of the abdominal organs to various classes of antimicrobial drugs [12, 22].

CONCLUSION

The results of the study on the incidence of purulent-septic complications in patients with diabetes mellitus are like official statistics. Multidrug-resistant and pan-resistant strains of microorganisms in patients with diabetes mellitus cause a tendency to increase the duration of purulent-septic complications and a high risk of septic shock. The introduction of measures of a personalized approach to optimize early antibiotic therapy is one of the most important measures for the prevention and treatment of purulent-septic complications.

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Conflict of interest - The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics approval and consent to participate - All patients gave written informed consent to participate in the study.

Consent for publication - The study is valid, and recognition by the organization is not required. The authors agree to open the publication.

Availability of data and material - Available

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QANDLI DIABET FONIDA QORIN BO'SHLIG'I SEPSISNI DAVOLASHDA ANTIBAKTERIAL DORILARNING FARMAKOLOGIK GURUHLARINI TANLASHNING MIKROBIOLOGIK ASOSLARI

Korixonov D.N.
Toshkent tibbiyot akademiyasi

Abstrakt

Dolzarbligi. Yiringli-septik asoratlarni davolash muammosi asosiy patogenlarning antibakterial preparatlarga qarshi chidamliligining barqaror o'sishi bilan bog'liq bo'lsa, antibiotiklarga chidamlilik profili mintaqaviy xususiyatlarni aniqlagan bo'lishi mumkin. Bu borada patogen qarshiligining etiologik tuzilishi va lokal ma'lumotlarini o'rganish natijalari asosida antibakterial dori vositalarini tanlash algoritmini ishlab chiqishda klinik va farmakologik yondashuvlarni qo'llash dolzarbdir.

Tadqiqot usullari. 2013-2022-yil davri uchun qorin bo'shlig'i sepsis bilan og'rilgan 105 nafar bemorning davolash natijalarini retrospektiv va bo'lajak tahlil qilish ishlari olib borildi. Asosiy guruhga (n=42) qandli diabet bilan og'rilgan qorin sepsis bilan og'rilgan barcha bemorlar kiritildi. Nazorat guruhiga (n=63) qo'shilish mezonlariga javob beradigan qandli diabetsiz qorin bo'shlig'i sepsis bilan og'rilgan barcha bemorlar kiritildi.

Natijalar. Ko'pincha diabet bilan og'rigan bemorlarda yiringli-septik asoratlar patogenlarining tuzilishi ko'p dori-shkafga chidamli mikroorganizmlar bilan ifodalanadi: Escherichia coli, Klebsiella spp., Candida jinsi qo'ziqorinlari, Proteus spp.

Xulosa. Qandli diabetning kelib chiqishiga qarshi yiringli-septik asoratlarni empirik boshlang'ich terapiya sxemalarida 3-4 avlod sefalosporinlari, amoksitsilin / klalavulanat, 3-avlod florokinolonlarini birinchi darajali agent sifatida ishlatish tavsiya etiladi. Septik shok rivojlanishi bilan Glikopeptit yoki Oxazolidinon bilan birgalikda karbapenemlar birinchi qator antibiotiklar sifatida eng samarali hisoblanadi.

Tayanch iboralar: Antibakterial dori vositalari, mikroorganizmlarning antibiotiklarga chidamliligi, klinik va farmakologik tadqiqot usullari, qorin bo'shlig'i sepsis, qandli diabet

МИКРОБИОЛОГИЧЕСКОЕ ОБОСНОВАНИЕ ВЫБОРА ФАРМАКОЛОГИЧЕСКИХ ГРУПП АНТИБАКТЕРИАЛЬНЫХ ПРЕПАРАТОВ ПРИ ЛЕЧЕНИИ АБДОМИНАЛЬНОГО СЕПСИСА НА ФОНЕ САХАРНОГО ДИАБЕТА

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Абстракт

Актуальность. Проблема лечения гнойно-септических осложнений связана с устойчивым повышением резистентности основных возбудителей к применяемым антибактериальным препаратам, при этом профиль антибиотикорезистентности может иметь ярко выраженные региональные особенности. В связи с этим актуальным является использование клинико-фармакологических подходов к разработке алгоритма подбора антибактериальных препаратов на основе результатов изучения этиологической структуры и локальных данных резистентности возбудителей.

Материал и методы. Проведен ретроспективный и проспективный анализ результатов лечения 105 пациентов с абдоминальным сепсисом за период 2013-2022 гг. В основную группу (n=42) вошли все пациенты с абдоминальным сепсисом с сахарным диабетом, а в контрольную группу (n=63) вошли все пациенты с абдоминальным сепсисом без сахарного диабета, которые соответствовали принципам критериев включения.

Результаты. Чаще всего структура возбудителей гнойно-септических осложнений у больных сахарным диабетом представлена мультирезистентными микроорганизмами: кишечной палочкой, Klebsiella spp., грибами рода Candida, Proteus spp.

Заключение. В схемах эмпирической начальной терапии гнойно-септических осложнений на фоне сахарного диабета целесообразно использовать комбинации цефалоспоринов 3-4 поколения, амоксициллина/клавуланата, фторхинолонов 3-го поколения с метронидазолом в качестве средств первой линии.

Ключевые слова: Антибактериальные препараты, антибиотикорезистентность микроорганизмов, клинические и фармакологические методы исследования, абдоминальный сепсис, сахарный диабет