



TASHKENT MEDICAL ACADEMY

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ANNIVERSARY



Journal of
Educational and
Scientific
Medicine



Issue 3 (2) | 2023



OAK.UZ
Google Scholar

Science Education Commission of the Cabinet
Ministry of the Republic of Uzbekistan

ISSN: 2181-3175

The Concept of Modern Nosocomial Infection from the Standpoint of a Rational Approach to Antimicrobial Pharmacotherapy

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ABSTRACT

Background. Systemic antimicrobial pharmacotherapy of modern nosocomial infections involving antibiotic-resistant gram-negative bacteria does not always comply with the principle of rationality, thereby reducing the quality and clinical effectiveness of their treatment. *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the leading gram-negative pathogens of modern nosocomial infections in many hospitals, the clinical strains of which are characterized by high-level of associated and cross-drug resistance.

Material. 770 patients aged 3 days to 92 years with documented nosocomial infection involving antibiotic-resistant gram-negative aerobic and facultative anaerobic bacteria were examined. The patients were hospitalized in intensive care units, surgical, somatic, gynaecological, pediatric and neonatology departments of the Multidisciplinary Clinic of the Tashkent Medical Academy.

Results. At the same time, there is a correlation between the frequency of isolation of these bacterial species and the age of patients, their sex, as well as the nature of the origin of clinical material for microbiological research. The use of most drugs of the beta-lactam class in the pharmacotherapy of modern nosocomial infections involving antibiotic-resistant gram-negative bacteria is associated with a high risk of treatment failure due to the wide distribution of beta-lactam products among hospital strains of microbes. The polymicrobial nature of modern nosocomial surgical infections, in contrast to nosocomial urinary infections, determines the appointment of targeted empirical combination antibiotic therapy.

Conclusion. Rational empirical antimicrobial pharmacotherapy of nosocomial infections should consider the results of monitoring the modern etiological structure of infectious pathology and current local data on the pharmacodynamic activity of antibiotics against potential pathogens in each individual hospital of a medical institution. At the same time, systemic empirical antimicrobial pharmacotherapy of modern nosocomial infections should include the universal use of regimens with the widest possible coverage of potential pathogens and considering their likely multiple antibiotic resistance.

Keywords: Nosocomial infection, antibiotic resistance, pharmacoepidemiologic study, antimicrobial pharmacotherapy

INTRODUCTION

Nosocomial infections are a serious problem in modern clinical medicine [4]. They worsen the prognosis for patients, increase the duration of

hospitalization and the cost of treatment, and contribute to the nosocomial spread of antibiotic-resistant strains [2,12,15].

The World Health Organization annually records up to 5,000 deaths from nosocomial infections in England.

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In the United States, one out of every 136 hospitalized patients develop a nosocomial infection, which is 2 million cases per year and leads to 80 thousand deaths annually. According to some prospective studies, the annual number of nosocomial infections in developing countries is on average, at least 2-2.5 million (1-1.5%), and annual economic losses - more than 5.0 million dollars [10, 11].

In many developing countries, there are no conditions for their pharmaceutical manufacturers who are ready to finance the entire chain - from development to the introduction of the original drug into medical practice. Regarding the current situation, the production of import-substituting generics becomes the most economically feasible. The real way to solve technological and economic problems for such pharmaceutical companies is the production of modern, effective, and safe generic drugs. In this regard, it is relevant for clinical pharmacologists to develop unified requirements for the evaluation and examination of the efficacy and safety of generic antimicrobials. Since data on the effects of antibiotics are constantly updated and refined, in such a difficult situation, the scientific awareness of all medical specialists is extremely important.

Given the above, conducting a comprehensive pharmacoepidemiological analysis of systemic antimicrobials in modern nosocomial infections involving antibiotic-resistant gram-negative bacteria is important. It is obvious that the problem of systemic antimicrobial pharmacotherapy of such infectious complications currently requires detailed clinical and laboratory studies, theoretical and organizational understanding, development, and implementation of the most effective and rational approaches to solving this problem.

MATERIAL AND METHODS

In the period from 2013 to 2022, 770 patients aged 3 days to 92 years with documented nosocomial infection involving antibiotic-resistant gram-negative aerobic and facultative anaerobic bacteria were examined. The patients were hospitalized in intensive care units, surgical, somatic, gynaecological, pediatric and neonatology departments of the Multidisciplinary Clinic of the Tashkent Medical Academy with diagnoses of nosocomial pneumonia, nosocomial surgical infection, nosocomial urinary tract infection and nosocomial sepsis.

The criteria for including bacterial strains in the study were as follows:

1. For non-fermenting gram-negative aerobic and facultative anaerobic bacteria (at least one of the signs):

resistance (intermediate or high) to ceftazidime; resistance (intermediate or high) to carbapenems.

2. For enterobacteria (at least one of the signs): resistance (intermediate or high) to at least one of the 3rd generations cephalosporins; resistance (intermediate or high) to 4th generation cephalosporins; resistance (intermediate or high) to protected penicillins; resistance (intermediate or high) to carbapenems; Positive product test, extended-spectrum beta-lactamases.

900 etiologically significant nosocomial strains of gram-negative bacteria were sent to our research microbiological laboratory. Verification of the species of crops was carried out based on morphological, tinctorial, cultural properties and biochemical characteristics using the BBL Crystal/NF test systems (Becton Dickinson, USA).

The pharmacodynamic activity of the original antimicrobials against a collection of strains of gram-negative bacteria was determined by the method of serial dilutions in microvolume, considering the natural antibiotic resistance of microbes, the criteria of the US National Committee on Clinical and Laboratory Standards (NCCLS, 2004; now CLSI) and using Mueller-Hinton broth balanced in cationic composition (Becton Dickinson, USA).

To identify producers of metallo-beta-lactamases among cultures of gram-negative bacteria resistant to Imipenem and/or Meropenem, the "double disc method" was used: discs with Imipenem 10 µg (Bio-Rad, USA), Meropenem 10 µg (Bio-Rad, USA) and ethylenediamine tetraacetate (5 µl of 500 mmol solution with pH = 8.0 per 1 disk, reagent manufactured by Sigma, the Netherlands). The production of enzymes was determined by the presence of an expanded growth inhibition zone around the carbapenem (Meropenem and/or Imipenem) disc opposite the ethylenediamine tetraacetate disc.

Statistical processing of the results of the study was carried out using the software package "Statistics for Windows 6.1." (Microsoft, USA). To determine the reliability of the detected trends and differences, the significance of correlations and factor weights, the calculations of the confidence interval, the Student's t-test (for pairs of normally distributed samples), hierarchical cluster analysis using the Pearson linear correlation coefficient and weighted pair-group averaging were used, respectively.

RESULTS

According to the clinical registration records of patients, the structure of consumption of antimicrobials for systemic use in modern nosocomial infections involving

antibiotic-resistant gram-negative bacteria has been established (Table 1).

Table 1
Structure of consumption of antimicrobial drugs in the treatment of modern nosocomial infections involving antibiotic-resistant gram-negative bacteria.

Class and group of antimicrobial drugs	Number of assignments absolute number	The relative number of assignments%
Penicillin	70	11.5
Cephalosporins	240	39.3
Carbapenems	50	8.2
Aminoglycosides	146	23.9
Fluoroquinolones	100	16.4
Other	5	0.8

Cephalosporins of the 3rd generation prevailed among cephalosporins (more than 70% of prescriptions in total), and Cefotaxime dominated among them (Table 2).

Table 2
Structure of consumption of cephalosporins in the treatment of modern nosocomial infections involving antibiotic-resistant gram-negative bacteria.

Generation	The name of the drug	Number of assignments absolute number	The relative number of assignments%
1	Cefazolin	26	10,8
	Cephalexin	4	1,7
2	Cefuroxime	5	2,1
3	Cefotaxime	81	33,8
	Ceftriaxone	42	17,5
	Ceftazidime	33	13,8
	Cefoperazone	18	7,5
4	Cefepime	22	9,2
Inhibitor-protected cephalosporins	Cefoperazone/Sulbactam	9	3,8

The proportion of the use of Cefepime was 9.2%, and the inhibitor of protected cephalosporins was 3.8%.

After beta-lactams, aminoglycosides were the second most frequently used class of antimicrobials. Of these, Amikacin had the largest share in the structure of consumption (61.6%), the number of prescriptions of which exceeds the value of the upper limit of the confidence interval for the appointment of aminoglycosides of all generations. Modern pharmacotherapy with Gentamicin and Netilmicin was carried out in 34.9% and 2.7% of cases, respectively (Table 3).

Table 3
Structure of consumption of aminoglycosides in the treatment of modern nosocomial infections involving antibiotic-resistant gram-negative bacteria.

Generation	The name of the drug	Number of assignments, absolute number	The relative number of assignments, %
1	Kanamycin	1	0,7
2	Gentamicin	51	34,9
	Netilmicin	4	2,7
3	Amikacin	90	61,6

Fluoroquinolones remained in third place as drugs for systemic pharmacotherapy of modern nosocomial infections involving antibiotic-resistant gram-negative bacteria. Pefloxacin (53%) and Ciprofloxacin (40%) had the highest specific gravity. Levofloxacin, Norfloxacin and Ofloxacin were used in 4, 2 and 1% of cases, respectively (Table 4).

Table 4
Structure of fluoroquinolone consumption in the treatment of modern nosocomial infections involving antibiotic-resistant gram-negative bacteria

Generation	The name of the drug	Number of assignments, absolute number	The relative number of assignments, %
1	Norfloxacin	2	2
2	Ofloxacin	1	1
	Pefloxacin	53	53
	Ciprofloxacin	40	40
3	Levofloxacin	4	4

During the study, facts of the use of Ampicillin / Oxacillin and kanamycin were revealed, of which only the latter retains its pharmacotherapeutic value as a second-line anti-tuberculosis drug and a means for intestinal decontamination before elective operations on the abdominal organs. The tablet drug Norfloxacin should be used only for the treatment of urinary tract infections and intestinal infections on an outpatient basis [14].

Thus, in modern nosocomial infections involving antibiotic-resistant gram-negative bacteria, there is a high proportion of consumption of penicillin drugs, except for protected inhibitors, 1st generation cephalosporins and 2nd generation aminoglycosides, which in modern conditions have long lost their antimicrobial activity due to the high level of resistance of hospital gram-negative pathogens.

After sieving bacterial strains, checking their purity, and verifying the species, the spectrum of antibiotic-resistant gram-negative aerobic and facultative-anaerobic microorganisms isolated from patients with nosocomial infection is represented by 3 groups.

Among Enterobacteriaceae, Klebsiella pneumoniae, Streptococcus pneumoniae and Escherichia coli were the most common species, accounting for almost 40% of documented cases of modern hospital-acquired infection. In addition, members of the family Enterobacteriaceae (Enterobacter cloacae and Proteus mirabilis) were sown in 6.1% of cases each, Klebsiella oxytoca - in 3.2%, Enterobacter aerogenes and Serratia marcescens - 1.9% each, Citrobacter freundii - in 1.3% of cases, etc.

The undoubted leader of the group of antibiotic-resistant non-fermenting gram-negative bacteria was Pseudomonas aeruginosa. This species accounted for a fifth (23.4%) of all cases of modern nosocomial infection. Bacterial cultures Acinetobacter baumannii were sown 3 times less frequently (8%) than Pseudomonas aeruginosa. Even less commonly, other members of the group of non-fermenting gram-negative bacteria were found Acinetobacter calcoaceticus (0,1%), Aeromonas hydrophila (0.1%), Burkholderia cepacia (0,4%), Chryseobacterium meningosepticum (0,1%), Pseudomonas fluorescens (0,1%), Pseudomonas putida (0.3%) and Stenotrophomonas maltophilia (1,9%).

In addition to the listed groups of microorganisms, in some cases (1.3%) with modern nosocomial infection, significant antibiotic-resistant gram-negative bacteria were sown, the results of species identification of strains of which were doubtful by the available test systems. Accordingly, they are assigned to a separate group of microorganisms - unidentified gram-negative microbes.

Evaluation of antimicrobial prescriptions was carried out in 282 patients with nosocomial infection with the participation of antibiotic-resistant gram-negative bacteria, which accounted for 36.6% of the total number of patients examined. A total of 59 different regimens of systemic empirical antimicrobial pharmacotherapy were considered, of which 12 were monotherapy, 19 were combination therapies against potential gram-negative pathogens, and 28 were combination therapies against mixed gram-negative and gram-positive microflora.

The following criteria for evaluating the performed antimicrobial pharmacotherapy were applied: quality (adequate or inadequate) and clinical efficacy (recovery, no effect or uncertain outcome of treatment). It is advisable to consider the evaluation of the prescriptions of empirical antimicrobial pharmacotherapy considering the structure of infectious pathology (nosocomial pneumonia, surgical infection, urinary tract infection).

Analyzing the quality of empirical antimicrobial combination and monotherapy for nosocomial pneumonia, it turned out that only in 61.7% of cases they were adequate. In 25 (13.9%) cases, empirical monotherapy regimens for nosocomial pneumonia involving antibiotic-resistant gram-negative bacteria were found to be inadequate, including 3 cases of prescribing drugs with a relatively narrow spectrum of their antimicrobial activity (narrow-spectrum penicillin and 1st generation cephalosporins), 2 cases of prescribing fluoroquinolones to young children, 6 cases of aminoglycosides and 14 cases when the starting monotherapy was changed during the first 48-72 hours. The relative number of inadequate regimens of systemic empirical combination pharmacotherapy was 1.8 times greater ($p > 0.05$) than with empirical monotherapy. Most often, the change of empirical combination pharmacotherapy due to its ineffectiveness was required after the appointment of aminopenicillins with Gentamicin.

Of the 124 patients with nosocomial pneumonia after systemic empirical antimicrobial pharmacotherapy, recovery was noted in 54 (43.5%). The number of recovered because of empirical monotherapy was 1.6 times higher than in the group of patients who were prescribed combination antimicrobial therapy. The absence of the effect of empirical monotherapy on nosocomial pneumonia is 8.9% of cases, which is 1.4 times less than the same indicator for the combined type of pharmacotherapy. However, all identified differences in the number of recovered patients, or those with no effect from treatment for the two compared groups, were statistically insignificant ($P > 0.05$).

Assessing the quality of pharmacotherapy for nosocomial surgical infection involving antibiotic-resistant gram-negative bacteria, it turned out that in 60% of cases, it was adequate. The proportion of adequate empirical combination and monotherapy regimens was not the same, 1.6 times greater when several drugs were administered simultaneously ($p < 0.05$). 24 (19.2%) empirical monotherapy regimens were found to be inadequate: pharmacotherapy with narrow-spectrum penicillin, aminopenicillins, 1st and 2nd generation cephalosporins, aminoglycosides. 26 (20.8%) empirical combination pharmacotherapy regimens were also inadequate. These included cases where narrow-spectrum penicillin, aminopenicillins, or 1st generation cephalosporins were prescribed for nosocomial surgical infection at the same time as fluoroquinolones or aminoglycosides. More often, a change during the first 2-3 days of antimicrobial pharmacotherapy of nosocomial surgical infection involving antibiotic-resistant gram-negative bacteria due to its ineffectiveness was required after using a combination of 3rd generation cephalosporins with aminoglycosides (6.4%) or aminopenicillins with aminoglycosides (4%).

Of the 93 patients with in-hospital surgical infection after systemic empirical antimicrobial pharmacotherapy, recovery was noted in 53 (57%). The number of patients who recovered because of empirical combination therapy was 1.4 times higher than in the group of patients who were prescribed empirical monotherapy ($p < 0.05$). At the same time, the lack of effect of empirical monotherapy was 1.3 times less than that of empirical combination therapy ($p < 0.05$).

Analyzing the quality of pharmacotherapy for nosocomial urinary tract infection with the participation of antibiotic-resistant gram-negative bacteria, it turned out that in 71.5% of cases, it was adequate. The proportion of adequate empirical combination and monotherapy regimens was not the same, 1.5 times greater when prescribing one antimicrobial drug ($p < 0.05$). In 11 (22.4%) cases, empirical monotherapy regimens were found to be inadequate, including episodes of the use of drugs with a relatively narrow spectrum of antimicrobial activity (aminopenicillins, 1st generation cephalosporins, 8-hydroxyquinoline derivatives) and aminoglycosides. In addition, 3 (6.1%) empirical combination pharmacotherapy regimens were inadequate when aminopenicillins and 1st generation cephalosporins with fluoroquinolones or aminoglycosides were used.

Of the 41 patients with nosocomial urinary tract infections, 15 (36.6%) recovered after systemic empirical

antimicrobial pharmacotherapy. The number of patients who recovered because of empirical monotherapy was 2.7 times higher than those who used empirical combination therapy ($p < 0.05$). At the same time, the absence of the effect of empirical monotherapy was 2 times greater than that of empirical combined antibacterial pharmacotherapy ($p < 0.05$).

DISCUSSION

It is known that the microflora in the case of surgical infection is a complex interacting association of gram-negative and gram-positive microorganisms, so it is extremely difficult to isolate the leading pathogen in it [1,13]. During this study, it was reliably established that the polymicrobial nature of the modern nosocomial surgical infection, in contrast to urinary infections, determines the appointment of systemic empirical combination antibiotic therapy for mixed gram-negative and gram-positive microflora.

The results obtained by clinical and laboratory studies confirmed the literature data that carbapenems (Imipenem and Meropenem) and Cefoperazone/Sulbactam have high pharmacodynamic activity against leading gram-negative pathogens (*Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) modern nosocomial infections, the clinical strains of which were resistant not only to beta-lactams but also differed in multidrug resistance. The pharmacotherapy agents listed above have exclusively parenteral dosage forms and belong to the drugs of the hospital segment of the pharmaceutical market [5,8,9].

Generic drugs are usually admitted to circulation after the expiration of the patent protection of the original drug, usually based on an assessment of reduced registration dossiers and bioequivalence data. There are no registered generics of Imipenem, Meropenem and Cefoperazone/Sulbactam in the medical literature and electronic databases available to us [6,7]. Consequently, the question of the therapeutic equivalence of generic antimicrobials Imipenem, Meropenem and Cefoperazone/Sulbactam remains unexplored [16].

In this situation, the awareness of medical specialists and patients is extremely important. In the United States, for example, for the purpose of regulating the use of generics, from the standpoint of therapeutic equivalence, there is a national centralized database - Approved Drug Products with Therapeutic Equivalence Evaluations [3]. The availability of objective information on the therapeutic equivalence of generics makes it possible to rea-

sonably use generic, including import-substituting, drugs, considering their efficacy, safety, and economic advantages, and hence to provide adequate medical care.

CONCLUSION

Antimicrobial drugs (from among those included in the administrative lists) for the systemic treatment of nosocomial infections involving antibiotic-resistant gram-negative bacteria are most often represented by cephalosporins and aminoglycosides of the 3rd generation - Cefotaxime, Ceftriaxone and, accordingly, Amikacin, as well as fluoroquinolones ($p < 0.05$). Their appointment is carried out mainly empirically as part of combination pharmacotherapy regimens of 2-6 systemic antimicrobials without prior and evidence-based pharmacoeconomic justification.

Long-term clinical and laboratory studies have confirmed that Imipenem, Meropenem and Cefoperazone/Sulbactam have high pharmacodynamic activity against *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* with multidrug resistance to 3-15 antibiotics.

The final data indicate the need to revise the nomenclature of antimicrobial drugs. So, it is advisable to consider the inclusion of a combination of Cefoperazone with Sulbactam. In addition, to conduct post-registration studies of the pharmacodynamic activity and therapeutic efficacy of Piperacillin/Tazobactam and Ticarcillin/Clavulanate to potential manufacturing companies on a wide range of clinical material, considering the principles of evidence-based medicine, to assess the prospects for their more active and reasonable use in medical practice.

Rational empirical antimicrobial pharmacotherapy of nosocomial infections should consider the results of monitoring the modern etiological structure of infectious pathology and current local data on the pharmacodynamic activity of antibiotics against potential pathogens in each individual hospital of a medical institution.

ETHICAL STANDARDS OF RESEARCH – the authors declare that all studies were reviewed and approved by the Bioethics Committee of the Ministry of Health of the Republic of Uzbekistan (minutes of meeting # 15 dated December 12, 2012). All patients gave written informed consent to participate in the study.

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.

DATA AVAILABILITY STATEMENT - The original contributions presented in the study are included in the article material, further inquiries can be directed to the corresponding authors.

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

FINANCING – No financial support has been provided for this work.

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**ANTIMIKROBIYAL FARMAKOTERAPIYAGA
RATSIONAL YONDASHUV NUQTAI NAZARI-
DAN NOSOKOMIAL INFEKTSIYA**

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ABSTRAKT

Dolzarbliigi. Antibiotiklarga chidamli gramm-manfiy bakteriyalar ishtirokidagi zamonaviy nozokomial infektsiyalarning tizimli antimikrobiyal farmakoterapiyasi har doim ham ratsionallik printsiyaga mos kelmaydi, shu bilan ularni davolash sifati va klinik samaradorligini pasaytiradi.

Material. Antibiotiklarga chidamli gramm-manfiy aerob va fakultativ anaerob bakteriyalar ishtirokida hujjatlashtirilgan nosokomial infektsiya bilan 3 yoshdan 92 yoshgacha bo'lgan jami 770 nafar bemor tekshirildi.

Natijalar. Antibiotiklarga chidamli gramm-manfiy bakteriyalar bilan bog'liq zamonaviy nozokomial infektsiyalarni farmakoterapiyasida aksariyat beta-laktam dori vositalarini qo'llash nosokomial mikroob shtammlari orasida beta-laktam dori vositalaridan keng foydalanish tufayli davolash qobiliyatining etishmasligi xavfi yuqori bo'lishi bilan bog'liq. Zamonaviy nozokomial xirurgik infektsiyalarning polimikrobiyal tabiati, nozokomial siydik yo'llari infektsiyalaridan farqli o'laroq, maqsadli tayinlanishini belgilaydi empirik kombinatsiya antibiotik terapiyasi.

Xulosa. Nozokomial infektsiyalarning ratsional empirik antimikrobiyal farmakoterapiyasi yuqumli patologiyaning zamonaviy etiologik tuzilishini monitoring natijalarini va tibbiyot muassasasining har bir alohida shifoxonasida antibiotiklarning farmakodinamik faolligi to'g'risidagi hozirgi mahalliy ma'lumotlarni hisobga olishi kerak.

Tayanch iboralar: nosokomial infektsiya, antibiotiklarga chidamlilik, farmakoepidemiologik o'rganish, mikroblarga qarshi farmakoterapiya

**ВНУТРИБОЛЬНИЧНАЯ ИНФЕКЦИЯ С
ПОЗИЦИИ РАЦИОНАЛЬНОГО ПОДХОДА К
АНТИМИКРОБНОЙ ФАРМАКОТЕРАПИИ**

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Абстракт

Актуальность. Системная антимикробная фармакотерапия современных внутрибольничных инфекций с участием антибиотикорезистентных грамотрицательных бактерий не всегда соответствует принципу рациональности, тем самым снижая качество и клиническую эффективность их лечения.

Материал. Обследовано 770 пациентов в возрасте от 3 дней до 92 лет с документально подтвержденной внутрибольничной инфекцией с участием антибиотикорезистентных грамотрицательных аэробных и факультативно-анаэробных бактерий.

Результаты. Применение большинства препаратов бета-лактаминового класса в фармакотерапии современных внутрибольничных инфекций с участием антибиотикорезистентных грамотрицательных бактерий связано с высоким риском неэффективности лечения в связи с широким распространением бета-лактаминных препаратов среди госпитальных штаммов микробов. Полимикробная природа современных внутрибольничных хирургических инфекций, в отличие от внутрибольничных инфекций мочевыводящих путей, обуславливает назначение таргетной эмпирической комбинированной антибиотикотерапии.

Заключение. Рациональная эмпирическая антимикробная фармакотерапия внутрибольничных инфекций должна учитывать результаты мониторинга современной этиологической структуры инфекционной патологии и актуальные локальные данные о фармакодинамической активности антибиотиков в отношении потенциальных возбудителей в каждом отдельном стационаре лечебного учреждения.

Ключевые слова: внутрибольничная инфекция, антибиотикорезистентность, фармакоэпидемиологическое исследование, антимикробная фармакотерапия