THE RESEARCH OF THE SUSCEPTIBILITY TO ANTIMICROBIAL MEDICINES OF ACINETOBACTER BAUMANNII AS PATHOGENS OF INFECTIOUS COMPLICATIONS IN PATIENTS WITH HARD BURNS

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Annotation. Antibiotic-resistant strains of Acinetobacter baumannii has become yet recognized one of the most leading causative pathogens of infectious complications in patients with severe burns. This greatly complicates the treatment of such patients and requires in-depth study with a prognostic determination of the dynamics of antimicrobial efficacy of antibacterial agents. The aim - to study the susceptibility to antibiotics in clinical isolates of A. baumannii, pathogens of infectious complications in patients with hard burns. From patients (n=435) with burns of the 2nd b - 3rd degree, isolates of A.baumannii were received in early period after burn trauma before antibiotic therapy. Patients who participated in the study received standard surgical, complex general and local treatment in the required volume according to the protocols for the treatment of this disease. In total, 222 clinical strains of A. baumannii were isolated and identified during 2011-2016. The susceptibility of clinical strains A. baumannii to the following beta-lactam antibiotics: ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, was determined by standard microbiological methods (qualitative disco-diffusion and quantitative double dilution methods). Using statistical methods, mathematical and analytical prognosis of the real sensitivity of A. baumannii strains to these antibiotics with the use of licensed computer programs “STATISTICA 7” was carried out; “Matlab 7.1”. The results of the study demonstrated a low susceptibility of clinical strains of A. baumannii to the studied beta-lactam antibiotics. The change in the antibiotic susceptibility profile of A. baumannii in 2011-2016 was established. Thus, the vast majority of strains were of low susceptibility to cefoperazone-sulbactam (55,6%), imipenem (57,1%) and meropenem (52,8%). In the dynamics, the prognostic decrease of the sensitivity in clinical isolates of Acinetobacteria to the antibiotics has been proved. The susceptibility of A. baumannii to amoxicillin-clavulanate was consistently low (less than 13,3%), and significantly decreased to cefoperazone-sulbactam (25,0%). The resistance of this pathogen to imipenem (up to 75,0%), meropenem (up to 84,3%) has been established to increase. At the same time, the gradual restoration of the susceptibility of A. baumannii, pathogens of infectious complications in patients with burns, were characterized by a decrease in sensitivity to inhibitor-protected penicillins, carbapenems except ampicillin-sulbactam, that proved their low effectiveness against this pathogen.

Keywords: Acinetobacter baumannii, antibiotics, susceptibility, burns, resistance.

Introduction

Antimicrobial remedies play the most important role in everyday medical practice. Nowadays, it is very difficult to imagine the how any of infection would go on without chemotherapy. Many diseases, which appeared at the beginning of “antibiotic era” and were successfully treated only by few injections of the remedy, but due to a quick decrease in the sensitivity of microorganisms, traditional antibiotics became ineffective. Wide uncontrolled use of antibacterial drugs has led to a rapid increase in the resistance of pathogens to antibiotics. Since antimicrobials have influenced in such a way on pathogenic and opportunistic microorganisms, the natural biological phenomenon of adaptation of pathogens to adverse environmental factors has been observed. In a result of breeding selection, sensitive strains of microorganisms perish and resistant to antimicrobial ones remain [1, 3].

According to the data of some researches works, nowadays, among a wide range of opportunistic microorganisms A.baumannii are considered to be among the leading causative agents of infectious complications in patients with severe burns.

In conditions of violation of immunobiological equilibrium the distribution of resistant clinical strains of Acinetobacteria significantly complicates the treatment of patients with severe burns and requires the study and prognostication of the dynamics of the use of antibacterial drugs [1, 7].

The aim - the research of the susceptibility to antibiotics in clinical isolates of A. baumannii, as causative agents of infectious complications in patients with severe burns.

Materials and methods

In the research there were enrolled patients who had undergone treatment at the burn department of the Vinnytsa Regional Clinical Hospital. N. I. Pirogov (n=435). Clinical strains of A. baumannii isolated before antimicrobial medication from patients with burns of the 2nd b - 3rd stages (burn area 30,0-85,0% of body surface). According
to the protocols of treatment, patients underwent surgery (early necrectomy in early three days, xenodermoplastics), received complex general management (balance resuscitation, antibacterial and symptomatic therapy) and topical treatment.

Microbiological study of biological material obtained from patients was performed in the certified scientific bacteriological laboratory of the Department of Microbiology of the National Pirogov Memorial Medical University, Vinnytsya (certificate of the Ministry of Health of Ukraine № 049/15 since 02.02.2015).

From patients in 2011-2016 there were isolated and identified 222 A.baumannii (2011 - 38 strains; 2012 - 40 strains; 2013 - 27 strains; 2014 - 34 strains; 2015 - 51 strains; 2016 - 32 strains). Bacterial identification was performed by conventional methods.

In this study, there were evaluated and compared in vitro activities of the ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, cefoperazone-sulbactam, meropenem, imipenem against A.baumannii clinical strains.

There susceptibility testing of A. baumannii to antibiotics was performed by microtube broth dilution or disk diffusion methods according to the recommendations of Ministry of Health of Ukraine № 167 "On approval of methodological guidelines for determining the sensitivity of microorganisms to antibacterial drugs" since 05.04.2007 [2]. The recommendations of European Committee on Antimicrobial Susceptibility Testing (EUCAST Expert rules) were used for the analysis of the susceptibility of A. baumannii clinical strains to antibiotics [6].

The results of the susceptibility testing of A. baumannii clinical strains to antimicrobials were analyzed by means of statistical methods, which gave the possibility to determine pattern correlation between numerical values of changing features and the probability of implementing these values in the series of conducted surveillances [5].

Mathematical analytical prediction provided for the determination of the actual sensitivity of clinical strains of A. baumannii and extrapolation of results to the studied system by constructing hypothetical mathematical models of prognostic susceptibility of Acinetobacteria to antibiotics by means of methods of normative analysis with a concrete definition of absolute and relative optimum values.

The reliability and accuracy of each developed mathematical model, susceptibility prediction of the pathogen to antimicrobials have been estimated by the coefficient of determination (r²). Processing of the received data was carried out using licensed packages of original computer programs "STATISTICA7"; "Matlab 7.11" [4].

For each sample of clinical isolates, A. baumannii at intervals of one year the arithmetic mean value (M), the standard mean error (m), the standard deviation (σ) have been calculated. Approximation and data interpolation was performed by using mathematical analysis methods. Due to this analytical dependencies of dynamic predictive parameters of sensitivity changes in such pathogens of infectious complications in patients with severe burns, as A. baumannii have been obtained.

**Results. Discussion**

The results of the research demonstrated low susceptibility of clinical strains of Acinetobacteria, isolated in 2011-2016. A change in the profile of antibiotic susceptibility A. baumannii has been established for six years. In 2011, the vast majority of strains were susceptible to cefoperazone-sulbactam (55,6%), imipenem (57,1%), and meropenem (52,8%). At the same time, sensitivity to ampicillin-sulbactam was determined in a small number of clinical strains A. baumannii (3,4%; Fig. 1).

For six years of observation, the susceptibility of the clinical isolates of Acinetobacteria has decreased to all studied antibiotics, except ampicillin-sulbactam.

Thus, the number of strains of A. baumannii to this antibiotic sensitive to this antibiotic has gradually increased from 3,4% in 2011 to 70,2%.

**Fig. 1.** The characteristics of susceptibility of clinical strains of A. baumannii to ampicillin-sulbactam (2011-2016 pp.; n=222), in %.

**Fig. 2.** The characteristics of susceptibility of clinical strains of A. baumannii to amoxicillin-clavulanate (2011-2016; n=222), in %.
Thus, the number of antibiotic-sensitive strains of A. baumannii gradually increased from 3.4% in 2011 to 70.2% (2015). These results can be explained, first of all, by the selective pressure of antibiotics that are used to treat infections caused by these microorganisms.

Susceptibility of the A. baumannii clinical strains to such semisynthetic penicillin antibiotic as amoxicillin-clavulanate has been constantly low and has not exceed 13.3% since 2012 throughout the entire observation period (Fig. 2).

Piperacillin-tazobactam, like amoxicillin-clavulanate, was ineffective in A. baumannii strains isolated from patients with severe burns. In 2012, only 7.5% of the clinical isolates of Acinetobacteria were susceptible to piperacillin-tazobactam.

Although, it is worth noting the tendency to slowly restoration of the susceptibility of Acinetobacteria to this antibiotic from 10.5% (2011) to 27.5% (2015; Fig. 3).

Analyzing the sensitivity of Acinetobacteria to cefoperazone-sulbactam, there has been found a significant decrease in the activity of this antibiotic in 2014 (25%) in comparison with the period of 2011-2013 (55.6-82.3% of susceptible A. baumannii), which has been observed in subsequent years (Fig. 4).

Susceptibility of clinical strains of A. baumannii to imipenem was low in 2011-2014 and could be characterized as relatively stable (25.6-57.1%; Fig. 5).

There has been determined the range of the number of resistant strains from 39.5% (2011) to 60.5% (2016).

Acinetobacteria clinical strains have been established to exhibit some susceptibility to meropenem only in 2011-2013 (33.3-52.8%). In the following years, a significant decrease in the effectiveness of meropenem was observed: the number of susceptible strains did not exceed 18.9-25.8%. Thus, their resistance had a tendency to increase, as the number of resistant strains reached 84.3% in 2015 (Fig. 6).

Conclusions and perspectives of further development

1. There has been established a change in the profile of antibiotic susceptibility in A. baumannii for six years, characterized by a decrease in the antimicrobial efficacy of amoxicillin-clavulanate, piperacillin-tazobactam, cefoperazone-sulbactam, carbapenems with the exception of ampicillin-sulbactam, to which Acinetobacteria retain sensitive (70.2%) Acinetobacteria strains (2015).
2. Clinical strains of A. baumannii obtain resistance to inhibitor-protected amino- and ureidopenicillins (amicillin-clavulanate, piperacillin-tazobactam), cephalosporins (cefoperazone-sulbactam), as evidenced by the low number of susceptible strains of the pathogen (less than 30% during 2011-2016).

3. Acinetobacteria as pathogens of infectious complications in patients with burns, had formed in the 2014-2016 resistance to imipenem (75%) and meropenem (84%), that indicated a decrease of their effectiveness against this pathogen.

References

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**ИССЛЕДОВАНИЕ ЧУВСТВИТЕЛЬНОСТИ К АНТИМИКРОБНЫМ ПРЕПАРАТАМ ACINETOBACTER BAUMANNII КАК ВОЗБУДИТЕЛЕЙ ИНФЕКЦИОННЫХ ОСЛОЖНЕНИЙ У БОЛЬНЫХ С ТЯЖЕЛЫМИ ОЖОГАМИ**

**Аннотация.** В наше время антибиотикорезистентные клинические штаммы Acinetobacter baumannii относят к ведущим возбудителям инфекционных осложнений у больных с тяжелыми ожогами. Это значительно усложняет лечение таких пациентов и требует углубленного изучения с прогностическим определением динамики антимикробной эффективности антибактериальных средств. Цель исследования заключалась в изучении чувствительности к антибиотикам клинических изолятв A.baumannii как возбудителей инфекционных осложнений у больных с тяжелыми ожогами. От пациентов (n=435) с ожогами II-б-III степени, выделяли штаммы A.baumannii в ранний период после ожоговой травмы перед антибактериальной терапией. Пациентам, которые принимали участие в исследовании, проводили стандартное хирургическое, комплексное общее и местное лечение в необходимом объеме согласно протоколам лечения этого заболевания. Всего в 2011-2016 гг. было выделено и выявлено 222 клинических штаммов A.baumannii. Чувствительность клинических штаммов A.baumannii к таким бета-лактамным антибиотикам, как: ампициллин-сульбактам, амоксициллин-клавуланат, пиперациллин-тазобактам, цефоперазон-сульбактам, имипенем, меропенем, определяли с помощью стандартных микробиологических методов (качественный диско-диффузный метод, количественный метод двукратных серийных разведений).

Используя статистические методы, проведено математико-аналитическое прогнозирование реальной чувствительности штаммов A.baumannii к этим антибиотикам с использованием лицензированных компьютерных программ "STATISTICA 7", "Matlab 7.11". Результаты исследования продемонстрировали низкую чувствительность клинических штаммов A.baumannii к изученным бета-лактамным антибиотикам. Установлено изменение профиля чувствительности антибиотиков A.baumannii в 2011-2016 гг. Так, по сравнению с 2011 годом уменьшилась чувствительность к цефоперазону-сульбактаму (55,6%), имипенему (57,1%) и меропенему (52,8%). В динамике показано прогностическое снижение чувствительности A.baumannii к ампициллину-сульбактаму (от 3,4% до 70,2%). A.baumannii как возбудители инфекционных осложнений у пациентов с ожогами, характеризовались снижением чувствительности к ингибитор-защищенным пеницилинам, кроме ампициллина-сульбактама, и карбапенемов, что свидетельствовало об их низкой эффективности против данного возбудителя.

**Ключевые слова:** Acinetobacter baumannii, антибиотики, чувствительность, ожоги, резистентность.