CARBAPENEM-RESISTANT *KLEBSIELLA PNEUMONIAE* BLOODSTREAM INFECTIONS: RETROSPECTIVE ANALYSIS

КАРБАПЕНЕМУСТОЙЧИВЫЕ ИНФЕКЦИИ КРОВОТОКА KLEBSIELLA PNEUMONIAE: РЕТРОСПЕКТИВНЫЙ АНАЛИЗ

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Bloodstream infections caused by carbamazepine-resistant Klebsiella pneumoniae (CR-CR) are a serious clinical problem worldwide. The main problem in the treatment of bloodstream infections is the search for effective antibiotic treatment regimens, since carbapenem resistance, Klebsiella pneumoniae, as a rule, has associated resistance to many non-ß-lactam antibiotics, and the bloodstream infections caused by them are accompanied by high attributable mortality. Recent studies have shown that high-dose carbapenem, extended meropenem infusion, and additional drugs such as aminoglycosides and colistin warrant investigation to increase treatment efficacy. In addition, there is evidence that the use of carbapenems in combination with other active agents may reduce mortality, especially when strains have low levels of resistance to these antimicrobials in vitro. Moreover, a number of reports indicate that combination therapy is often more effective than monotherapy. Despite the promising prospects of combination therapy, challenges remain in finding optimal and effective treatment regimens. This study highlights the complexity of controlling bloodstream infections and highlights the need to find optimal strategies for their therapy.

Инфекции кровотока, вызванные устойчивостью *Klebsiella pneumoniae* к карбамазепину (КР-КП), представляют собой серьезную клиническую проблему во всем мире. Основная проблема лечения инфекций кровотока заключается в поиске эффективных схем лечения антибиотиками, поскольку устойчивость к карбапенемам *Klebsiella pneumoniae*, как правило, имеют ассоциированную устойчивость ко многим не ß-лактамным антибиотикам, а вызываемые ими инфекции кровотока сопровождаются высокой атрибутивной летальностью. Недавние исследования показали, что высокие дозы карбапенем, расширенное инфузирование меропенемом, а также дополнительные препараты, такие как аминогликозиды и колистин, требуют исследования для увеличения эффективности лечения. Кроме того, имеются данные указывающие на то, что использование карбапенемов в сочетании с другими активными агентами может способствовать снижению смертности, особенно когда штаммы имеют низкий уровень устойчивости к этим противомикробным препаратам *in vitro*. Более того, ряд сообщений свидетельствует о том, что комбинированная терапия часто более эффективна, чем монотерапия. Несмотря на многообещающие перспективы комбинированной терапии, сохраняются проблемы в поиске оптимальных и эффективных схем лечения. Это исследование подчеркивает сложность борьбы с инфекциями кровотока и подчеркивает необходимость поиска оптимальных стратегий для их терапии.

Keywords: Klebsiella pneumoniae, carbamazepine, bloodstream infections, antibiotic resistance, antimicrobial drugs.

Ключевые слова: Klebsiella pneumoniae, карбамазепин, инфекции кровотока, антибиотикорезистентность, противомикробные препараты.

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Bloodstream infection denotes the presence of pathogenic microorganisms in a patient's blood, whether or not accompanied by symptoms or signs of infection. Positive blood cultures are typically indicative of such infections, which can progress to severe conditions like sepsis, septic shock, bacteremia, and multiple organ dysfunction syndrome (MODS), often culminating in high mortality rates. This poses a substantial global public health burden, necessitating effective diagnostic and treatment strategies [1].

At present, blood culture remains the cornerstone for diagnosing bloodstream infections, crucially facilitating the isolation of infecting pathogens and guiding precise treatment plans through antimicrobial susceptibility testing .

Carbapenems stand out as broad-spectrum antibiotics renowned for their potent antibacterial activity against both aerobic and anaerobic bacteria. Particularly noteworthy is their efficacy against multidrug-resistant Gram-negative bacilli, earning them the moniker “last line of defense” against bacterial resistance.

Klebsiella pneumoniae, a member of the Enterobacteriaceae family, emerges as a common opportunistic pathogen with clinical significance. While primarily colonizing the respiratory tract, it can also inhabit various bodily sites, including the urinary, gastrointestinal, reproductive tracts, as well as the bloodstream and nervous system. Notably, Klebsiella pneumoniae infections, especially bloodstream infections, exhibit alarmingly high mortality rates, reaching 37–50 %.

The focal point of this study lies in the analysis of drug resistance patterns and risk factors associated with mortality in carbapenem-resistant Klebsiella pneumoniae (CR-KP) bloodstream infections. For patients necessitating treatment with multiple antibiotics concurrently, in vitro combination sensitivity tests are conducted to facilitate prompt empirical antibacterial therapy. Adjustments to treatment regimens are then made based on susceptibility results, highlighting the feasibility of certain combination therapies in clinical practice.

Clinical data of patients diagnosed with carbapenem-resistant Klebsiella pneumoniae (CR-KP) bloodstream infections and admitted to Shaanxi Provincial People’s Hospital between January 2020 and December 2020 were screened. All patients had bloodstream infection of multidrug-resistant Klebsiella pneumoniae which was the most basic eligibility criterion for the study.

Patients meeting the following criteria were included: having at least one positive blood culture for CRKP, meeting diagnostic criteria for bloodstream infection (body temperature >38°C or <36°C, possibly accompanied by chills), and presenting with one of the following: (1) Evidence of invasion portal or metastatic foci; (2) Isolation and culture results indicating Klebsiella pneumoniae bacterial strain concentration >10^(7) CFU/ml; (3) Demonstrated resistance to meropenem and/or imipenem based on susceptibility results(with imipenem and meropenem resistance as the criteria for carbapenem resistance), confirming CR-KP positivity.

Additionally, patients exhibiting rash or petechiae, hepatosplenomegaly, and increased neutrophil count with left shift in blood without other explanatory causes were included. Cases with multiple pathogenic microorganisms isolated from blood cultures were excluded.

Initially, there were more than 400 cases of Klebsiella pneumoniae bloodstream infection. After the first grouping, a variety of medical records that did not meet the criteria was excluded, and 102 patients with carbapenem-resistant bloodstream infection were sorted out. After the second grouping according to the exclusion criteria, two groups of 91 patients survived and 11 patients died due to treatment failure were analyzed. Subsequently, according to the direction of the study, 11 patients with CR-KP bloodstream infection who died were selected for the study.

Collection of clinical data encompassed demographic characteristics (gender and age) of patients, department of onset of bloodstream infection (intensive care unit [ICU] or non-ICU), source of bloodstream infection, clinical manifestations (presence of septic shock), bacterial resistance and susceptibility analysis, antibacterial drug treatment regimen, and effectiveness of anti-infection measures.

General data: all 11 patients included in the study presented with carbapenem-resistant Klebsiella pneumoniae (CRKP) bloodstream infections. Among them, 4 were male and 7 were female, with ages ranging from 59 to 85 years. Distribution by department revealed 6 cases in the intensive care unit (ICU) and 5 cases in non-ICU departments. The sources of infection were identified as the urinary tract (4 cases), lungs (5 cases), and central venous catheter-related (2 cases). Notably, six patients developed septic shock during the course of their illness.

Drug sensitivity results: antimicrobial susceptibility test and zymogram analysis of CRKP isolated from 11 patients were performed. The results of drug sensitivity test shown that microbial strains were sensitive to tigecycline, but all of them were resistant to imipenem and meropenem, and some strains were sensitive to fosfomycin. In addition, CRKP strains from 11 patients were zymogram analyzed, and 10 were KPC-type, of which one was zinc-dependent metal-like β-lactamase (MβLs), a minimally resistant phenotype that is rare and rarely observed even in clinical isolates because MβL producers often have other mechanisms that increase the level of carbapenem resistance.

Biochemical and serological data: all the patients in this study had elevated white blood cells count, C-reactive protein, serum amyloid A and procalcitonin (CRP, SAA, and PCT respectively) values. When compared the PCT values before and after antibiotic treatment in this patient, it was found that the PCT value was high before death and did not decrease, which supports the limited efficacy of tigecycline-combined antibiotic therapy against CR-KP strains.

Carbapenem-resistant Klebsiella pneumoniae (CR-KP) poses a significant global health threat, commonly mediated by the production of KPC enzymes, which hydrolyze carbapenems and other β-lactam antibiotics [2, 3]. Studies report lower survival rates in patients receiving combination therapy compared to monotherapy, especially in high-risk patients. However, the most effective combination regimen remains uncertain [2, 3]. All microbial strains will be tested for drug resistance, and the drug will be adjusted according to the results of dr g resistance and the clinical situation.

In our study, most patients received tigecycline-based combination therapy, had severe status and subsequently died. Interestingly, some studies suggest that tigecycline-containing regimens may even increase mortality rates in CR-KP bloodstream infections, possibly due to factors like higher illness severity scores and suboptimal serum concentrations [2, 4].

In this study, tigecycline was almost the only antibiotic available that was sensitive (some patients were sensitive to fosfomycin), so most patients were treated with tigecycline plus other antibiotics (fosfomycin or polymyxin and so on). Predictions were made based on the results that the main cause of death was bloodstream infection caused by carbapenem-resistant Klebsiella pneumoniae, which was almost pansusceptible to antibiotics, making it difficult to choose antibiotic

treatment and facing a possible “no cure” state in clinical treatment, where the patient had no high-order antibiotics to treat the disease. In the literature there was also raised the possibility that the use of tigecycline may increase mortality, so it should be discussed whether the use of tigecycline is also a factor in the death of patients.

It is worth mentioning that there are still imperfections in this study. The interpretation of the survey results in this study is limited by the sample size, and the KP resistant strains have geographical differences and resistance migration. In future studies, large samples, multi-center and multi-region in-depth studies are needed to further investigate the death of patients caused by CR-KP.

In the past few decades, the interaction of multiple mechanisms has made KP resistant to carbapenems. More targeted new antibiotics are being developed, and it is believed that the worldwide problem of CRKP treatment will be solved as soon as possible in the near future.

In described case with 11 patients with blood-born CR-KP antibiotic treatment plan was dynamically adjusted according to the drug sensitivity results of the laboratory, and the tigecycline-based combination of different antibiotics was used. Nevertheless that gave little effect, and eventually all these patients died due to the aggravation of bloodstream infection and various complications.

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ДИНАМИКА КЛЕТОК ПАМЯТИ ПОСЛЕ ВАКЦИНАЦИИ ПРОТИВ ИНФЕКЦИИ, ВЫЗВАННОЙ ВИРУСОМ SARS-COV-2

MEMORY CELLS DYNAMICS AFTER VACCINATION AGAINST SARS-COV-2 INFECTION

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Вакцинирование считается эффективным методом предотвращения и контроля распространения инфекционных заболеваний, в том числе вызванных вирусом SARS-CoV-2. В статье представлена динамика клеток памяти у 15-ти вакцинированных вакциной «Vero Cell» и «Спутник Лайт» в качестве бустера добровольцев. Установлено увеличение наивных В клеток-памяти, плазмобластов с тенденцией к увеличению тер-