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FACTORS OF BRUCELLOSIS CHRONICITY: MODERN ASPECTS OF PATHOGENESIS, DIAGNOSTICS AND TREATMENT

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Abstract
Brucellosis remains one of the most significant zoonotic infections in the world , caused by bacteria of the genus Brucella , especially common in regions with developed agriculture. The chronic form of the disease is a serious medical and socio-economic problem associated with a long course, relapses and multiple complications. This article reviews current data on the factors contributing to the chronicity of brucellosis, including bacterial, immunological and external aspects. The biological properties of the pathogen, features of the immune response, diagnostic and therapeutic aspects, as well as the influence of social and epidemiological factors are analyzed. Particular attention is paid to new approaches to the diagnosis, treatment and prevention of chronic brucellosis, based on the latest research in molecular biology, immunology and pharmacotherapy.

Keywords: Brucellosis, chronicity, pathogenesis, immune response, antibiotic therapy, immunotherapy, biofilms, persistence.

Introduction

Brucellosis is an infectious disease caused by bacteria of the genus Brucella , which are transmitted to humans from infected animals. Despite significant advances in diagnostics and treatment, the problem of brucellosis chronicity remains relevant. The chronic form of the disease is characterized by a long course, relapses and the development of complications such as arthritis, spondylitis, neurological disorders and cardiovascular damage. Understanding the factors that contribute to chronicity is key to developing effective treatment and prevention strategies.

The aim of the study was to investigate the factors in the development of chronic brucellosis based on literary sources over the past 5 years.

Materials and Methods

To prepare this review, scientific articles published in international databases (PubMed, Scopus, Web of Science) over the past 5 years were analyzed. The criteria for selecting articles were their relevance, scientific novelty, and relevance to the research topic. The works devoted to the pathogenesis of brucellosis, immune mechanisms of chronicity, as well as modern methods of diagnosis and treatment were reviewed. Particular attention was paid to clinical studies devoted to the effectiveness of new therapeutic approaches.

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Results

Pathogenesis of brucellosis and mechanisms of chronicization. Brucellosis begins with the penetration of bacteria into the body through mucous membranes or damaged skin. The pathogen has a unique ability to survive and reproduce inside macrophages, which allows it to avoid the immune response. Chronicization of infection occurs as a result of a complex interaction between bacterial virulence factors, the host immune response, and external conditions [1,2].

Factors contributing to the chronicity of brucellosis

Bacterial factors. The biological properties of the pathogen are characterized by the fact that bacteria of the Brucella genus have the ability to intracellular persistence, which is one of the key factors of chronicity. They infect macrophages and avoid destruction by suppressing the phagocytic burst, inhibiting the fusion of the phagosome with the lysosome, and modulating the body's immune response.

In addition, brucellae have low immunogenicity, which complicates the formation of a stable immune response and contributes to the latent course of infection [1]. Studies show that the pathogen is able to modulate the expression of macrophage genes, suppressing the synthesis of nitric oxide, which plays an important role in the destruction of intracellular pathogens [2].

The ability of Brucella to intracellular persistence inside macrophages, dendritic cells and other immunocompetent cells makes its elimination difficult. At the same time, recent studies have shown that Brucella can form biofilms that protect bacteria from the action of antibiotics and the immune system. Changes in the surface antigens of the pathogen also contribute to evasion of the immune response.

In addition, bacteria secrete effector proteins that modulate the host's immune response, promoting their survival.

Immunological aspects of chronicization. The human immune system plays an important role in infection control; however, brucellosis is characterized by dysfunction of T-cell immunity (decreased activity of CD8+ T-lymphocytes), impaired production of proinflammatory cytokines (IFN-γ, TNF-α), and hyperactivation of regulatory T-cells that suppress antibacterial immunity. These mechanisms lead to insufficient control over the pathogen and the development of chronic inflammation. Studies have shown that chronic brucellosis is accompanied by an imbalance between proinflammatory and anti-inflammatory cytokines, which contributes to the persistence of infection [3]. Concomitant diseases such as diabetes mellitus, HIV infection, or long-term use of immunosuppressive drugs increase the risk of chronicization. Some researchers point to a higher risk of chronicization in the elderly and women.

Genetic factors of predisposition. Genetic predisposition may play an important role in the chronicity of brucellosis. Studies have shown that certain polymorphisms of genes regulating innate immunity may increase the risk of chronic infection. In particular, variations in the TLR4 and TNF-α genes are associated with increased susceptibility to pathogen persistence [8].

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The influence of the microbiome on the course of infection. Modern studies demonstrate that the composition of the intestinal microbiome can affect the effectiveness of the immune response in brucellosis. An imbalance between beneficial and pathogenic microorganisms in the intestine can weaken immune mechanisms, contributing to the chronicity of the infection. Experiments on animal models have shown that restoration of the microbiota with probiotics can enhance the antibacterial immune response [5,9].

External factors leading to chronicity of the process - untimely diagnostics: late initiation of treatment increases the likelihood of the infection becoming chronic. In some cases, irrational antibiotic therapy, incorrect choice of drugs, insufficient dosage or duration of treatment contribute to the development of bacterial resistance. Along with this, such socio-economic conditions as low standard of living, insufficient public awareness and limited access to medical care aggravate the problem of chronicity.

Diagnosis of chronic brucellosis

Diagnosis of chronic brucellosis is a complex task due to the non-specificity of symptoms and limited sensitivity of traditional methods. Modern approaches include: serological methods (ELISA, RPGA, agglutination reaction), molecular methods (PCR for detection of Brucella DNA), cultural methods (blood, bone marrow or other biological material culture), instrumental methods (ultrasound, MRI, CT for detection of complications) [7].

However, serological tests (Wright reaction, ELISA) may give false negative results in chronic cases. Cultural methods are highly specific but require a long time.

Modern molecular genetic methods such as PCR have high sensitivity and specificity, but their availability is limited in endemic regions [6].

Therapeutic difficulties

Antibacterial therapy of acute brucellosis includes the combined use of doxycycline and rifampicin, but in the chronic form, treatment is significantly more complicated. The main reasons for the ineffectiveness of therapy are the intracellular localization of the pathogen, the formation of persistent forms of bacteria, the development of antibiotic resistance, and insufficient duration of therapy.

Studies have shown that the combination of doxycycline with hydroxychloroquine increases the effectiveness of therapy by enhancing the intracellular penetration of antibiotics [9,10].

In addition, patients often interrupt treatment due to side effects of drugs, which contributes to the chronicity of the process.

Social and epidemiological factors influencing the chronicity of brucellosis include late diagnosis and untimely treatment, lack of mass vaccination of animals in endemic regions, insufficient public awareness of preventive measures, contact with infected animals and consumption of contaminated products (unpasteurized milk, cheese).

Thus, the chronicity of brucellosis is a multifactorial process involving both bacterial and host-associated mechanisms. Understanding these factors opens up new perspectives for the development of effective treatment and prevention methods. Further research in the field of

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immunopathogenesis, molecular biology and pharmacotherapy will help to reduce the incidence of chronic forms of brucellosis and improve the prognosis for patients.

Conclusion

The chronicity of brucellosis is caused by the complex impact of biological, immunological, genetic, diagnostic and therapeutic factors. To reduce the prevalence of chronic forms of the disease, it is necessary to improve early diagnostic methods, develop more effective treatment regimens and carry out large-scale preventive measures. Only a comprehensive approach will reduce the incidence and prevent complications of chronic brucellosis.

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