International Journal of Studies in Natural and Medical Sciences
Volume 3 Issue 3, March - 2024
ISSN (E): 2949-8848
Scholarsdigest.org

THE PROBLEM OF INFECTION IN MEDICINE

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Abstract:
Analyzed were the problems of infection in medicine covering the outstanding achievements in the field of microbiology, development of effective antibacterial drugs - first sulfonamides, and then antibiotics with the emergence of epidemiology and the creation of vaccines. Established were the features of evolution of the infectious process due to the «return» of infections that were inherited in the past centuries, and associated with the emergence of new infectious diseases, 35 of which are the result of interspecies «jumps» of the pathogens from animals to humans; ascertained were the changes in the behavior of the bacteria with their recent characteristic «social» behavior, manifested primarily in the ability to form structured communities of bacteria. Stressed was the need for adequate laboratory diagnosis of infections involving the use of current advances in genetics, molecular biology, metagenomic and proteomic technologies, opening up the perspectives for a fundamental change in the quality of etiologic diagnosis, the use of amplification test-systems, blood cultures, mass spectrometry, etiotropic and efferent therapy. Furthermore, attention should be paid to the development of new methods of usage of antibacterial agents and monitoring their effectiveness, and implementation of the principles of preventive rotation of broad-spectrum antibiotics.

Keywords: infectious diseases, general genetics, immunity, anti-microbial agents, immunotherapy.

Introduction

Infectious diseases arose long before the appearance of humans. The bones of dinosaurs, mammoths, cave bears and other ancient animals show traces of osteomyelitis. Among human ancestors, infectious bone lesions were noted in Pithecanthropus from the island of Java, who lived 1-2 million years ago. Thus, humanity, even at the dawn of its existence, encountered numerous infectious diseases. It is obvious that in terms of quantity, total mass, reproduction rate and duration of existence on Earth, bacteria are absolutely superior to humans. That is why, as society emerged and human social lifestyle developed, many infections became widespread. In general, three historical stages in the relationship between humanity and infections can be distinguished.

The first stage was characterized by the widespread spread of “pestilence” or “endemic” infectious diseases, unrestricted by anything other than the natural resistance of the human body. The second stage occurred in the 19th century, when the understanding of the essence of infectious diseases and the discovery of their causative agents began; the

first scientifically based measures to combat infections appeared. It was then that the prerequisites were created for the successful development of all the main branches of infectology: microbiology, epidemiology and infectious diseases themselves as an independent clinical discipline and a new clinical specialty. The third stage began in the 20th century and was marked by an unprecedented active fight against infectious diseases. The outstanding successes of microbiology and the creation of effective antibacterial drugs - first sulfonamides, and then antibiotics - coupled with the development of epidemiology and the creation of vaccines by the middle of the 20th century gave rise to the illusion of the possibility of completely eradicating infectious diseases in the country and on the entire planet.

Indeed, epidemics of plague, cholera, typhoid and typhus that had raged for many centuries were curbed, smallpox was eliminated, and the incidence of polio, measles, whooping cough, mumps, and diphtheria significantly decreased. The mortality rate from infectious diseases has decreased: for especially dangerous infections by 10 times, and for some others - by 100 times or more. These successes were largely due to fundamental scientific research. Thus, in the 20th century, 23 Nobel Prizes were awarded for work in the field of infectious pathology; in the last 40 years alone, 9 prizes were awarded for discoveries in the field of virology (mainly oncovirology) and 6 in the field of immunology. In 2005, awards were presented for work on studying the influence of the bacterium Helicobacter pylori on the occurrence of gastritis and gastric and duodenal ulcers, in 2008 - for the discovery of the human papillomavirus, which causes cervical cancer, as well as for the discovery of the human immunodeficiency virus. Significant achievements include the formation of the doctrine of sapronoses, the discovery of prions as a fundamentally new class of infectious diseases, as well as uncultivable forms of bacteria.

However, unfortunately, in practice, many far-reaching plans to combat infections were not destined to come true. Defects in the organization and implementation of vaccination, socio-economic cataclysms and difficulties, as well as a number of other objective and subjective factors led to a deterioration in the epidemiological situation and to serious epidemics. At the same time, the widespread and uncontrolled use of etiotropic drugs quickly caused the emergence of resistant and atypical forms of most current pathogens of infectious diseases. A race began to create more and more new antibacterial drugs, most of which quickly became ineffective. The same fate awaited the antiviral drugs that appeared in the last quarter of the 20th century.

Infectious and parasitic diseases account for 25% of all deaths in the world (more than 50 million annually), and taking into account the role of infection in the pathogenesis of “non-infectious” diseases - almost 35%. In Russia, from 30 to 50 million cases of infectious diseases are registered annually. Every third case and every fifth day of temporary disability due to illness is associated with infectious pathology. Direct and indirect losses from infections, including disability, amount to more than 1.5 trillion rubles.

A feature of the current stage of development of the doctrine of infectious pathology is the combination of two distinct trends. The first is due to the so-called “recurring infections,” i.e., those we inherited from previous centuries. Among them are tuberculosis, malaria, leishmaniasis, sexually transmitted infections (syphilis, etc.). The second is associated with the emergence of new infections. The share of known pathogenic bacteria is small and amounts to only 12% of the total estimated number, and for viruses it is even less - about 4%. It is no coincidence that in recent decades more than 30 new, or rather, newly identified infections have been described - among them HIV infection, Lyme disease, ehrlichiosis, legionellosis, prion diseases, a number of dangerous viral fevers, campylobacteriosis, viral hepatitis E, C, D, F, papillomavirus infection and many others. It is possible that this trend reflects the natural evolution of human infectious diseases.

Among the serious infectious diseases that have been reported in the past three decades, at least 35 are the result of interspecies jumps from animals to humans. In this regard, it is appropriate to recall diseases that are currently still practically unknown or have just been described, but will certainly be widely diagnosed in the 21st century.

Only in the last 10 years have we learned about new pathogens of viral infections such as metapneumovirus, bocavirus, coronavirus, etc. At the same time, the etiology of classical somatic diseases is increasingly being deciphered. Thus, many malignant neoplasms (papillomavirus, herpesviruses, hepatitis B and C viruses, lymphotropic viruses LVI, II, etc.), myocarditis (cardiotropic enteroviruses, Coxsackie viruses), peptic ulcer (H. pylori), etc. have a proven infectious etiology. Unfortunately, there are also unpredictable problems of the 21st century. The fact is that the development of genetics and the improvement of microbiological technologies have led to the emergence of a real possibility of creating microorganisms with altered genetic properties. Such pathogens may have increased resistance to antibiotics, be a weapon of bioterrorism, and create significant difficulties in diagnosis and therapy. Even microorganisms previously considered opportunistic or “harmless” can, under certain conditions, cause serious diseases. Thus, cryptosporidium, regarded as harmless commensals until the early 70s of the last century, leads to severe lesions in AIDS patients. An even more surprising situation is associated with Saccharomycetes. It turned out that S. boulardi and S. cerevisiae, widely used in the manufacture of popular probiotic products and dietary supplements, are capable of causing serious invasive infections (91 documented cases) in immunosuppressed patients, newborns and children in the first years of life.

In recent years, our understanding of the behavior of bacteria has changed significantly. Many microbes are characterized by “social” behavior, manifested primarily by the ability to form structured communities of bacteria, so-called biofilms. Such a community is typically embedded in a polymer matrix and attached to inert or living surfaces.

As part of biofilms, bacteria acquire new properties: resistance to host resistance factors and the ability to generate a subpopulation of “persisters”. The latter are particularly resistant to antibacterial drugs, as a result of which the infection becomes chronic and difficult to treat. Persisters are present in any bacterial population and are characterized by a sharply slow metabolism. Their proportion increases in the stationary phase of bacterial growth, and they remain viable in the presence of antibiotics and under stress, and resume growth after removal of antibacterial drugs. Thus, persisters represent a “dormant” subpopulation that is resistant to stress.

Other signs of “social” behavior of bacteria are the manifestation of virulence only under certain conditions (for example, when in the environment or in low concentrations in the host’s body, bacterial virulence factors are not produced), as well as such a phenomenon as altruism (the programmed death of part of the microbial population in benefit another). These factors require new approaches to assessing the mechanisms of pathogen virulence. At present, it can be considered proven that the signal for the production of virulence factors is either contact with host epithelial cells (expression of the third type of transport system - “molecular needle”), or exposure to autoinducers of the “quorum sensing” systems.

The mechanism of virulence regulation due to “quorum sensing” is much more complex. As an example, the regulation of virulence for Pseudomonas aeruginosa (P. aeruginosa) can be considered. At low levels of contamination, P. aeruginosa does not synthesize virulence factors (elastase, alkaline phosphatase, rhamnolipids, pyocyanin, toxin A, etc.), but when a high critical concentration of bacteria is reached, the synthesis of virulence factors is naturally turned on. The biological meaning of this behavior is completely obvious: low concentrations of virulence factors will not have a negative effect on the host organism and the microbial population can continue to exist in the host organism. It is advisable to activate the synthesis of virulence factors only at a certain density of the bacterial population, when the issue of lack of nutrients for the increased number of bacteria becomes acute. Such a mechanism for turning on synthesis can be the production of low molecular weight compounds by the pathogen - homosiderin lactone. Subsequently, the death of part of the population (altruism) is possible with the preservation of persisters and the transition to the stationary phase.

The described mechanisms make clear many phenomena of the evolution of the infectious process, including an increase in the proportion of atypical, protracted and chronic forms of infectious diseases (pathogen resistance, changes in the reactivity of the macroorganism), more frequent development of mixed infections, superinfection, prolonged persistence of the pathogen, updating of opportunistic flora, increased frequency of mycoses, etc.

The study of the problem of infection in medicine in recent years has acquired a pronounced interdisciplinary character. There is practically no clinical specialty where issues related to infectious pathology do not arise in one way or another.

Other fundamentally new approaches to etiotropic therapy include attempts to create drugs based on endolysins from bacteriphages and inhibitors of sortases—enzymes involved in the assembly of villi—bacterial organelles responsible for the development of the initial stage of infectious processes—adhesion. Research continues on the creation of drugs based on defensins - proteins of animal origin that have antibacterial activity.

Theoretically, blocking the expression of virulence genes using synthetic antisense oligonucleotides that specifically bind to mRNA encoding virulence factors seems very promising. Small interfering RNAs (siRNAs) also have the ability to "turn off" individual genes.

Evidence-based medicine, pharmacoepidemiology, pharmacoeconomics are called upon to study in detail the effect of drugs on the population of not only microorganisms, but also on humanity itself; promote rational and cost-effective use of the most effective and safe medicines. Unfortunately, in recent years, the rapid formation and spread of resistance caused by the irrational consumption of antibiotics has been associated with significant human and financial losses for society.

This threat has long been recognized by the world community; a global strategy to curb resistance was proposed by WHO back in 2001. But only in 2009 did the leadership of North America and the European Union put forward an initiative to create a transatlantic group to combat antibacterial resistance, supported by professional communities. It provides for the emergence of 10 new antibacterial drugs by 2020. In addition, promising development of new methods of using antibacterial agents, monitoring the effectiveness of antibacterial therapy, multicenter resistance studies, and the introduction of the principles of proactive rotation of broad-spectrum antibiotics are required in order to curb the formation and spread of resistant strains. Obviously, this will require the adoption of urgent measures of both an administrative and educational nature, carried out at the federal and regional levels, as well as coordination of efforts on a global scale and the integration of Uzbekistan into relevant international structures.

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