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Anti-infective Therapy Principles in Diseases Caused by Bacterial Biological Agents

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Authors' contributions

This work was carried out in collaboration between all authors. Authors VO, LEI and DMP designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MN, SNB, GVD and RGH managed the analyses of the study. Authors VO, LEI and DMP managed the literature searches. All authors read and approved the final manuscript.

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Policy Article

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ABSTRACT

The international situation requires the strengthening of national security measures, including CBRN field and public health. Infectious diseases, and especially infectious-contagious diseases, represent the main threat to public health and have the highest prevalence of morbidity and mortality. These are classified by the World Health Organization in first group of human diseases. The situation may be even worse concerning biological warfare (BWA) and bioterrorism agents.

The great successes of modern medicine, looking from a holistic perspective at the species level, are based on vaccination and antibiotherapy. But, lately, some serious problems arose. The antibiotics (AB), antibacterial miracle drugs, are losing their effectiveness due to the increase in antibiotic resistance (AMR) of bacteria, a phenomenon that will worsen in the future; so, we are already discussing the end of the antibiotic era and the need for new anti-infective therapy concepts. And, as if this medical catastrophe was not enough, the "anti-vaccine" movement that undermines the specific prophylaxis of infectious diseases also appeared. Moreover, in this dangerous context to public health, the threats of biological warfare and bioterrorism are outlined.

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1. INTRODUCTION

The international situation calls for the strengthening of the national security measures, including CBRN field and public health, under the conditions of a "hybrid war" risk. At the same time, a new threat to public health emerges: *the spread of the microbial resistance phenomenon*, which will lead to the "end of the era of antibiotics". Particularily because the biological warfare agents (BWA) are selected or genetically modified to be more pathogenic, more virulent, more resistant to the environment and more resistant to antibiotics. Their use would cause the spread of infectious and contagious diseases that are difficult to prevent and treat, so morbidity and mortality among militaries and civilians can be catastrophic. The principles of anti-infective medical protection should be kept up-to-date for achieving a realistic documentation through studies and research on the therapy of infectious diseases caused by bacterial biological warfare and bioterrorism agents in the post-antibiotic era. This includes the treatment (preventive, curative and recovery) of infected individuals with particularly dangerous biological agents, the medical intervention in epidemics and medical countermeasures in the biological attack [1,2,3,4].

2. INFECTIOUS DISEASES

The infectious diseases are the most important cause of disease, being recognized by the World Health Organization (WHO) as the first in pathology and therapeutics. Of these, bacteriosis is the most important, both as "natural" diseases and as artificially induced diseases, through biological attack/war or bioterrorist attack. Infection should be understood as a dual relationship between the host organism and the pathogenic microbe that parasites it and causes the disease condition. Both the disease and its treatment are presented as a kind of an equation with several unknowns: different biological agents with various species and strain characteristics, different host organisms with various individual characteristics including immunological, different possible or applicable treatments, etc. [5].

The great successes of modern medicine, looking from a holistic perspective at the species level, are based on vaccination and antibiotherapy. But, lately, some serious problems arose. The antibiotics (AB), antibacterial miracle drugs, are losing their effectiveness due to the increase in antibiotic resistance (AMR) of bacteria, a phenomenon that will worsen in the future; so, we are already discussing *the end of the antibiotic era* and the need for new anti-infective therapy concepts. And, as if this medical catastrophe was not enough, the "anti-vaccine" movement that undermines the specific prophylaxis of infectious diseases also appeared. Moreover, in this dangerous context to public health, the threats of biological warfare and bioterrorism are outlined [2,3].

It is necessary to establish a new anti-infective therapy strategy for the post-antibiotic era, a complex, exhaustive approach based on the WHO's new holistic concept "One Health", which covers the link between the health of humans, animals, the environment, of the Biosphere as a whole.

This approach is all the more important in the field of protection against biological weapons/agents, due to the fact that living agents, primarily bacterial biological warfare agents (BWA), are genetically selected or modified. But, any other pathogenic bacteria that could be used by bioterrorists can be drug resistant, multidrug-resistant or all resistant to antibiotics, causing infections and possibly epidemics against which current medicine is not prepared with effective countermeasures. In terms of major infectious risks, there is no question of "whether" but "when" [6,7].

The *proactive* attitude is based on a concept of revolutionary anti-infective therapy, based on the retrospective experience and successes, and adapted to the level of modern science and medical-pharmaceutical practice for the near or more distant future [8].

Infectious pathology is caused by pathogenic or conditionally pathogenic microorganisms that parasite other beings. Pathogenic microbes have been and continue to be the main cause of human morbidity. Directly or indirectly, they are also the leading cause of mortality. These diseases can be infectious-contagious or seemingly non contagious [9].

At present, military regulations describe various modern weapons that have as a war load bacterial biological warfare agents (BWA), viruses or toxines, with lethal or incapacitating effects, with a single agent or mixture, or in combination with chemical or radiological agents. This conditioning of the biological weapon potentiates the effects and reduces the effectiveness of medical countermeasures. Military documents list CBRN agents - for example, in the *North Atlantic Treaty Organization, NATO Standardization Agency, Standardisation Agreement STANAG 4632 from 2005 "Deployable NBC Analytical Laboratory"* is also in the list of BWA bacteria and identification methods. With regard to these BWA bacteria explicitly described in the military regulations and literature, military medicine must also take into account the pathogenic agents that are known to have caused wartime outbreaks both to campaigning troops and to the civilian populations as well as the microbes which were or might be used by terrorists for bioterrorist attacks on troops or the population of the enemy country [10,11,12].

Out of all pathogenic microorganisms and their toxins, the epidemiologists from the *Centers of Disease Control and Prevention* (CDC) Atlanta USA and from the *European Centers of Disease Control and Prevention* (ECDC) selected the most significant and classified these into three categories, depending on the hazard [13].

The maximum risk group according to CDC: A Category of diseases/agents. It includes micro-organisms that pose a risk to national security because of its ease of dissemination or human-to-human transmission, resulting in a high mortality rate and having a major potential impact on the public health, potentially causing panic and social disruption, and requiring special preparations for the public health. These correspond to the classification made by the European Medicines Agency (EMA) in Category I of major infectious diseases for which treatment exists: anthrax, plague, tularemia, smallpox, viral hemorrhagic fever, botulism, brucellosis, Q fever, glanders and melioidosis [14].

The high risk group according to CDC: category B of diseases/agents. It includes microorganisms that can be disseminated relatively easily resulting in moderate morbidity and low mortality rate, but require specific means of diagnosis and disease monitoring. These are found in the European Medicines Agency (EMA) classification in category II of other infectious bacterial diseases for which treatment exists: psittacosis, exanthema, typhus, tuberculosis, shigella, salmonellosis and cholera [14].

The medium risk group according to CDC: Category C of diseases/agents. It includes emerging pathogenic microbes that can be "engineered" for mass dissemination for the future due to their availability, ease of production and dissemination, having a high morbidity potential and high mortality rate, with a major impact on public health. These correspond to the European Medicines Agency (EMA), with category III of Biological agents for which there is currently no specific recommended treatment: enterohemorrhagic *Escherichia coli*, cryptosporidiosis, viral equine encephalitis, nipahvirus, other hemorrhagic viral fever (tick-borne encephalitis, yellow fever, hantavirus, marburg, ebola), staphylococcal enterotoxin B, *Clostridium perfringens* epsilon toxin, ricin toxin [14].

In the low risk group for public health, we consider that all other pathogenic microbes can be included, over 1.200 species being known in medical microbiology [15,16].

3. THERAPY

Anti-infective therapy has undergone important changes and is constantly dynamic. Therapy of infectious diseases in the post-antibiotic era should be tackled in a complex way, taking into account the evolution of antibiotic therapy, immunotherapy, complementary treatments, aduvant drugs and contributing factors. The approach must be exhaustive and flexible, adapted to each case, because *we treat the sick individuals and not diseases* [17]. In this field, medicine demonstrates once again that it is not only science (based on the methods of several sciences) but also art (based on the experience and clinical flair of the doctor) [18].

We need to establish a general anti-infective therapeutic approach in correspondence with the pathogenic bacteria (community, nosocomial or biological agent), the severity, the epidemic spread and the pharmaco-economics, taking into account the logistical possibilities for effective medical countermeasures [1].

The problem is multiple: anti-infective therapy, antibacterial antibiotherapy, optimization of antibiotherapy [19], current problems related to

the growth and spread of the bacterial resistance phenomenon, adjuvant anti-infective therapy, insisting on antibacterial immunotherapy, to ultimately substantiate the therapy principles of infectious diseases caused by bacteria during the post-antibiotic era. We need to refer in particular to the bacteria biological warfare and bioterrorism agents, which present the maximum level of risk at the present moment and in the future. The guiding idea is to provide therapeutic Guidelines as a useful guide not only for the modern therapy of diseases caused by biological bacterial warfare (BWA) or bioterrorism agents, but also as a general guide to anti-infective therapy during the post-antibiotic era for infections with multiresistant or all-resistant germs [20].

The therapy of infectious diseases caused by biological warfare and bioterrorism agents represents a major challenge for current medicine. Microbial resistance to antimicrobial chemotherapics (antibacterial, antiviral, antifungal and antiparasitic) is increasing, as is the case with biocide resistance (disinfectants, insecticides, raticides, etc.). After the fear expressed at the beginning of this century that we are heading towards the "end of the antibiotics era", the first bacteria resistant to all antibiotics for therapeutic use were identified in 2016 and the first deaths were recorded. So, in general, infectious diseases are more difficult to treat with the therapeutic arsenal we have at hand, and even if new anti-infective drugs enter the therapeutic use, a microbial / drug competition is created by the *selective pressure effect caused by the actual treatment of the disease*. The situation is all the more serious if we take into account the diseases caused by *biological attacks* with biological warfare or bioterrorism agents that are selected or modified to be more pathogenic, more virulent, more resistant to the environment and resistant to treatment. The European Medicines Agency has developed therapeutic guidelines for these diseases, but the phenomenon of microbial resistance creates major risks [21,22,23].

The anti-infective therapy in current medical practice. Treatment in infectious diseases is mainly based on drugs from the antimicrobial chemotherapics group: antibacterial (antibiotics), antivirals, antifungal and antiparasitic [24].

4. THE THERAPEUTIC APPROACH

The anti-infective treatment involves several stages, according to an algorithm:

- The prophylactic treatment, by the specific vaccination of the risk groups, with the expected biological agents antigens; in the case of homologous contamination, the person immunized either does not make the infection or makes it in its easiest form;
- The post-exposure prophylactic treatment, with appropriate decontamination and chemotherapics immediately administered to exposed / contaminated persons;
- Early etiologic treatment in patients - with appropriate chemotherapics (injectable and / or oral), supplemented with adjuvant treatement, symptomatic, for the maintenance of the vital functions, etc.;
- The recovery treatment, for convalescents in view of their rehabilitation, capacity to fight, work and life skills. The specific antibacterial therapy is mainly based on antibacterial chemotherapics: sulfonamides (synthetic) discovered by the Germans [25] and antibiotics (biosynthetic) discovered by the English and the American since the 1930s [26]. They entered therapeutic use during the Second World War. After the war ended, antibiotherapy developed quantitatively and qualitatively, and antibiotics gradually became the most important group of drugs in medical practice and for the pharmaceutical industry. It was assumed that infectious diseases would be definitively defeated, even eradicated [27]. But, in parallel, was also observed the appearance of the phenomenon of bacterial resistance to antibiotics acquired as a result of the *selective pressure effect*. As new antibiotics (AB) was discovered, the biochemical mechanisms of AB action in the bacterial cell were explained, as well as the mechanisms of bacterial resistance to AB. Those with low toxicity and with no unwanted side effects were conditioned as medications and came into therapeutic use. Besides natural antibiotics (obtained by biosynthesis), chemical synthesis and semi-synthesis antibiotics have also been developed with improved properties: environmental resistance (eg the lyophilization technique and specific packaging), broad or broadened spectrum (eg ampicillin), increased efficiency (eg oxacillin), oral forms of compliance (eg phenoxymethylpenicillin), widening of the interval between injections (benzatinpenicillin), increased antibiotic combination efficacy (eg *trimethoprim* with

sulfamethoxazole), combating bacterial resistance by association with betalactamase inhibitors (eg. *Augmentin*) etc. But with regard to pathogenic bacteria, it is noted that antibiotherapy acts as a selective pressure factor that accelerates the installation and spread of resistance precisely to the antibiotics used in practice, according to the "action creates reaction" principle. It means that the data of the problem must be known exactly, presenting itself as an equation with several unknowns. On the one hand we have the infectious microbe and its pathogenic and resistance mechanisms. On the other hand, we have the infected body with its clinical manifestations (the disease) and the resistance mechanisms (the immunity). In addition, we have the anti-infective etiologic drugs with the antibacterial action mechanisms and the side effects, the adjuvant therapy, the role of the internal and external environment, the psychosocial context, etc. [28,29].

Biofilms and microbial resistance. Biofilms are films made up of microorganisms on wet or underwater surfaces, living or nonliving. Natural biofilms are often seen on wet surfaces, as a slippery sludge, both in nature and in the industrial or domestic environment, but their scientific study is relatively recent. Due to the diversity of biofilms, there are several definitions that refer to some or several of their features. The film may be cellular monolayer or multilayer, consisting of one or more species in association, as a microbiocenosis (microbiotic) with different aspects, stretches, thicknesses, colours, etc. [30].

From the medical point of view, the most important property of biofilms is the increase in the resistance they acquire against physical, chemical and biological aggressions from the environment, compared to the resistance of the same microbes but in the planktonic state. This natural behaviour reduces the effectiveness of antibiotherapy, of the antisepsis, disinfection, decontamination, sterilization and, implicitly, hygiene in the hospital environment. This favours "hospital flora", nosocomial infections and microbial resistance to antimicrobial substances, with all the consequences we know. The recent catastrophe with many victims of the fire from *Colectiv club* is an undesirable example of unwanted overmortality through infectious complications that can not be effectively treated with the current means. The estimates of the specialists made at the triage on the first day were of "over 60 dead" and, indeed, 64 burned victims died in hospitals in the country and abroad [31,32].

5. OPTIMIZATION OF THE ANTI-INFECTIVE THERAPY

For the therapy of infectious diseases caused by bacterial biological warfare and bioterrorism agents in the post-antibiotic era, we formulated a series of optimization proposals and efficiency.

5.1 Proposals for Completing the Therapeutic Plans in case of Antibiotherapy Ineffectiveness

Antibiotherapy, as the main current therapeutic procedure for diseases caused by biological warfare and bioterrorism agents, may not be effective for many reasons. First, BWA is by definition "militarized" biological agents, that is selected or genetically engineered to meet the criteria for biological weapons. They are more pathogenic, more virulent, more resistant to the environment and more resistant to treatment, possibly to all antibiotics for therapeutic use. In parallel, the natural tendency, accelerated by the unintended action of humans, increases the resistance of bacteria by the selective pressure effect in contact with antibiotics. On the other hand, decreasing the natural resistance of the human body through diseases, intoxication, irradiation or deprivation causes infectious diseases to be more severe and anti-infective treatment does not work effectively [4].

The general recommendation is to at least protect risk groups well in advance (military, medical staff, officials, children, etc.) through preventive vaccination against BWA where there is a vaccine available or can be produced in case of major force. In Romania, the Cantacuzino Institute produced and has in its portfolio (but no longer has a manufacturing authorization) the *tularemic vaccine*, the *cholera vaccine* and others for human use. The Pasteur Institute Bucharest and S.C. Romvac S.A. Bucharest manufactures the activated charcoal vaccines (anthrax) for veterinary use.

For antibiotherapy in case of therapeutic failure, 2-3 antibiotics must be combined, preferably

injectable antibiotics, one of choice and one alternative, as recommended by the European Medicines Agency (EMA UE), confirmed by the antibiogram [33].

Combining antibiotherapy with intravenous administration of specific therapeutic serum or curative vaccine. In Romania, the Cantacuzino Institute produced and has in its portfolio (but no longer has a manufacturing authorization) the *anticharcoal serum* (antianthrax) ampoules and others for human use.

Combining antibiotherapy with intravenous administration of immunostimulators or immunomodulators. In Romania, the Cantacuzino Institute produced and has in its portfolio (but no longer has a manufacturing authorization) *human Gammaglobulin ampoules,* Immunostimulator *Polidin ampoules* and Immunomodulator *Cantastim ampoules* and others for human use. Combining antibiotherapy with intravenous administration of specific and nonspecific gammaglobulines (preformed antibodies).

Depending on the needs and possibilities, adjuvant treatments will be combined at the recommendation of the attending physician: physical methods (oxygen therapy, assisted ventilation, hyperthermia or hypothermia, small surgery interventions for the repair of infectious outbreaks, enemas, rubbings, etc.); Chemical methods (symptomatic drugs, medicines for supporting the vital functions, medicinal teas, disinfectants, antiseptics, insecticides, insect repellents, etc); Biological methods (autohemotherapy, revulsion, serotherapy, etc.). In some situations, an integrated intervention is required, for example in the plague epidemic, the complex treatment of the patient (antibiotherapy, immunotherapy, adjuvant and maintenance treatments of the vital functions etc.) is combined with the disinfection of the infectious material, the disinsection of the vectors and the pest extermination in the anthropic environment [15].

Any medications or therapeutic procedures that contribute to healing or improving the condition of the patient may be applied according to medical logic and clinical experience provided they are compatible with each other and that the side effects do not exceed the therapeutic benefit. Although we can simultaneously face a huge number of patients with the same symptoms and requiring the same medical measures and the same medication, none can be left untreated or on a waiting list because the disease does not wait. In this situation, science and medical art combine with logistics and diplomacy for the benefit of the patient. But, the patient is not just our ordinary military, he can be an ally, a neutral, an enemy or a civilian of ours, neutral or enemy. The duty of the military medical service is to take good care of them and to transfer them, as the case may be, to the responsibility of the medical civil service, with specific recommendations for diagnosis, prophylaxis, treatment and recovery.

5.2 Proposals to Strengthen the Capability of Medical Counter-measures in the Biological Attack

Fundamental and applied scientific research, *in vitro* and *in vivo,* will be focused on the discovery of new therapeutics and optimizing existing ones.

It is indicated to develop therapeutic guidelines in collaboration with experienced infectious practitioners for each disease caused by BWA or bioterrorism that can disseminate dissemination by publishing in scientific journals and communicating to scientific manifestations the principles of post-antibiotic therapy in these diseases.

Experimental and constructive simulation experiments, *in silico* (computer), tactical and strategic, in collaboration with the *War Gaming and Doctrinal Experimentations Center*, can be carried out for the effects of biological attack and logistics of medical countermeasures [34].

It is recommended to permanently update the contingency plans and sanitary inventories for cases of biological attack at the level of the Ministry of National Defense, the Ministry of Health, the Ministry of Internal Affairs (MAI), the Office for Special Problems of the Government.

Last but not least, it is useful to carry out the census of the forces and means necessary for national countermeasures at national level (CIMIC), including production capacities and their real capabilities in the past, now and in the future.

Consideration should be given and establish the flows for supply (insided the country and

imported) with medicines and sanitary-pharmaceutical materials, raw materials, qualified personnel, logistics and financing flows (domestic and imported) medicines and sanitary materials pharmaceutical raw materials, personnel, logistics and finance.

Medical and paramedical staff, military and civilian population must be trained by medical education and training (training) for countermeasures in case of biological or combined attacks.

The national economy, economic agents (state and private), the territory and international relations, as well as the media must be trapped for countermeasures in case of biological or combined attacks.

Legislative proposals must be drafted by legal practitioners for the implementation of medical and paramedical countermeasures in the event of biological or combined attacks to maintain military combat capabilities and preserve public health.

In situations of force majeure, the Cantacuzino Institute, along with the Institute of Virology, the Pasteur Institute of Bucharest and the Military Medical Research Center, could undertake, if ordered, the production of prophylactic and curative vaccines for the products of the portfolio and the tests necessary for their administration to the specified risk groups, based on a specific derogation, by virtue of the exception provided in the Medicines Law.

6. CONCLUSIONS

Antibiotherapy is becoming less and less effective and will need to be optimized and supported by adjunctive therapies: immunotherapy with serums, vaccines, immunostimulants and others, physical, chemical, biological and other procedures to potentiate the anti-infective treatment, but with respect to the primum non nocere principle.

In situations of force majeure, the Cantacuzino Institute, along other partners, could undertake the production of vaccines for the products of the portfolio and the tests necessary for their administration to the specified risk groups, based on a specific derogation, by virtue of the exception provided.

Corroborating all the available therapeutic means contributes to optimizing the personalized treatment, taking into consideration that we treat "the sick and not the disease", and complex treatment will have a total and potentiated effect on the entire sick organism, favouring the healing.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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