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Anti-infective Therapy Principles in DiseasesCaused by Bacterial Biological Agents

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ABSTRACT

National security measures, particularly those in the CBRN area and in public health, must be strengthened in light of the current international scenario. The greatest risk to public health and the highest rates of morbidity and death are caused by infectious illnesses, particularly infectious-contagious diseases. The World Health Organization places these illnesses in the first category of those that affect humans. Concerning BWA and bioterrorism agents, the situation may be substantially worse.

When considered as a whole, at the level of each species, vaccination and antibiotherapy are at the foundation of contemporary medicine's greatest triumphs. However, recently several major issues have emerged. Antibiotic resistance (AMR) among bacteria is a growing problem that threatens the effectiveness of these once-miraculous drugs; as a result, we are already talking about the end of the antibiotic era and the need for new ideas in anti-infective therapy. And if that health crisis wasn't bad enough, the "anti-vaccine" movement emerged to undercut targeted prevention of infectious illnesses. Moreover, the hazards of biological warfare and bioterrorism in this setting are described.

Keywords: Biological agents; biological weapons; infectious diseases; anti-infective therapy; anti- infective medical protection.

1. INTRODUCTION

Under the circumstances of a "hybrid war" danger, the international scenario necessitates a strengthening of national security measures, including CBRN field and public health. Meanwhile, a new public health crisis is developing due to the "end of the era of antibiotics" brought on by the expansion of the phenomenon of microbial resistance. Because BWA are chosen or genetically manipulated to be more pathogenic, virulent, environmental, and antibiotic resistant, they pose a particularly high risk.

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Infectious and contagious illnesses would spread from their usage, leading to high rates of illness and death among military personnel and civilians alike. In the post-antibiotic era, it is important to keep the concepts of anti-infective medical defense current in order to provide a realistic record of the management of infectious disorders caused by bacterial biological warfare and bioterrorism agents. This comprises medical countermeasures in the case of a biological assault as well as the medical intervention in epidemics and the treatment (preventative, curative, and recovery) of infected patients with especially deadly biological agents [1,2,3,4].

2. INFECTIOUS DISEASES

Infectious diseases are the leading cause of worry when it comes to global health. the primary focus of treatment and research of the World Health Organization. Bacterial infections are among the most worrying health risks today for both "natural" and "man-made" causes, such as in a biological war or by bioterrorists. Symbiotic relationship between the host and the parasite germs responsible for infectious disease. Unknown factors in an equation describing a disease and its treatment include the species and strain of the biological agent, the host organism, and the immunological characteristics of the host, as well as the treatments that may or may not be applicable.

When looking at the achievements of modern medicine from a species-level perspective, vaccination and antibiotic usage are two major contributors. antibiotherapy. However, some big problems have surfaced lately. The development of antibiotic resistance (AMR) in bacteria poses a rising danger to the efficacy of these once-miraculous treatments, prompting calls for the end of the antibiotic era and the development of novel approaches to treating infectious diseases. The "anti-vaccine" movement has evolved to undermine effective measures to avoid infectious diseases, as if the current health crisis weren't awful enough. Also discussed are the risks associated with biological warfare and bioterrorism in this environment [2,3].

Considering the interdependence of human, animal, environmental, and Biosphere health, a new, complex, and broad approach to anti-infective treatment is required for the post-antibiotic era.

Since most biological warfare agents (BWA) are live organisms that have been genetically chosen or manipulated, this strategy takes on added significance in the area of protecting against biological weapons and agents. However, any other harmful bacteria that may be utilized by bioterrorists may be drug-resistant, multidrug-resistant, or completely resistant to antibiotics, resulting in diseases and perhaps epidemics for which modern medicine is not equipped to provide effective countermeasures. When it comes to severe infectious hazards, there is no such thing as "if" [6, 7].

The future-focused, preventative stance is grounded on a novel anti-infective treatment paradigm that draws on past experience and triumphs while also incorporating cutting-edge findings in science and medical-pharmaceutical practice [8].

Parasitic microbes, either fully or partially pathogenic, are responsible for infectious disease. Human illness is still mostly precipitated by bacteria that are pathogenic. They are also the primary cause of death, either directly or indirectly. Both infectious and ostensibly non-infectious illnesses fall within this category [9]. Current military laws detail a wide range of contemporary weapons that may carry a biological warfare agent (BWA) such as bacteria, a virus, or a toxin with potentially deadly or incapacitating effects, either alone or in combination with other agents such as chemicals or radiation. Because of this training, the biological weapon is more dangerous and less susceptible to treatment. When it comes to military publications, CBRN agents are often included; for instance, the "Deployable NBC Analytical Laboratory" and BWA bacteria and identification procedures are included in the 2005 NATO Standardization Agency Standardisation Agreement STANAG 4632. Although the military regulations and literature focus on the BWA bacteria specifically, military medicine must also account for pathogenic agents known to have caused outbreaks during wartime among both campaigning troops and civilian populations, as well as microbes which were or might be used by terrorists for bioterrorist attacks on troops or the population of the enemy country [10,11,12].

Epidemiologists from the CDC in Atlanta, USA, and the ECDC in Europe chose the most dangerous pathogenic microorganisms and toxins and grouped them into three categories according to their potential for harm [13].

Highest-risk population for a certain set of CDC-identified pathogens. Included are microorganisms that could threaten national security due to their rapid spread or human-to-human transmission, high mortality rate, and potentially devastating effect on public health, as well as their potential to cause widespread panic and social upheaval and the need for emergency public health measures. Anthrax, plague, tularemia, smallpox, viral hemorrhagic fever, botulism, brucellosis, Q fever, glanders, and melioidosis are all important infectious illnesses for which effective therapy is available, as classified by the European Medicines Agency (EMA) [14].

Category B illnesses and agents represent the highest

risk group identified by the CDC. Some of the bacteria in this category are readily spread and cause mild to severe illness with a low fatality rate, but they must be monitored and diagnosed in very particular ways. You can look them up in the EMA categorization system.

psittacosis, exanthema, typhus, TB, shigella, salmonellosis, and cholera are into the second group of infectious bacterial disorders for which there is an established therapy [14].

Category C diseases/agents are considered to be a moderate risk category by the CDC. Emerging pathogenic microorganisms are included because of their high morbidity potential and death rate, as well as the fact that they are readily available, easy to produce, and may have a widespread influence on public health if "engineered" for widespread transmission. Diseases like tick-borne encephalitis, yellow fever, hantavirus, marburg, and ebola, as well as bacterial toxins like staphylococcal enterotoxin B and Clostridium perfringens epsilon toxin, and ricin, fall under category III of Biological agents by the European Medicines Agency (EMA) [14].

We believe the additional 1,200 species of harmful microorganisms recognized in medical microbiology to be included in the low risk category for public health [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 (injectableand / 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 theanti-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 theindustrial 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, theCantacuzino 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 theirreal 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 eventof 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.

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