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Research strategies for the treatment of biothreats

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Whether it is a layperson in the street or a politician in the Senate, there is widespread fear over the consequences of biothreats. In response to these fears, a wide range of treatments has been developed. These include antibiotics (conventional and unconventional uses), nucleic acids (analogues, antisense, ribozymes and DNAzymes), immunomodulators, antibodies, bacteriophage therapy and micro-encapsulation. Furthermore, there are often additional benefits when these therapeutics are used in combination, rather than alone. Although there has been much investment in therapeutics against a terrorist threat for reasons of national security, there are likely to be far greater benefits and applications on domestic and world health.

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Introduction

The topic of 'biothreats' is a broad one, with several threat agents (e.g. bacteria, viruses or toxins), targets (humans, animals or plants) and methods of release that might be intentional (e.g. a biological released by a terrorist or a military force) or unintentional (e.g. the entry of an exotic disease by an infected carrier). For the purpose of this review, the topic of 'biothreats' will be limited to biologicals that might be released into the human population by a hostile force.

The threat of biologicals is both more and less threatening than commonly perceived. For several infectious agents, there are about a trillion particles per gram. Theoretically, one would need only the weight of a paperclip of agent to contaminate an area 1 km in diameter. The threat is greater still when one considers that, unlike chemicals, some biological agents can grow inside the host, increase their numbers and, in some cases, spread from host to host. However, it should be understood that these agents are biologicals, with biological weaknesses. With the appropriate disinfectant, protection, therapy, containment and knowledge, many were manageable in the past and can also be managed now. There continues to be fear over the dire consequences of anthrax, smallpox and plague. Certainly, these threats should be taken seriously, with the realization that casualties will be high if nothing is done [1]. However, progress has been made in defining the response to an outbreak, stockpiling antibiotics or inhibitors for exceptional demands, and in developing therapeutics. This review discusses these therapeutics, with an emphasis on progress made in the past few years.

The threat

If one reviews what biological agents have been used in past incidences, one sees a general pattern. *Bacillus anthracis*, once acquired, is easily produced on simple medium, grows rapidly and develops tough long-lasting spores that can be easily disseminated; these traits are probably the reasons why it was used as a threat agent in the USA in recent years. Although *Brucella* seldom kills, it is highly infectious and readily acquired in regions where it is a common illness. From 1983 to 1985, Kuwait dealt with a 100-fold increase in the number of brucellosis patients [2]. This unusual 'spike' of cases suggests that *Brucella* might have been used as a biological weapon. Ricin is less toxic than other toxins and, being a toxin, it does not replicate. However, it can readily be isolated from castor beans, which are grown throughout the world. The toxin has been used in several potential or realized incidences in the USA and Europe. *Salmonella typhimurium* is seldom life-threatening and yet it was used to infect over 700 people eating or working in restaurants in Oregon in the US [3]. The pattern one sees is that if the biological can be acquired and is hazardous then it could be used as a threat. With such vague guidance, it is likely that generic therapeutics, with broad efficacy against a wide range of identified or unidentified threats, will be the focus of future research and development.

Therapeutics

Conventional uses

Table 1 summarizes antibiotics that are either recommended or not recommended for the treatment of some biothreats infections [2,4–7]. These recommendations are likely to change as new antibiotics become available or as more strains of the infectious agent are tested.

Table 1

Summary of therapeutics for the treatment of biothreats.

Infectious agent	Recommended antibiotic after infection	Antibiotic not recommended (e.g. owing to resistance, ineffectiveness)
Bacteria		
Bacillus anthracis (anthrax)	Ciprofloxacin or doxycycline with two additional antibiotics (e.g. rifampin, penicillin)	Penicillins (as single agent), trimethoprim, sulfamethoxazole
Brucella spp. (brucellosis)	Doxycycline plus streptomycin or rifampin	Sulphonamide, erythromycin, vancomycin
Burkholderia mallei (glanders)	Doxycycline, ceftazidime plus trimethoprim/sulfamethoxazole	Ampicillin, chloramphenicol
Burkholderia pseudomallei (melioidosis)	Doxycycline, ceftazidime plus trimethoprim	Gentamicin, rifampicin
Coxiella burnetti (Q fever)	Ciprofloxacin, doxycycline	Penicillins, cephalosporins, aminoglycosides, amikacin
Francisella tularensis (tularemia)	Ciprofloxacin, doxycycline, streptomycin, gentamicin	Penicillin, ceftazidime, vancomycin, sulfonamide
Vibrio cholera (cholera)	Ciprofloxacin, doxycycline, norfloxacin	Penicillin, colistin, sulfadiazine
Yersinia pestis (plague)	Doxycycline, streptomycin, gentamicin, ciprofloxacin	Lindamycin, novobiocin, clofazamine
Viruses		
Encephalitis viruses (Western, Eastern, Venezuelan equine encephalitis)	Interferon-α	Ribavirin
Hemorrhagic fever viruses (Lassa fever, Argentine hemorrhagic fever, Crimean Congo hemorrhagic fever, Rift Valley fever, Hantavirus)	Ribavirin, immune globulin	
Variola (smallpox)	Cidofovir, vaccinia immune globulin	(No antiviral is effective once symptoms appear)

Difficulties with the conventional use of antibiotics are that multi-resistant strains can either be selected from clinical isolates or created by genetic manipulation, leaving many of the established antibiotics ineffective. Other limitations are that the therapy might have begun too late to be of any use, there may be differences between *in vitro* antibiotic testing and *in vivo* efficacy, the infectious agent may resurface from the patient's cells or tissues several weeks after the completion of a treatment regime, and the possibility of non-compliance by the patient. Side effects such as intestinal upset, headache, nausea and vomiting make completion of the drug regime difficult. It is largely because of these complications that, for American postal workers who were potentially exposed to anthrax, non-compliance was as high as 60% [8].

Unconvential uses

Antibiotics are used to inhibit bacteria and fungi. It is known that viruses and toxins are not affected by these compounds. However, for some viral infections, such as smallpox in humans, complications can arise from bacteria contaminating and infiltrating the lesions caused by the virus. Antibiotic use was shown to reduce these secondary bacterial infections, although for smallpox the infections were so severe that antibiotic use had little effect on mortality [9]. For other agents such as influenza, its destruction of the respiratory epithelium allows secondary bacterial invaders, especially staphylococci, to flourish and enhance the development of pneumonia [10]. Therefore, even though antibiotics can be ineffective against the initial viral infection, their use should be considered for the prevention of secondary bacterial infections.

For the other potential biothreat — toxins — a radical approach has been the use of antibacterials to treat animals. Rifampin, which is hydrophobic and inhibits toxin entry into organs such as the liver, was found to be an effective therapeutic against the algal bloom toxin microcystin [11]. In a similar manner, several antibiotics have been tested for the inhibition of ricin poisoning of mice. For those antibiotics tested, tetracycline and ciprofloxacin did delay the effects of ricin, but only for a few days (Sabuda D and Cherwonogrodzky JW, unpublished).

The currently held view is that antibiotics are molecules, either natural or synthetic, that inhibit or kill bacteria or fungi. However, perhaps this action is a secondary effect. Bacilli, actinomycetes or fungi, which change from vegetative cells to spores, produce antibiotics at the time of transition. An insect that changes from a larva to a pupa to an adult also produces antibiotics, called cecropins [12]. These changes of morphology require inhibitors of metabolic pathways. By extrapolation, the discovery of novel antibiotics might be enhanced by a closer inspection of the metabolic pathways in changing lifeforms. It has also been found that some antibiotics (e.g. ceftazidime, ofloxacin, trimethoprim) can shift *B. pseudomallei* from a virulent to a non-virulent form by inducing the expression of filaments [13]. Concentrations as low as 1/20 of the minimum inhibitory concentration of ciprofloxacin suppressed the expression of exoenzymes for *Pseudomonas*

aeruginosa in a rat model for cystic fibrosis [14]. Therefore, even antibiotics that appear to be ineffective against the growth of a target pathogen might have a profound effect in reducing the virulence of the infectious agent in the host.

Other inhibitors

Some inhibitors bind to the essential enzymes of threat agents while leaving those of the patient unaffected. Neomycin B and its synthetic derivatives, for example, are antibacterial for *B. anthracis* but also inhibit the proteolytic activity of its lethal factor toxin. These compounds would be ideal for the anthrax-infected patient, inhibiting the viability of the bacterium and neutralizing the toxin in the blood stream [15]. Another example of an enzyme inhibitor is trimethoprim, an inhibitor of dihydrofolate reductase, a key enzyme of bacterial metabolism. However, trimethoprim does not bind to the dihydrofolate reductase of *B. anthracis*, rendering the bacterium insensitive to this antibiotic. By cloning this enzyme from *B. anthracis* and then testing compounds or their derivatives for inhibition, a better screen could be devised for the selection of effective inhibitors of this bacterium [5].

For inhibitors of toxins, there are several publications and commercialized products for *in vitro* studies. Within our laboratory, we have focused on *in vivo* studies. Pentapeptides that mimic sites on SNAP-25 (synaptosome associated protein 25) initially had no inhibitory effect on the lethal effects of botulinum toxin A in a mouse model. However, when bovine serum albumin was injected with the pentapeptides, inhibition of the toxin was observed. We propose that, *in vivo*, the pentapeptide inhibitors were hydrolyzed by serum proteases unless protected by high amounts of additional protein (Pontarollo RA, Nagata LP and Cherwonogrodzky JW, unpublished). In a similar manner, some inhibitors developed to inhibit botulinum toxin are resistant to proteolytic degradation, although the intent has been to inhibit the proteolytic activity of botulinum toxins (which are also proteases). Such compounds have been made with 'non-natural amino acids' [16], revised amino acid sequences [17] or additional groups [18], which has enhanced their ability to inhibit botulinum toxin.

For the ricin A-chain, substrates that were synthesized to resemble its target, a genetic sequence on the 28S rRNA, were found to be potent inhibitors of the toxin when chemically modified to prevent hydrolysis [19]. For staphylococcal enterotoxin B toxicity, a clever approach has been to suppress not the toxin, but its downstream effects on the immune system. Therapeutic effects were observed both for *in vitro* (cultured spleen cells) and *in vivo* (mice) systems [20•]. Possibly not one but different therapeutics in tandem are needed to treat some toxins that might be used as biothreat agents.

Anti-viral drugs

As evident from Table 1, commercially available drugs for the treatment of viral biothreats are limited. Aside from testing existing drugs (adefovir, cidofovir, ribavarin, valaciclovir) against different viruses, other compounds appear promising, such as cytokines, drugs extracted from plant or marine life, ligands, metals, protease inducers or inhibitors, and receptor mimics. The use of AZT (3′-azido-3′-deoxythymidine or zidovudine) for the treatment of HIV is familiar to even the lay public. This nucleic acid analogue interferes with the viral reverse transcriptase and hence HIV replication. There are also broader applications of anti-virals than initially realized. Ara-C (1-beta-D-arabinofuranosylcytosine), a DNA polymerase inhibitor, can inhibit the replication of Borna disease virus, an RNA virus. Limitations to the use of analogues to inhibit viral replication are their toxicity to the patient and the ability of the viral variants to become resistant, even to multiple inhibitors [21,22]. In addition, many of the current anti-viral drugs have been optimized for specific diseases (e.g. HIV) and their efficacy against biothreat viruses is often untested.

Nucleic acid inhibitors

Antisense oligonucleotide therapy uses single-stranded sequences, either RNA or DNA, that are complementary to the host mRNA used for the synthesis of viral proteins. Inhibition is by the formation of double-stranded RNA that is degraded by the host's RNases or by the double-stranded region blocking the sequential translation of the mRNA. The use of antisense oligonucleotides for anti-viral therapy *in vivo* was previously limited by their poor entry into the target host cell and their subsequent degradation [23]. Despite these limitations, antisense oligoncleotides injected subcutaneously into mice did inhibit the expression of a hepatitis C-vaccinia virus recombinant [24]. In human clinical trials (for HIV-1-infected patients), the strategy has been to introduce a gene coding for the antisense sequence directly into the cells by using a retroviral vector [23].

A further development of oligonucleotide therapy is the use of ribozymes (catalytic RNA molecules that loop, bind to the viral RNA, cleave the site, and are then released intact) and DNAzymes (catalytic synthetic DNA strands that cleave RNA). These strands can be engineered to have an affinity for viral, rather than mammalian, RNA [25]. Their potential as anti-virals has been shown in the example of an anti-HIV-1 ribozyme delivered by a retroviral vector, which cleared the virus from mature human hematopoietic cells taken from patients with multi-drug-resistant HIV infections [26].

Immunomodulators

Examples of immunomodulators with encouraging efficacy against biothreats are poly-ICLC (double-stranded polyriboinosinic-polyribocytidylic acid stabilized with

poly-L-lysine carboxymethyl cellulose) and CpG (an unmethylated nucleotide sequence rich in cytosine and guanosine residues). The immune system of rodents or primates senses these as foreign, with the CpG strand probably resembling sequences more common to an invading bacterium than to host DNA. Upon activation of the immune response, cytokines are produced and natural killer cells are activated. The response is generic and able to prevent infections caused by a wide range of viruses (e.g. Western encephalitis virus) [27]. As these drugs are activators of the immune system, many have been more effective in the prevention of infections rather than in their treatment [28].

The field of immunomodulators is a large one, and Table 2 provides a shortened summary of an assessment done by Biophage Pharma Inc (Montreal, Quebec) under contract for DRDC Suffield.

If one selects those drugs that have been through clinical trials, and then those that are available either as an investigational new drug or as a commercial product, only a few — carbohydrates extracted from micro-organisms — remain. A closer inspection of carbohydrates as immunomodulators yields a general pattern. Relative to carbohydrates within the host, carbohydrates extracted from micro-organisms are polymers of either unusual sugars with active side groups or common sugars with unusual linkages [29–31]. These characteristics possibly alert the immune system to the presence of something foreign, and so initiates its activation.

Table 2

The most commonly used immune modulators.

Immune system-derived biologicals	Bacterial/fungal extracts
Interferons	Bacterial cell wall
Thymic hormones	Muramylpeptides
Interleukins	Glucans
Cell stimulatory factors	OM-85 (Broncho-Vaxon®)
Others (dialyzable leucocyte extracts, bradykinin antagonists, melatonin, antril, ibuprofen)	Ribomunyl®
	Bestatin
	Endotoxins
Sulphur-containing drugs	**Nucleic acid analogues**
Levamisole	Isoprinosine
Thiols	NPT 15392
Other sulphur-containing drugs	Methyl IMP
	Pyrimidinoles
Chemically defined drugs	**Biologically active peptides**
MVE-2	Tuftsin (Thr-Lys-Pro-Arg)
Cyanoaziridine	Polyerga
Pentoxifylline	Melopeptides
Cefodizime	Defensins
Pidotimod	SK7F-107647
Virulizin™	ST 789
Immunonutrients	**Conjugates/combinations/ adjuvants**
Herbal extracts	Liposomal interleukin-6
Polyunsaturated fatty acids	Interleukin-2–diphtheria toxin conjugate
Saponins	Stimulon™
Megadose vitamins	Vaxel™
	Immunax™

At DRDC Suffield, we have been investigating immunomodulators as a defence against, and treatment for, biothreats. Initially, there was concern that for treated mice the heightened activity of white blood cells would exhaust the immune system, leading to compromised health. Instead, mice given immunomodulators appeared healthier than untreated controls over the course of 15 months. Possibly these compounds enhanced their immunity against common sub-clinical infections that cause wear-and-tear of an animal's physiology during its lifetime (Cherwonogrodzky JW and Stady ND, unpublished).

Antibodies

It is an ironic occurrence but perhaps one of the largest volunteer immunizations against a toxin threat has been inadvertent. Individuals receiving botulinum toxin, either for physiological illnesses [32] or for cosmetics, eventually produce enough antibody to cause 'therapy failure'. They have been vaccinated and are now resistant to the effects of botulinum toxin.

Developing antibodies as a defence strategy against biological weapons has already been extensively reviewed. There are antibodies, either already available or in the process of being developed, against a wide range of potential bioterrorist agents such as anthrax, smallpox, botulinum toxin, tularemia and plague [33,34]. It was believed that antibodies were useful only against pathogens outside the cell and flourishing in the serum, whereas cellular immunity was useful only against pathogens inside the cell such as parasites, mycobacteria, fungi and viruses. Recently, however, monoclonal antibodies have been shown to be effective even against the latter (e.g. *Mycobacterium tuberculosis*) [34]. In the past, there was also concern about 'serum sickness' or adverse reactions of humans upon receiving animal serum. The effects can be lessened by the purification of the antibody fraction so as to eliminate a large portion of the animal serum component. A more recent advance has been the ability to create human antibodies *in vitro* with cloned specificity against the threat agent and which can be mass-produced [33].

In the production of monoclonal antibodies against toxins, a distinction must be made between binding and neutralizing antibodies. An antibody can bind to a toxin but, if this binding is at a region different from its enzymic site, the antibody may be of little use. One approach to increase the chances of selecting a monoclonal hybridoma that produces neutralizing antibodies used ricin's toxicity as an advantage. Mice were vaccinated with low amounts of ricin, spleen cells were harvested and then fused with

myeloma cells. The hybridomae were cultured in 96-well microtitre plates and then poisoned with ricin. Only the hybridoma cell lines that produced enough anti-ricin antibodies to neutralize the toxin survived [35]. Not only did this greatly increase the chances for finding clones that produced high amounts of neutralizing antibody, but there was also a great saving of time and effort to do so.

Bacteriophage therapy

Bacteriophages are viruses that infect and grow only within certain species or strains of bacteria. Although some can leave the bacterium without lyzing the cell (e.g. bacteriophage M13 of the 'fd' helical filamentous phages that extrude through the cell wall of the viable host) [36], many disrupt the cell and disperse to find other identical bacteria. Some have also evolved mechanisms for penetrating the protective shields of bacteria, such as spore formation (i.e. the phage waits for the spore to germinate then infects the vegetative cell) [37] or capsules (these have enzymes that degrade the capsule) [38].

As bacteriophages are specific for bacteria and harmless for humans, 'phage therapy' has been used clinically in the former Soviet Union and Eastern Europe for several decades. In the UK and US, results have been remarkably successful with few gastrointestinal or allergic side effects and a success rate of 80–95% [39]. In recent years, it has not been the threat of bioterrorism, but rather the alarming increase of antibiotic-resistant bacteria in the public health sector, that has brought new attention to bacteriophages as therapeutic agents. Unlike antibiotics, bacteriophage can grow within the host bacterium, increasing their numbers to enhance their effectiveness against an infectious bacterium. By the process of selection, these can also change as their target bacterium changes, so resistance is less problematic with phage therapy as it is with antibiotic use. A disadvantage is that bacteriophages are so specific that either 'phage cocktails' (a collection of bacteriophages) or bacteriophage isolated from the specific bacterium infecting a patient must be used. An exception to the above successes has been our own study with bacteriophage therapy of brucellosis mice. Upon infecting mice with *Brucella abortus* and treating with bacteriophage, these mice had 200-fold more Brucella in their spleens than did infected controls. We believe that, in this instance, bacteriophage therapy had been too efficient, lysing the bacteria, releasing endotoxin and suppressing the immune system, thereby allowing the remaining bacteria to flourish inside the mice (Cherwonogrodzky JW and Knodel MH, unpublished).

The greatest obstacle, perhaps, might be one of economics. Phage therapy has been used for several decades and is unpatentable. Furthermore, companies might find their own bacteriophages in the environment or clinical isolate to circumvent the issue of ownership by others [40].

Micro-encapsulation

Despite aggressive antibiotic therapy, five of the 11 Americans who developed inhalational anthrax as a result of bioterrorist incidences died from the disease. Although this death rate could have been 95–100% if untreated, the goal for the development and use of therapeutics against the biothreats should be to save every life.

The limitations on therapeutic measures against biothreats are that many of the drugs are degraded, diluted or secreted from the body. Other complications are that some drugs are insoluble in serum or must be used sparingly owing to their toxicity. An exciting measure that overcomes many of these problems is the use of micro-encapsulation. By encapsulating the therapeutics in microspheres [41–43], drugs can be delivered in concentrated form to facultative intracellular pathogens within white blood cells that would otherwise have escaped antibiotic treatment [44].

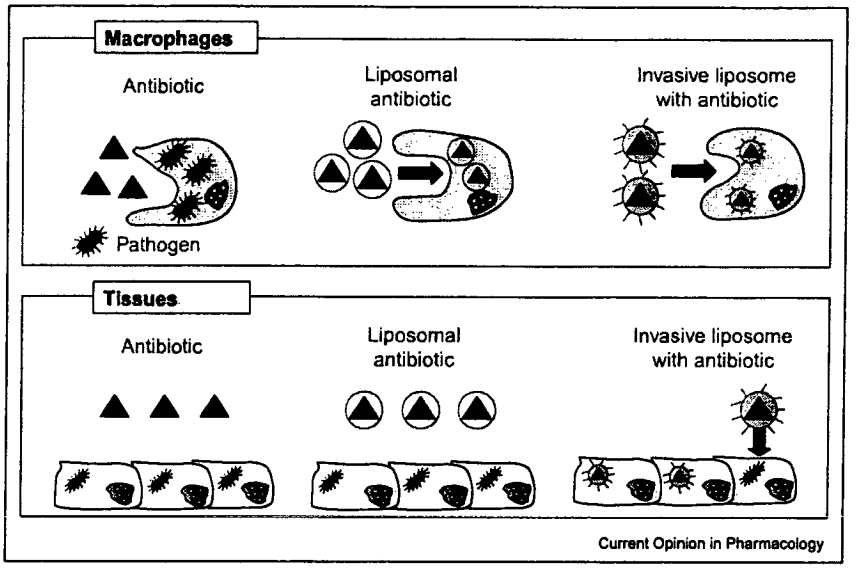
Unfortunately, some biothreat agents, such as viruses and some bacteria, can penetrate non-phagocytic cells [45]. Figure 1 portrays the limitations and solutions for the delivery of therapeutics. For many of the biothreats, a common characteristic is that they have sugars on their outer wall that resemble that of *Brucella*. This sugar possibly assists penetration by taking advantage of the mannose receptors on the mammalian envelope [46]. By using *Brucella melitensis* polysaccharide in the formulation of liposomes, an 'invasive liposome' can be created. These carriers of antibiotics (e.g. ciprofloxacin) have an enhanced capability, relative to previous liposome formulations, for penetrating and delivering the therapeutic into the cell [47]. By understanding the versatility and capabilities of biothreat agents, we can perhaps learn how to use their own mechanisms against them.

Miscellaneous

For people exposed to *B. anthracis* spores, it is now recommended that, apart from aggressive antibiotic therapy, a series of vaccinations also be implemented. The spores are not as uniform as once believed, and although many of the spores will germinate rapidly in the serum or inside a cell, others will lag behind, germinating several weeks later. Antibiotic therapy will protect the patient for the short term, but vaccination is needed for long-term protection after antibiotic treatment has been discontinued [8].

Under current consideration is the possibility that prion diseases may become the biothreats of the future. Much progress has been made to understand prion disease, and one interesting aspect is the role of metal ions on its protein structure. It is believed that some metals, such as copper, play a key role in locking the prion protein in the normal rather than abnormal form [48]. Monoclonal antibodies directed against the normal protein form have

Figure 1



Schematic comparison on the mechanism for free, liposomal and invasive liposomal antibiotic delivery to macrophages or tissue cells. Left-hand side of the figure: although antibiotics can act on the pathogen when it is in the serum, these are less effective when the biothreat is sequested inside white blood cells or cells of tissues. Middle of the figure: liposomal drugs can be engulfed by macrophages and delivered in concentrated from to the sequestered pathogen. Liposomes do not normally penetrate non-phagocytic cells. Right-hand side of the figure: some pathogens are invasive because these have evolved mechanisms for penetrating the host cell. Liposomes modified with these mechanisms are 'invasive' and can deliver antibiotics both to phagocytic and non-phagocytic cells.

been shown to reduce the symptoms of prion-infected mice. Although the interpretation has been that the antibody reduced the amount of protein converted to the abnormal form [48], perhaps another is that the antibody stabilized the protein into the normal form.

The diversity of bacteria has become more evident in recent years with the discovery of colourless sulphur bacteria that are 100-fold larger, and the nanobacteria that are 100-fold smaller, than a common soil bacterium. The latter are difficult to detect, not only because of their small size, but also because they produce a protective calcium coat that has been implicated in stone formation in the urinary tract. Whether nanobacteria are potential future biothreats is debatable. However, our present knowledge of nanobacteria is that, like other bacteria, these can be treated with common antibiotics [49].

Conclusions

Biothreats are currently viewed as biological weapons that could devastate a battalion in a biological warfare scenario or a large populated area after a terrorist attack. Various publications and working groups have addressed the topic of readiness and the availability/effectiveness of therapeutics to be used should an attack occur. It has been noted that antibiotics are seldom totally effective against bacterial infections, the microbial threat may have been genetically manipulated to be resistant to the therapy of choice, there is a paucity of anti-viral agents, several of the new therapeutics are overtly toxic, and having sufficient supplies of drugs or antibodies to protect a nation against these threats could be years away. However, progress is being made every day: new drugs or formulations are being discovered, federal approval or clinical trials are underway, the threats rather than simulants are being studied and tested for vulnerabilities, and talented investigators are making their novel insights known. The strengths of these measures are greater still when one considers that the use of these in combination has far greater benefits than when used individually (e.g using two or three antibiotics together, or the placement of antiviral drugs within liposomes). The author is still concerned about the current limitations of treatments against threat agents. It is likely, however, that these limitations are only temporary, to be dispelled once the promising drugs and formulations are made available.

In my view, the large investment in biodefence is having a positive impact not only on national security but also on domestic and global health. The same infectious bacterium that can be used as a biothreat is the same bacterium that might be endemic in a foreign country or reside within the wildlife near one's home. It matters little how the infectious or toxic agent has become a threat; the main issue is how the affected patient can be treated and how the illness can be cleared to save the life at risk.

In addition, the same novel therapies that are being developed to treat civilians or military personnel exposed to biothreats might have far broader applications to patients struggling with life-threatening infections in the intensive care ward of a hospital, a cystic fibrosis clinic or a burns unit. It may be an irony of our time that, although the terrorist has used biothreats to put lives at risk, the response has instead led to novel therapeutics and formulations that in the near future will save lives from infectious diseases or toxins.

Acknowledgements

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- • of special interest
- •• of outstanding interest

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One can save the patient by treating the symptoms rather than the cause. This gives new hope for toxin treatments.

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