Antibodies for defense against biological attack

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The recent anthrax mail attacks in the United States have demonstrated the vulnerability of the public to biological terrorism and stimulated a debate on how to protect against this threat. Immunity to a biological agent can be conferred by active or passive immunization. Active immunization involves vaccination to elicit a protective immune response and can provide long-lasting protection. In the event of a biological attack, however, the usefulness of active immunization may be limited. Vaccine efficacy often requires time, multiple doses, and a competent immune system. Prophylactic immunization might provide an effective defense against biological agents but has the disadvantage that many individuals would have to be vaccinated to protect against an attack that might never occur. In this situation, even a small number of vaccine-related side effects would be unacceptable. In addition, vaccines do not induce protective immunity in all recipients, especially immunocompromised individuals[1].

In contrast, passive immunization involves the administration of preformed antibody to provide a state of immediate immunity. The two forms of immunization are used together in certain circumstances, such as rabies prophylaxis following possible exposure, where a passive antibody provides immediate protection and a vaccine elicits a protective immune response.

In the early 1900s, antibody therapy was used against a variety of infectious diseases, including pneumococcal pneumonia, meningococcal meningitis, diphtheria, and measles[2]. Administration of passive antibodies has an excellent track record of efficacy and safety against viral infections, as demonstrated by the current use of immunoglobulins to treat diseases caused by cytomegalovirus, respiratory syncytial virus, hepatitis B, and parvovirus, among others[3]. Antibodies also remain the only agents available to neutralize toxins *in vivo* and are currently used for the treatment of tetanus, botulism, diphtheria, and venomous conditions[3].

Of the 17 agents listed by the Center for Disease Control as major biological warfare agents, four are toxins, seven are viruses, and six are bacteria. For *B. anthracis* (anthrax), passive administration of antitoxin provides full protection against experimental infection[4]. A search of the literature reveals reports of protective antibodies against most, if not all, major biological warfare agents.

Current biotechnology can generate human immunoglobulins for use in the prophylaxis and therapy of diseases caused by biological warfare agents. In the past, the development of antibody-based therapies for infectious diseases was hindered by their high cost relative to antimicrobial drugs, the need for diagnosis before use, and their exquisite specificity for particular pathogens, which limited their market size and reduced their commercial attractiveness[2]. However, the lessons from the recent anthrax attack suggest that these issues do not necessary apply when considering the use of antibodies in biological defense. For example, the potential market size for an antibody active against a biological agent equals the size of the population at risk.

In fact, there are distinct advantages in using passive antibody therapy for protection against a biological agents, such as anthrax-seeded letters. As human IgG has a serum half-life of 20 days, one infusion of human antibody to anthrax toxin could theoretically have protected exposed individuals for months. Certainly, a one-time infusion of human IgG has significant advantages relative to the two-month course of ciprofloxacin prescribed to exposed persons with regards to compliance, drug-related toxicity, and the selection of resistance among non-targeted bacteria. Furthermore, an antitoxin preparation would have protected against *B. anthracis* spores even if drug-resistant strains had been used in the attack.

The natural function of antibodies can be enhanced by conjugating them to toxins, radionucleotides, and drugs. Like all defenses, antibody-based strategies are vulnerable to countermeasures and could be rendered useless by the use of antigenically diverse biological agents. In response, antibody-based therapies can be designed to recognize multiple epitopes. In this regard, polyclonal preparations containing antibodies to many epitopes might have advantages over single monoclonal antibodies (mAbs). It should be possible to combine mAbs against biological warfare agents to generate defined preparations with multiple specificities. In an arms race between making protective antibodies and engineering agents to elude antibody-mediated protection, the defense has the advantage, as it is easier to make a new antibody than to engineer an antigenic site while retaining biological activity.

An antibody-based defense strategy would complement the development of vaccines and new antimicrobial drugs by providing an alternative with its own set of advantages. Antibody preparations can usually be developed faster than vaccines or drugs. Almost a century ago, Flexner[5] demonstrated the speed with which antibody therapies can be developed when he made an effective horse antiserum for treating meningococcal meningitis in the midst of an epidemic. Passive antibody could also be useful for preventing disease among vaccinated individuals exposed to massive doses of a biological agent, as in those circumstances the immune response elicited by a vaccine may be overwhelmed. A protective antibody suitable for passive immunization could be used in concert with vaccines and drugs to provide a multilayered defense against attacks with biological agents.

It should be possible to create a strategic reserve of immunoglobulins against the major biological warfare agents that can be rapidly administered to exposed individuals in the event of an attack. The availability of a strategic reserve of specific antibody preparations would have a significant deterrent value, as aggressors would be aware that the lethality of their weapon could potentially be counteracted by prompt administration of antibody to susceptible individuals. As antibody can be administered intramuscularly, immunoglobulin preparations could be packaged in self-injectable, disposable, single-use containers. Self-administration of antidote would avoid taxing the health-care system with the need for intravenous administration. Given the stability of immunoglobulin preparations, it should be possible to store antibody lots for years. Developing, producing, and stockpiling antibody reagents for defense against biological agents is a sensible strategy that needs to be considered as we take steps to prepare against the threat of biological warfare and bioterrorism.

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