Return to the Past: The Case for Antibody-Based Therapies in Infectious Diseases

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In the preantibiotic era, passive antibody administration (serum therapy) was useful for the treatment of many infectious diseases. The introduction of antimicrobial chemotherapy in the 1940s led to the rapid abandonment of many forms of passive antibody therapy. Chemotherapy was more effective and less toxic than antibody therapy. In this last decade of the 20th century the efficacy of antimicrobial chemotherapy is diminishing because of the rapidly escalating number of immunocompromised individuals, the emergence of new pathogens, the reemergence of old pathogens, and widespread development of resistance to antimicrobial drugs. This diminishment in the effectiveness of chemotherapy has been paralleled by advances in monoclonal antibody technology that have made feasible the generation of human antibodies. This combination of factors makes passive antibody therapy an option worthy of serious consideration. We propose that for every pathogen there exists an antibody that will modify the infection to the benefit of the host. Such antibodies are potential antimicrobial agents. Antibody-based therapies have significant advantages and disadvantages relative to standard chemotherapy. The reintroduction of antibody-based therapy would require major changes in the practices of infectious disease specialists.

The antibiotic era is about 60 years old. As we approach the 21st century, the progress made in controlling infections is threatened by the growing numbers of immunosuppressed individuals; the emergence of new pathogens; the reemergence of old pathogens; and the widespread resistance of organisms to antimicrobial drugs. Each development poses its own set of challenges; in combination, these developments are already undermining the efficacy of antimicrobial chemotherapy. There is a worldwide epidemic of immunosuppression due to malnutrition, AIDS, medical therapies for cancer and autoimmune diseases, and organ transplantation. Immunosuppressed hosts provide ecological niches for low-virulence microorganisms [1]. In addition, antimicrobial drugs are less effective and sometimes are unable to eradicate infection in individuals with impaired immunity. Classical pathogens such as *Mycobacterium tuberculosis* and *Treponema pallidum* have reemerged and are difficult to treat in immunosuppressed individuals [2, 3]. The increasing frequency of drug-resistant organisms is an equally alarming development, and resistance may be developing faster

than new antibiotics can be introduced [4]. For example, in one New York City hospital, the percentage of vancomycin-susceptible *Enterococcus faecium* decreased from 86% to 26% in 2 years [5]. The problem of resistance is not limited to bacteria; there are numerous reports of fluconazole-resistant *Candida albicans* [6].

We briefly review the use of antibody-based therapy in the early 20th century and make the case for reintroducing passive antibody administration for the treatment of infectious diseases. Advances in monoclonal antibody (mAb) technology provide new opportunities for developing antibody-based therapies. In the case of pathogens for which antimicrobial chemotherapy already exists, antibody-based therapies could be used with existing chemotherapy to improve outcome and possibly reduce the development of resistance. In the case of pathogens for which no effective chemotherapy exists, antibody-based therapies could be used for primary therapy. Given the diminishing efficacy of existing antimicrobials because of widespread resistance and the difficulties of treating infections in immunosuppressed individuals, the reintroduction of antibody-based therapies is an option that should be given serious consideration. This reintroduction would require major changes in the practice of infectious disease medicine.

Serum Therapy

The administration of immune serum (usually animal) for the treatment of infections was called serum therapy and was introduced in the 1890s for the treatment of diphtheria. By the 1930s, serum therapy was widely used for the treatment of

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Table 1. Infectious diseases that were treated with antibody-based therapies in the preantibiotic era.

References	Disease	Class, organism
Bacteria		
[7]	Pneumonia	<i>Streptococcus pneumoniae</i>
[7]	Meningitis	<i>Neisseria meningitidis</i>
[8–10]	Meningitis	<i>Haemophilus influenzae</i>
[11–17]	Erysipelas; scarlet fever	Group A <i>Streptococcus</i>
[18–20]	Whooping cough	<i>Bordetella pertussis</i>
[21]	Anthrax	<i>Bacillus anthracis</i>
[22]	Botulism	<i>Clostridium botulinum</i>
[16]	Gas gangrene	<i>Clostridium perfringens</i>
[23, 24]	Tetanus	<i>Clostridium tetani</i>
[25]	Brucellosis	<i>Brucella abortus</i>
[26,27]	Dysentery	<i>Shigella dysenteriae</i>
[28]	Tularemia	<i>Francisella tularensis</i>
[11]	Diphtheria	<i>Corynebacterium diphtheriae</i>
Viruses		
[29, 30]	Measles	Measles
[31, 32]	Poliomyelitis	Poliomyelitis
[33, 34]	Mumps	Mumps
[33, 35]	Chickenpox	Varicella zoster

NOTE. This is not a complete list.

bacterial and viral infections (table 1). For example, in the late 1930s, 86% of patients with type I pneumococcal pneumonia admitted to Boston City Hospital were treated with type-specific serum [36]. From 1927 to 1932 at Bellevue Hospital (New York), >3,000 patients with erysipelas were treated with serum [37] (figure 1). The efficacy of serum therapy varied with the type or severity of infection. Several large controlled studies revealed that type-specific serum reduced the mortality of pneumococcal pneumonia [7].

Serum therapy also appears to have significantly reduced mortality due to meningococcal meningitis in some epidemics [7, 38]. Serum therapy reduced mortality due to *Haemophilus influenzae* meningitis, but the effect was small [8–10]. Serum therapy for erysipelas reduced mortality in comparison to historical controls [37, 39]. Serum therapy reduced mortality in diphtheria, and antibody therapy continues to be used today to treat this disease [40]. The efficacy of serum therapy for whooping cough, anthrax, dysentery (*Shigella dysenteriae*), and gas gangrene was uncertain. Human convalescent serum was effective for prophylaxis of measles, which had a mortality rate of 6%–7% in some populations [29–31]. The effectiveness of serum in the pre-paralytic stage of poliomyelitis was uncertain [31, 32]. No consistently effective sera were developed against many pathogens, including *Staphylococcus* [41], *Mycobacterium*, and *Salmonella* species [42].

The historical use of serum therapy provides lessons for the effective use and development of antibody-based therapies. Accurate microbiological diagnosis was essential for successful treatment, and serum therapy was most effective when used for prophylaxis or for therapy early in the course of infection.

Nevertheless, it was possible to treat established bacterial infections such as meningococcal meningitis and pneumococcal pneumonia if antibody was administered shortly after symptoms began [7]. Antibodies functioned as direct antibacterial agents (e.g., pneumococcal antisera) or antitoxins (e.g., diphtherial antisera). Nonphysiological and nontherapeutic animal models of infection allowed investigators to successfully identify clinically useful antibody reagents [7]. A considerable amount of basic immunologic and microbiological research was required to develop each serum, and many fundamental discoveries were made in the search for better sera. (The contributions of pneumococcal research to basic science are discussed in [43].)

Abandonment of Serum Therapy in the 1940s

Sulfonamides were introduced in 1935 and rapidly became the standard therapy for many infections [44]. Because antimicrobial chemotherapy had significant advantages over serum therapy, the latter was largely abandoned. Systemic administration of animal sera caused fevers, chills, and allergic reactions [23, 45]; “serum sickness,” a self-limited syndrome characterized by rash, proteinuria, and arthralgias, occurred in 10%–50% of patients because of immune complex disease. In addition, strain typing was necessary for choosing pneumococcal antisera; there was significant lot-to-lot variation in serum efficacy [46]; and dosing was based on clinical experience. Inadequate dosage, delays in treatment, errors in typing, mixed infections, and complicated infections (e.g., empyema) could result in failure of serum therapy [47]. Serum was expensive because of the costs of animal husbandry, antibody purification, refrigeration, and reliance on mouse protection tests for standardization.

Chemotherapy was less toxic and more effective than serum therapy. Treatment with type-specific serum reduced the mortality of pneumococcal pneumonia from 30%–40% to 10%–20% [7], whereas the mortality rate among patients treated with sulfonamide was 7% [48]. Serum therapy reduced the mortality rate of erysipelas from 10% to 7% [37], whereas the mortality rate for patients treated with sulfonamides was 1%–2% [49]. For meningococcal meningitis, the efficacy of serum depended on the epidemic. In the mid-1930s, Waghelstein [50] reported that the mortality rate for patients with meningococcal meningitis who were treated at Sydenham Hospital (Baltimore, MD) with sulfonamide was 15.3% and for those treated with serum it was 27%. In controlled trials, the superiority of chemotherapy over serum therapy was less evident. For example, the mortality among patients with meningococcal meningitis who were treated early with adequate serum therapy was 16.7% vs. 11.6% for sulfanilamide therapy [50]. The mortality among patients with pneumococcal pneumonia treated with antimicrobial drugs or serum was 11% and 16.7%, respectively, but there was no difference in the mortality rates among younger

Antitoxin Treatment of Erysipelas

SYMMERS AND LEWIS (Bellevue Hospital, New York) reporting in the *Journal of the American Medical Association*, September 24, 1932, state:

"For the past five years the use of antitoxin has been a routine measure in the treatment of erysipelas at Bellevue Hospital."

"The average duration of the disease is reduced about 60 per cent."

"The number of deaths in more than 3300 patients was reduced about 30 per cent."

Erysipelas Streptococcus Antitoxin Lederle (refined and concentrated) is used at Bellevue Hospital. It is supplied in packages of one therapeutic dose of approximately ten cubic centimeters.

Literature sent on request.

LEDERLE LABORATORIES, INC. NEW YORK

Figure 1. Lederle advertisement for erysipelas antiserum that appeared in the 15 March 1933 issue of the *New York State Journal of Medicine*. The data cited were published in [37].

patients, and younger patients who received serum recovered faster than those who received antimicrobials [51].

In the early days of the antibiotic era there was interest in using combination therapies with antibiotics and serum. Sulfonamides and serum had a synergistic or additive effect against *Streptococcus pneumoniae* [52–55], streptococci [56], and meningococci [57]. The finding that sulfonamides made pneumococci more susceptible to antibody-mediated phagocytosis supported the idea of combination therapy [58]. It was similarly recognized that sulfonamides, unlike antibody, did not neutralize bacterial toxins or modify the course of disease caused by diphtheria or tetanus toxins [59]. Combination therapy was recommended for scarlet fever [60], pneumococcal pneumonia [44, 54, 61], whooping cough [20] and meningitis due to pneumococcus [8, 62], meningococcus [8, 50, 63, 64], or *H. influenzae* [8]. However, the side effects of serum made the potential benefits of combination therapy marginal [50].

In summary, serum therapy was abandoned because of toxicity, difficulty in administration, narrow specificity, lot-to-lot variation, and expense. Chemotherapy was less toxic and easier to use, lots were more consistent, and it was more effective in eradicating infection. In addition, there was no need for strain typing with chemotherapy. However, it is ironic that the broad antimicrobial activity of these drugs used for chemotherapy

might have contributed to widespread resistance, and today susceptibility testing is essential to the selection of appropriate antimicrobial drugs.

Antibody Therapy Today

Although antibodies are no longer used directly as antibacterial drugs, they continue to be used in infectious diseases (for recent reviews see [65–67]). The majority of antibody preparations are now human. Antibody administration reduces infection in individuals with immunodeficiencies [65–68] and is effective for postexposure prophylaxis against measles, hepatitis A and B, rabies, and varicella viruses. Specific antibody is used for the treatment of botulism [22], diphtheria [40], tetanus [22], snake bites [69], and spider stings [70]. Passive antibody administration has been used for prophylaxis and/or therapy of several viral infections, including cytomegalovirus (CMV) [71, 72], rotavirus [73], Lassa virus [74], varicella [75], enterovirus [76, 77], and parvovirus B19 infections [78]. In recent years, there has been renewed interest in the use of antibody preparations to prevent infection in high-risk groups. Intravenous administration of polyclonal antibody has been reported to reduce the number of infections in patients with AIDS [79–81], patients in surgical intensive care units [82], organ transplant

recipients [83], and neonates [84, 85] (for critical reviews and commentary on this practice see [86–89]).

Antibody therapy is used for a variety of illnesses that may or may not be infectious, including autoimmune thrombocytopenia, Kawasaki disease, and autoimmune neuromuscular diseases [65, 66]. Passive antibody administration is used for prevention of Rh-hemolytic disease [90]. Equine lymphocyte antiserum [91] and murine mAbs to lymphocytes are used to prevent organ rejection [92]. Digitalis-binding antibodies are useful for the treatment of digoxin toxicity [93]. Thus, antibody therapy is still widely used in medicine, but its role in the treatment of infections is limited largely to viral and toxin neutralization and replacement therapy in patients with immunoglobulin deficiencies.

Advances in mAb Technologies

In reconsidering the antibody option it is clear that heterologous antibody (i.e., serum therapy) is a poor choice because of toxicity. Human immune sera have fewer side effects, but there are concerns about availability, potency, and consistency. A major disadvantage of all immune sera is that specific antibodies make up a small minority of the antibody present. There is significant variation in pathogen-specific opsonic activity of commercially available immunoglobulin preparations [94]. There is also concern about the potential of human sera to transmit infectious agents [95].

The discovery of hybridoma technology in 1975 [96] and recent advances in mAb technology, including the generation of humanized antibodies [97], make mAb-based therapies a more attractive therapeutic option. In contrast to polyclonal sera, mAbs are homogeneous and reproducible reagents that can be generated in large amounts. Generation of mAbs from mice and rats is still easier and more efficient than production of human mAbs. However, several technologies are available for the humanization of murine mAbs and generation of human mAbs [97]. Mouse–human chimeric antibodies can be constructed by linking the genes expressing the mouse variable region to human constant region genes [97]. The result is a molecule that is mostly human and has a longer half-life than the murine precursor [98]. As an alternative, the antigen binding regions of murine mAbs can be grafted into human antibody frameworks by molecular techniques [97], resulting in molecules that are almost completely human in origin. Other strategies to generate human antibodies are the transformation of human B cells, the generation of recombinant antibody libraries from human B cells, and the use of transgenic mice that have the human immunoglobulin locus.

Recent Setbacks for mAb-Based Therapies: Historical Perspective

Clinical trials of antiendotoxin mAbs for gram-negative sepsis have produced inconclusive results [99, 100]. When the

difficulties encountered in developing antiendotoxin mAb strategies are considered in the context of the development of serum therapy, they do not seem unusual or unexpected. For example, passive protection with pneumococcal antisera was demonstrated in 1891 by the Klemperers [101], but 30–40 years elapsed before serum therapy for pneumococcal pneumonia was widely accepted. For pneumococcal antiserum therapy to be consistently successful, several developments were necessary. These included the appreciation of antigenic variation in pneumococci [102], the need for type-specific sera [103], the development of rapid in vitro assays to establish antigenic type (i.e., capsular swelling and agglutination reactions) [104], the development of methods to standardize potency (mouse protection test) [46], and improved purification techniques that would reduce the toxicity of serum. For meningococcal antisera the situation was reversed; Flexner's serum significantly reduced mortality in early epidemics of meningitis [38] but was subsequently less effective, possibly as a result of antigenic changes in *Neisseria meningitidis* [7]. Research into better meningococcal antisera was then hampered by the lack of useful animal models, loss of strain virulence in vitro, and poor understanding of the antigenic diversity of *N. meningitidis* [105, 106]. A lesson from the preantibiotic era is that a considerable amount of basic research on the immunology and pathogenesis of each infection is usually necessary before antibody therapy can be developed that will be successful in clinical practice.

Advantages and Disadvantages of mAb-Based Therapies

Spectrum of activity. Antibodies can modify bacterial, fungal, parasitic, and viral infections and are a class of biological agents with broad antimicrobial activity against diverse pathogens. Antibody-based therapies are usually pathogen-specific and have the theoretical advantage that they should not affect the normal flora of the patient or select for resistance in nontargeted microbes. Nevertheless, narrow specificity is a disadvantage because mixed infections may not be treated by a single antibody preparation. Pneumonia due to *S. pneumoniae* with more than one serotype was recognized as a reason for the failure of type-specific serum therapy [107]. One solution is to use cocktails of mAbs active against common antigenic types. Cocktails may be designed to include mAbs to multiple serotypes and mAbs with multiple isotypes to enhance antibody effector function. Pathogen-specific drugs (such as mAbs) are less attractive to the pharmaceutical industry because the narrow specificity reduces the potential market for the drug. However, the increasing incidence of resistant organisms resulting from the use of broad-spectrum antibiotic regimens could make pathogen-specific drugs attractive to drug companies. Precedents for the development of pathogen-specific drugs already exist in the area of antiviral drug research.

Mechanisms of action. Antibodies mediate protection by a variety of mechanisms. Direct antibody mechanisms of action include inhibition of attachment, agglutination (and immobili-

zation), viral neutralization, toxin neutralization, antibody-directed cellular cytotoxicity, complement activation, and opsonization [108]. Antibody therapy has the potential to enhance immune function in immunosuppressed hosts. However, since the mechanism of action of many antibodies involves promoting microbial clearance through nonspecific cellular immunity, antibody-based therapies may be less effective in individuals with defective macrophage, neutrophil, and natural killer cell function. In this regard, it is encouraging that antibodies are effective against *Pseudomonas aeruginosa* in neutropenic mice [109] and that they can reduce the number of infections in pediatric patients with AIDS [79].

Antibodies are usually considered to be "protective" effector molecules of the immune system. However, not all antibody responses to pathogens are protective and some may be deleterious to the host. For example, some viral-specific antibodies are capable of enhancing infection [110]. Thus, antibody molecules being considered for clinical development will require extensive testing in vitro and in vivo. Studies of the mechanisms of antibody action are important for understanding the mode of protection and for designing clinical trials.

Pharmacokinetics. The pharmacokinetics of human IgG suggests several useful characteristics for its role as an anti-infective agent. These include a long half-life (~20 days [111]), good tissue penetration [112], and, depending on the isotype, the ability to either cross the placenta to provide antibody protection to fetuses and newborns [113] or to be excluded from the placenta if fetal toxicity is a concern. Heterologous mAbs (i.e., murine mAbs) have shorter half-lives in humans, but chimeric and humanized mAbs have longer half-lives than their murine precursors. mAbs with a longer half-life can, in principle, be engineered by altering the regions of the constant domain that regulate clearance.

A disadvantage of antibody-based therapies is the need for systemic administration. Oral administration is unlikely to be effective, with the possible exception of therapy for enteric pathogens [73, 114]. The blood-brain barrier is a potential obstacle for antibody therapy for infections of the brain. However, in infections of the brain in which there is inflammation, there is increased antibody penetration, and intravenous administration of antibodies appears to have been successfully used for therapy of meningococcal meningitis [115]. Antibody-based therapies can also be administered directly into the subarachnoid space, as has been done for the treatment of meningococcal and *H. influenzae* meningitis [8, 38]. Enhanced penetration of the brain can be achieved by modifying the charge of the molecule [116] or by linking it to carrier proteins that cross the blood-brain barrier [117]. Antibody therapy for brain infections may be feasible if the blood-brain barrier is leaky, if antibody is administered directly into the subarachnoid space, or if antibodies with greater brain penetration are used. Additional research into the pharmacokinetics of antibodies in infection is likely to be required for optimal use of antibody-based therapies. Studies of antibody binding to tumors have revealed

complex pharmacokinetics [112]. There may be problems with antibody penetration into abscesses as have been found with tumors.

Toxicity. Immunoglobulins are generally safe drugs [67]. Nevertheless, serious side effects have been reported with high-dose (0.5–2 g/kg) antibody therapy, including rare cases of renal failure [118], aseptic meningitis [119], and thromboembolic events [120, 121]. High-dose immunoglobulin therapy is unlikely to be required in anti-infective mAb therapy. In the past, serum therapy was effective against various pathogens despite the fact that immune sera contained only small amounts of specific antibody. mAbs have significantly higher specific activity than polyclonal preparations. For example, 0.7 mg of two anti-tetanus toxin human mAbs provides the same activity as 100–170 mg of immune globulin [122]. Thus, the toxicities described for high-dose immunoglobulin therapy may not be relevant in anti-infective therapies with mAbs.

Until fully human mAbs are available, rodent, mouse-human chimeric, or humanized mAbs are therapeutic options. For over a decade, murine mAbs directed against T cells have been used to prevent organ graft rejection in humans [92]. A murine IgM to endotoxin (E5) was tested in 247 patients with sepsis and appeared to be a safe treatment [123]. Although administration of murine mAbs is generally well tolerated in humans, allergic reactions occur in 1%–2% of patients [123] and most patients develop antibody responses to the murine mAbs that may interfere with their therapeutic function [43, 124]. Experience with human-mouse chimeric antibodies and humanized mAbs is accumulating rapidly as clinical trials with several compounds progress. A chimeric anti-CD4 mAb for the treatment of rheumatoid arthritis has been well tolerated [125], but approximately half the patients had infusion-related side effects (headaches, nausea, fever, and chills), which were diminished by slowing the infusion rate [125]. Mouse-human chimeric and humanized mAbs are less immunogenic than their murine precursors [98, 126], but anti-idiotypic responses occur after repeated treatments [127]. Overall, the experience with chimeric and humanized mAbs suggests that they are relatively safe compounds [98, 125–128].

Antigenic variation and antibody resistance. The efficacy of antibody-based therapies may be diminished by antigenic changes in the pathogen. This could be minimized by antigenic surveillance systems, as is presently done for influenza virus. Antibody-resistant mutants can be generated in the laboratory [129], and it is likely that the same can occur in patients. Mechanisms of antibody resistance include mutations that change the antigenic site and protease production. Antibody use may select for antigenically distinct variants. Evidence for the horizontal transfer of IgA protease genes exists in *Neisseria gonorrhoeae* and it is conceivable that widespread antibody use would result in selection of protease-producing strains for many pathogens [130]. Thus, large-scale use of antibody-based therapies may result in rapid emergence of antibody resistance in a manner analogous to that of antibiotic resistance. However,

one advantage of antibody-based therapies is the versatility of antibody compounds. For example, emergence of an antibody-resistant strain could be countered by a new antibody directed toward the mutated epitope or another antigenic target. Emergence of protease-producing strains could be countered by designing antibodies without protease cleavage sites (although these may then be recognized as foreign and be immunogenic) or by addition of antiprotease mAbs. Selection of antibody-resistant organisms could be minimized by using cocktails of mAbs directed at multiple antigenic targets or by using a combination of antibodies and antimicrobials.

Cost. Cost effectiveness is a significant concern that is likely to be a major obstacle for the development of passive antibody therapies. Antibody prophylaxis for CMV infections can cost \$4,000 to \$9,000 per patient [71]. The cost effectiveness of antibody therapy for prevention of infection in leukemic patients has been questioned [88, 131]. However, in selected populations such as premature infants, antibody therapy may be cost effective [85]. Furthermore, the cost of a drug when first introduced may not reflect its long-term costs given the potential for improvements in technology and production. mAbs are presently made in tissue culture, so the cost of production is high. mAbs can be made in bacteria or yeast, and less costly means of production might be developed [97]. In the past, serum therapy was used despite its high cost because it was believed to be effective. New antibody-based therapies are likely to be used if they prove to be effective.

A Proposal

For pathogens such as *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*, there is a large body of experimental and clinical evidence to support the development of passive antibody therapy. However, for many pathogens, antibody immunity has not been proven to be important. For example, *Cryptococcus neoformans* is a fungus for which the importance of antibody immunity is uncertain. However, administration of preformed antibodies can modify the course of cryptococcal infection in various animal models [132–136], and the combination of antibody and amphotericin B is a more effective treatment than the use of either agent alone [137–139]. Studies with mAbs have shown that there are protective, nonprotective, and deleterious antibodies to the *C. neoformans* capsule polysaccharide [136]. Heavy chain isotype [136, 140] and epitope specificity [141] are important determinants of protective efficacy. The existence of protective and nonprotective antibodies against *C. neoformans*, a fungus for which antibody immunity may or may not be important, provides a paradigm that may be applicable to other pathogens.

We propose the hypothesis that for every pathogen there exists an antibody that will modify the course of infection to the benefit of the host; such antibodies are candidates for development as antimicrobial drugs. Our proposal includes the use of antibodies for intracellular pathogens; for example, anti-

bodies may exist that could prevent cell entry of intracellular bacteria and/or shift the intracellular location of such bacteria by promoting internalization through Fc receptors. An mAb that inhibits intracellular *Toxoplasma gondii* infection has recently been described [142]. In addition, antibodies have been described that can neutralize viruses intracellularly [143] or penetrate the nuclear membrane [144].

Our proposal is not limited to those pathogens for which antibody immunity has been demonstrated to be protective. Conclusions on the importance of antibody immunity are usually based on observations made with polyclonal sera (i.e., passive protection or correlation of immunity with the presence of antibody). Since polyclonal sera might contain protective antibodies, nonprotective antibodies, and disease-enhancing antibodies, the existence of protective antibodies cannot be ruled out on the basis of absence of protection in experiments involving passive transfer of polyclonal sera or immunizations. Conversely, experiments that demonstrate that polyclonal sera can mediate protection indicate the existence of protective antibodies. For pathogens for which polyclonal antibody has shown no protection, the question of whether useful antibodies exist must be reevaluated with mAbs since the presence of nonprotective or deleterious antibodies in polyclonal sera could create confounding variables. A corollary of our proposal is that antibody-based therapies may be developed against pathogens for which antibody immunity is not considered to be important.

Opportunities for Antibody-Based Therapies

Infections that are difficult to treat and that can be modified by antibody immunity provide a logical starting point for the development of antibody-based therapies. Antibodies have historically been more effective in prophylaxis than in therapy. Antibody-based therapies have traditionally been most effective in infections where viral and toxin neutralization modifies the course of the disease. However, most of the historical experience was gained with polyclonal preparations of uncertain composition and may or may not be applicable to mAb preparations with high activity.

Opportunistic infections. Infections with low-virulence organisms in immunosuppressed individuals are often difficult to treat and are sometimes incurable. Since the problem is deficient immunity, antibody therapy is an attractive option because antibodies can enhance immune function. Table 2 lists examples of opportunistic pathogens for which antibody can modify the course of infection.

Antibiotic resistance. Drug-resistant organisms are targets for development of antibody-based therapies. The spread of penicillin-resistant *S. pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and multiply-drug-resistant *E. faecium* has limited the useful antibiotic arsenal against these pathogens [4, 6, 153]. For pneumococcus, antibody therapy has been shown to be useful [7]. Antibody may be useful against staphylococcal infection [154, 155]. For *E. faecium*, the role of antibody immu-

Table 2. Opportunistic pathogens for which experimental data suggest a potential role for antibody-based therapies.

References	Pathogen
[145]	<i>Pneumocystis carinii</i>
[146]	<i>Cryptosporidium parvum</i>
[142]	<i>Toxoplasma gondii</i>
[135, 136, 147]	<i>Cryptococcus neoformans</i>
[148]	<i>Candida albicans</i>
[149]	Herpes simplex virus
[71, 150]	Cytomegalovirus
[151, 152]	<i>Pseudomonas aeruginosa</i>

NOTE. This is not a complete list.

nity is uncertain, but some patients make opsonic antibodies, which might be protective [156]. Significant work has already been done in the development of pseudomonal antibodies for resistant gram-negative organisms (table 2). The addition of antibody-based therapies to chemotherapy may slow the development of resistance and improve outcome.

Toxin neutralization. The ability to neutralize toxins is a unique characteristic of antibody-based therapies. Antitoxin antibodies are useful for the treatment of diphtheria, tetanus, botulism, snake bites, and black widow bites (see above). Recent attempts to develop antibody therapy for gram-negative sepsis have focused on mAbs to neutralize endotoxin [123, 157, 158] and cytokines [159]. For experimental pseudomonas

sepsis, combination therapy with mAbs to endotoxin and tumor necrosis factor was superior to therapy with a single mAb [160]. Examples of potential targets for antibody-based therapy include the toxins and proteases associated with toxic shock syndromes [161, 162]. Combination therapy with antibodies to exotoxins could improve outcome, but cocktails of mAbs may be necessary because of toxin heterogeneity [162]. Intravenous immunoglobulin administration has been associated with dramatic clinical improvement in a patient with *Streptococcus pyogenes* toxic shock syndrome [163].

Antivirals. Virus neutralization is an established property of antibodies. In the preantibiotic era, serum was used for prophylaxis of measles, chickenpox, mumps, and poliomyelitis. Recently, the potential of antibody therapy against many viruses, including hepatitis B [164], HIV [165], respiratory syncytial virus [166], CMV [150], and parvovirus [167], has received considerable attention. Newly identified viral illnesses are targets for antibody drug research.

Combination of antibody therapy and chemotherapy. Antibody-based therapies are unlikely to be used alone unless they are the only available therapy or are being used for prophylaxis of infection. Combinations of antibody therapy and chemotherapy offer theoretical advantages. Antibodies promote microbial killing directly by a complement-mediated lytic process or indirectly by enhancing nonspecific immune mechanisms. Table 3 lists examples of bacterial, fungal, and viral pathogens for which combination therapy has shown promise. Combination therapy could reduce the amount of either agent required to

Table 3. Pathogens for which the combination of chemotherapy and antibody based therapy has shown some promise.

References	Pathogen	Chemotherapy	Antibody
[57, 168]	<i>Neisseria meningitidis</i>	Sulfanilamide	Horse immune sera
[55]	<i>Streptococcus pneumoniae</i>	Sulfapyridine	Rabbit immune sera
[8, 9]	<i>Haemophilus influenzae</i>	Sulfonamide	Rabbit, horse immune sera
[169]	<i>Staphylococcus aureus</i>	Penicillin	Human gamma globulin
[170]	<i>S. aureus</i>	Chloramphenicol	Human gamma globulin
[171]	Group A <i>Streptococcus</i>	Sulfanilamide	Rabbit immune sera
[170]	Group A <i>Streptococcus</i>	Chloramphenicol	Human gamma globulin
[167]	Group B <i>Streptococcus</i>	Penicillin	Human immune sera
[109]	<i>Pseudomonas aeruginosa</i>	Sparfloxacin	Human IgG1 mAb
[172]	<i>P. aeruginosa</i>	Imipenem/aminoglycoside	Human IgM mAb
[173]	<i>P. aeruginosa</i>	Ciprofloxacin	Murine E5 LPS antibodies
[170]	<i>P. aeruginosa</i>	Chloramphenicol	Human gamma globulin
[172]	<i>Escherichia coli</i>	Cephalosporin/aminoglycoside	Murine E5 LPS antibodies
[174]	<i>Shistosoma mansoni</i>	Praziquantel	Rabbit immune sera
[175]	<i>Candida albicans</i>	Amphotericin B	Human gamma globulin
[137]	<i>Cryptococcus neoformans</i>	Amphotericin B	Rabbit immune sera
[138, 139]	<i>C. neoformans</i>		Murine IgG1 mAb
[176]	<i>C. neoformans</i>	5-Flucytosine	Murine IgG1 mAb
[177]	Lassa virus	Ribavirin	Monkey immune sera
[72, 178]	Cytomegalovirus	Ganciclovir	Murine immune sera
[179]	Herpes simplex virus	Adenine arabinoside	Rabbit and human sera
[180]	Herpes simplex virus	Acycloguanosine	Human immune globulin

NOTE. This is not a complete list.

achieve a therapeutic effect. For example, some antibiotics are quite toxic, and the ability to reduce doses could lessen side effects. In a similar vein, the addition of chemotherapy to antibody therapy could reduce the amount of antibody necessary to achieve a therapeutic effect, which would lessen the cost of therapy.

Antibody-Based Therapies and the Practice of Infectious Diseases

The availability of broad-spectrum antibiotics has diminished the need for making exact microbiological diagnoses. For example, gram-negative sepsis or presumed fungal infections can be treated with empirical therapy without identifying the pathogen. This situation is in contrast to the practice of infectious diseases in the 1930s when identification of the pathogen (and its serotype) was necessary for choosing the correct antiserum. For antigenically diverse pathogens such as *S. pneumoniae*, rapid protocols were developed for typing strains. The present practice of infectious diseases is not unlike a gambling strategy where the probability of infection by a given microbe is matched to the likelihood of activity by the available antibiotics. This has resulted in great emphasis on broad-spectrum antibiotic "coverage" and less emphasis on making an exact microbiological diagnosis. Although the relative merits of this practice are beyond the scope of this article, widespread antimicrobial resistance is decreasing the effectiveness of existing antibiotics, and increased caution is warranted when designing broad-spectrum combinations.

A return to antibody therapy would force greater emphasis on precise microbiological diagnosis and would foster the development of more accurate and more rapid diagnostic strategies. The use of antibody-based therapies may also require antigenic screening in the clinical laboratory, a practice not unlike the present one of antimicrobial susceptibility testing. In cost-conscious times these measures may not immediately appear to be attractive. In this regard it is worth remembering that penicillin was unobtainable in 1943 [181] but half a century later it is one of our least-expensive therapies. When one is reconsidering the option of antibody-based therapies, it is important not to underestimate the human capacity for improving technology and the effect of the pressures of a competitive market on long-term costs.

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