

REVIEW ARTICLES

Crisis in Infectious Diseases: Time for a New Paradigm?

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Current practices in the treatment of infectious diseases are the result of two fundamental changes in antimicrobial therapy that occurred in the mid-20th century: the transition from pathogen-specific therapy to non-pathogen-specific therapy and the shift toward emphasis on antiinfective strategies that target microbial pathogens over those that enhance host immunity. The alarming rise in antimicrobial-resistant strains, the increasing frequency of serious infections in immunocompromised patients, and the paucity of new types of antibiotics suggest the need for reevaluation of the manner in which infections are treated. In the short term, the situation may be addressed—at least in part—by increased emphasis on improved diagnosis and, when possible, the use of specific or narrow-spectrum treatments. In the long term, a return to pathogen-specific therapy, possibly in combination with adjunctive immunotherapy, may be an attractive and desirable option provided that significant advances are made in diagnostic microbiology and drug discovery.

In this last decade of the 20th century, the successful implementation of antimicrobial chemotherapy is becoming increasingly difficult because of (1) an epidemic of immunocompromised patients, for whom antimicrobial therapy is less effective; (2) the emergence of new pathogens and the reemergence of old pathogens; and (3) widespread drug resistance. Problems in antimicrobial therapy have been extensively discussed in the medical literature [1–7].

In the early days of the antibiotic era, the majority of bacterial isolates were susceptible to antimicrobial chemotherapy, and infections occurred primarily in patients with intact immunity. In 1956 Jawetz stated that “the position of antimicrobial agents in medical therapy is highly satisfactory” and that the “majority of bacterial infections can be cured simply, effectively, and cheaply” [8]. Unfortunately, this statement is no longer true. This article examines the current crisis from a historical perspective and suggests that the existing paradigm for the use of antimicrobial therapy is rapidly becoming obsolete.

The Transition to Non-Pathogen-Specific Antimicrobial Therapy

Before the discovery of sulfonamide in 1935, the antimicrobial arsenal consisted of pathogen-specific drugs (compounds

useful for treating one or a few infections) that required a microbial diagnosis prior to use: quinine for malaria, arsphenamine for syphilis, and serum therapies [9]. Heterologous immune sera were used for treatment of pneumococcal pneumonia, meningococcal meningitis, erysipelas, diphtheria, tetanus, and other conditions [10, 11]. Another pathogen-specific treatment was bacteriophage therapy [12].

Unlike earlier antibacterial drugs such as optochin [13] (figure 1), the sulfonamides were nonspecific antimicrobial agents because they had activity against many different bacteria. The introduction of sulfonamide therapy marked a fundamental change from pathogen-specific therapy to non-pathogen-specific therapy that allowed prompt and effective treatment of bacterial infections without the necessity of identifying the pathogens involved.

Current strategies for drug discovery favor development of drugs with good pharmacological profiles and antimicrobial activity against diverse bacteria [15]. Antifungal therapy has always been non-pathogen-specific. The first effective antifungal agent, amphotericin B, was active against several species of fungi. In contrast, there is no precedent for broad-spectrum antiviral drugs. The few antiviral drugs available are effective against individual classes of viruses, and their use is facilitated by the distinctive clinical syndromes associated with viral infections. Hence, antibacterial and antifungal therapies are, with few exceptions, non-pathogen-specific, whereas antiviral drugs are pathogen-specific.

The market for an antimicrobial drug is proportional to its activity and to the prevalence of infections caused by susceptible organisms. Non-pathogen-specific drugs have larger markets than pathogen-specific drugs. In general, broad-spectrum drugs are popular with non-infectious disease specialists. In contrast, the emphasis on empirical therapy, combined with the lack of early microbiological diagnoses, made narrower-

Received 12 March 1996; revised 26 June 1996.

Grant support: National Institutes of Health (grants AI22774 and AI13342).

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Clinical Infectious Diseases 1996;23:790–4

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1058-4838/96/2304-0020\$02.00

In Pneumonia

Start treatment early

In the

Optochin Base
ETHYLHYDROCUPREINE

treatment of pneumonia valuable time may often be saved if the physician will carry a small vial of *Optochin Base* (powder or tablets) in his bag and thus be prepared to begin treatment immediately upon diagnosis.

Literature on request

MERCK & CO. Limited **Montreal**

Figure 1. Advertisement for optochin (ethylhydrocupreine) that appeared in the March 1931 issue of the *Canadian Medical Association Journal* (reprinted with permission). Optochin was an early antimicrobial agent with antipneumococcal activity that was used for treatment of pneumonia but was unsuccessful because of toxicity [14].

spectrum drugs like cefsulodin (a cephalosporin active against *Pseudomonas aeruginosa* and *Staphylococcus aureus* [16]) difficult to use effectively; thus, this particular drug was never widely used.

The emphasis on a non-pathogen-specific antimicrobial strategy in the design, selection, and implementation of anti-infective therapy has had a significant cost. Resistance developed rapidly to many early antimicrobial drugs. Most strains of *S. aureus* were susceptible to penicillin in 1941, but the majority of isolates were resistant by the late 1940s [17]. Non-pathogen-specific antibacterial therapy produced alterations in the host flora that predisposed to secondary infections with fungi or drug-resistant bacteria. In 1970 Finland reported an increasing incidence of gram-negative bacteremia associated with high mortality, such that by 1965 the mortality due to bacteremic infections was no different than that in 1935 [18].

Other problems associated with non-pathogen-specific drugs include the development of antibiotic-associated *Clostridium difficile* colitis [19] and vancomycin-resistant *Enterococcus faecium* bacteremia after therapy with antimicrobials active

against anaerobes [20]. Nosocomial *Candida albicans* infections are now common and are almost always associated with prior antibacterial therapy [14]. Recently, ventilator-associated pneumonia was shown to be associated with a sevenfold higher mortality if the patient received prior antimicrobial therapy [21], a finding attributed to a shift in the microbial causes of pneumonia (from gram-positive cocci and *Haemophilus influenzae* to resistant gram-negative bacteria like *P. aeruginosa*) [21–23].

The Practice of Empiricism

The principle of early empirical therapy for infectious diseases dates from the experience with serum therapy. The realization that type-specific serum was most effective against pneumococcal pneumonia when administered early in the course of infection led to the development of rapid protocols for the isolation and typing of pneumococci from sputum [24]. An early form of empirical therapy was the use of mixtures of type-specific sera pending the identification of the pneumococcal strain type [25, 26]. Similarly, presumed bacterial meningitis was treated empirically with antimeningococcal serum [27].

Empirical therapy involves a twofold gamble: first, that the patient has an infection, and second, that appropriate antibiotics are selected. Choosing antimicrobial drugs is, to a large extent, the art of matching the probability of infection with a given pathogen with the probability that the drugs are active against that pathogen. To select empirical antimicrobial therapy, the physician must perform a complex mental exercise in which the variables include the presumed site of infection, the antimicrobial spectrum of the available drugs, the antimicrobial susceptibility of the local flora, dosing, and the expected side effects of treatment vs. the consequences of nontreatment.

Numerous studies have documented problems with the selection of antimicrobial therapy by physicians [28–31]. The concern that the information necessary for selecting empirical therapy is more than one individual can process has led to the development of computer programs to help physicians choose antimicrobial regimens [32]. Indeed, a computer program was significantly more effective than physicians in selecting empirical antimicrobial regimens active against pathogens later recovered from patients [32].

Empirical administration of appropriate antimicrobial drugs can improve the chances of survival for some patients with severe infections [9, 32–34]. Recommendations for empirical therapy have been made for a variety of clinical syndromes in which the identity of the pathogen(s) is presumed but not always confirmed, such as community-acquired pneumonia [35], neonatal sepsis [34], and fever in neutropenic patients [36]. Recent guidelines for the care of adults with community-acquired pneumonia emphasize empirical selection of drugs on the basis of algorithms derived from clinical observations [35]. Empirical antimicrobial regimens have evolved with the recognition of new pathogens, the emergence of antimicrobial drug resistance, and the introduction of new antibiotics [18, 37].

In the practice of empirical therapy, microbiological information (i.e., culture data) is usually employed to optimize antimicrobial regimens rather than to direct their selection. Once microbiological information is available, most experienced physicians change therapy to drugs with a narrower spectrum of activity, but this is often not possible because such drugs are not available for many nosocomial pathogens (e.g., *P. aeruginosa* and *Enterobacter* species). Furthermore, the possibility of polymicrobial infections in critically ill patients often discourages the use of narrower-spectrum drugs. When no microbiological diagnosis is made, the choice of antimicrobial therapy is determined by clinical response.

In the absence of rapid diagnostic techniques, the practice of empirical therapy for patients with presumed infections must continue. However, testimonial to the need for caution is the fact that broad-spectrum therapies may contribute to the emergence of resistant bacterial strains [31, 38]. Kollef has called the practice of broad-spectrum antimicrobial therapy in intensive care units “spiralling empiricism” [31], a phrase that highlights the haphazard and unscientific decision-making involved in the empirical use of antibiotics.

The Forgotten Host

In the second half of the 20th century, the conceptual approach to the management of infectious diseases is that vaccination prevents infections and antimicrobial chemotherapy fights established infection. Consistent with this approach, a number of effective vaccines have been introduced, including those to prevent poliomyelitis, hepatitis B, and *H. influenzae* infection, although little emphasis has been placed on the potential use of immunotherapy for infection. This is a fundamentally different strategy from that of the preantibiotic era, when providing optimal conditions for host recovery [8] and enhancing immunity through antibody administration were the backbone of antiinfective therapy. Jawetz used the phrase “the forgotten host” to lament the change in therapeutic emphasis from host to pathogen [8].

Microbicidal therapies were very effective during the early years of the antibiotic era because most life-threatening infections occurred in immunocompetent hosts. However, microbicidal therapies are generally less effective for immunocompromised patients [6, 7, 39]. Opportunistic infections such as HIV-associated cryptococcosis and toxoplasmosis, invasive aspergillosis, and other infections in immunosuppressed patients often cannot be cured with antimicrobial drugs. The difficulties encountered in treating infections in immunosuppressed patients indicate the limitations of antimicrobial chemotherapy and suggest a need for immunotherapeutic alternatives.

Immunotherapeutic modalities can be either specific, such as antibody therapy, or nonspecific, such as the use of cytokines and granulocyte transfusions. The potential of antibody therapy as an adjunct to antimicrobial therapy remains largely untapped, despite enormous advances in the technology of human antibody production [40]. A variety of technologies are now

available for the generation of human antibodies. The use of human monoclonal antibodies would avoid the toxicity of heterologous sera that contributed to the abandonment of antibody therapy in the 1940s [10, 11].

A variety of cytokines and growth factors have shown promise for treatment of specific infections, and administration of granulocyte colony-stimulating factor can reduce the length of neutropenia and associated infections [33, 41]. Immunotherapy for infections has a rational basis and enormous potential. However, its application to infectious disease would require a shift in emphasis from killing microbes directly to helping the host to eradicate the infection.

Underdevelopment of Diagnostic Microbiology

For many infectious diseases there has been relatively little progress in diagnostic techniques over the past half-century. Syphilis is still diagnosed by dark-field microscopy or serology; malaria is still diagnosed by blood smear; and culture remains the “gold standard” for diagnosis of invasive bacterial infections. The technology for the identification and recovery of pathogens from body fluids has improved in the last 50 years, but most of the innovations have been evolutionary rather than revolutionary.

In some areas there has been a decline in diagnostic efficacy: in the 1930s recovery of pneumococci from the sputum of patients with lobar pneumonia for typing could be accomplished in several hours by mouse passage [24]. Today, a definitive diagnosis of pneumococcal pneumonia depends upon the recovery of pneumococci from blood cultures, which requires about 48 hours. Simple tests like the gram stain that can provide useful information for the evaluation of pneumonia [42, 43] are done poorly or not at all [44].

A recent study reported that gram-stain examination of sputum was performed for only 58% of patients with pneumonia and that such examinations were associated with a 50% false-positive rate for the diagnosis of pneumococcal pneumonia [44]. When the sputum gram stain revealed a predominant organism, single-agent therapy was more likely to be selected for pneumonia, a circumstance suggesting that early microbiological information could translate into narrower-spectrum antimicrobial therapy [44].

The inability of current techniques in diagnostic microbiology to provide rapid and accurate identification of pathogens in most infections has undoubtedly contributed to the emphasis on empirical therapy. Limitations in diagnostic techniques may also hinder progress in some areas. Evaluation of novel therapies such as with antibodies to endotoxin [45, 46] and IL-1 receptor antagonists [47] has proved difficult because it is not possible to identify prospectively patients who may benefit from these compounds.

The Current Paradigm

The current paradigm for antimicrobial therapy can be summarized as follows: broad-spectrum activity is a desirable

quality in an antimicrobial drug; empirical therapy with broad-spectrum agents has a high benefit-to-risk ratio; and antiinfective therapy should target microbial physiology with the aim of killing or inhibiting microorganisms. The success of this strategy depends upon the availability of drugs with low toxicity, a low prevalence of resistant microorganisms, and the occurrence of infection in human hosts with intact immunity. In recent years the prevalence of resistant microorganisms has increased faster than new antimicrobials have been introduced into practice [5], and there has been a dramatic increase in the number of immunocompromised hosts as a result of HIV infection, organ transplantation, chronic degenerative diseases, and improvements in cancer care [6, 7]. Hence, the conditions that led to the current paradigm are no longer true. Regaining the upper hand in the battle against infections may not be possible if we continue to operate within the existing conceptual framework of antiinfective practice.

A Proposal

I propose that we consider a new paradigm for the treatment of infectious diseases, based on reversal of the historical trends that have contributed to the present difficulties: first, deemphasize non-pathogen-specific therapy in favor of the use of pathogen-specific drugs; second, replace empiricism with determinism by developing and using rapid and accurate diagnostic technologies to make precise microbiological diagnoses in infectious diseases; and third, intervene on the side of the host with antiinfective immunotherapy.

Toward a New Paradigm

Implementation of this proposal requires the availability of pathogen-specific drugs, rapid diagnostic strategies, and therapies to enhance immunity—none of which are available. Nevertheless, advances in the biological sciences suggest that this proposal could become reality if a consensus for it develops among infectious disease specialists.

Despite their scarcity, pathogen-specific drugs are effective and there is broad consensus for their use. Several pathogen-specific therapies already exist, such as the use of isoniazid for tuberculosis, pentamidine for *Pneumocystis carinii* infection, and antiviral drugs. Development of additional pathogen-specific drugs would require rational drug design to exploit biochemical differences between microbes [48, 49]. Rapid advances in the understanding of microbial molecular genetics suggest that many targets will be available for rational drug discovery. A precedent for this approach is provided by existing drug-discovery strategies for viruses, which target specific viruses. Some companies are already searching for narrow-spectrum drugs against methicillin-resistant staphylococci, vancomycin-resistant enterococci, and penicillin-resistant streptococci and pneumococci [50].

If one assumes that pathogen-specific drugs can be made, the main obstacles to the development and reintroduction of

pathogen-specific therapy would be unfavorable economics and the absence of rapid and accurate diagnostic techniques to support their use. Smaller markets and high development costs are significant obstacles to the development of pathogen-specific drugs. However, incentives for commercial development of pathogen-specific drugs could be created, such as those designed to promote drug discovery for diseases that affect few individuals (orphan drugs). Furthermore, as resistant microbes proliferate and existing drug options are exhausted for a given pathogen, a market is being created for pathogen-specific drugs active against the resistant strains. For example, the problem of nosocomial infections with resistant *E. faecium* strains [51] suggests that an *E. faecium*-specific drug would be marketed if available.

The development of pathogen-specific drugs will not solve the problem of drug resistance. Isoniazid-resistant *Mycobacterium tuberculosis* strains have proliferated despite the narrow spectrum of this drug. The likelihood of emergence of resistance to a drug is dependent on its mechanism of action, the frequency of drug-resistance genes in the genetic pool of microorganisms, and the efficiency of genetic transfer mechanisms in susceptible populations [1–3, 15, 52–54].

Pathogen-specific drugs have the theoretical advantage of targeting disease-causing microbes without causing great disruptions in the host's microbial flora. This could reduce the incidence of superinfection with resistant organisms or fungi. Furthermore, pathogen-specific drugs are unlikely to select drug-resistant strains among nontargeted microbes, and this could slow the emergence of drug-resistant organisms.

Since pathogen-specific drugs cannot be used effectively without identification of pathogens, the introduction of pathogen-specific therapies would require major innovations in diagnostic microbiology. Recent advances such as PCR, DNA typing, antigen detection, and nucleic acid hybridization could be developed further to provide rapid diagnostic information. Broad-spectrum drugs would retain a niche in the formulary for the treatment of polymicrobial infections. However, physicians' approach to patients with presumed infection would change from choosing empirical therapy to establishing a diagnosis that would permit the use of specific therapy.

Antiinfective immunotherapy will be a new horizon for the infectious disease consultant. Immunoglobulin [55], cytokines, and growth factors [33, 41] are used against infections in some clinical situations, but most, if not all, current antibacterial and antifungal therapies utilize drugs designed to kill microbes directly. It is conceivable that therapeutic interventions to enhance the host immunity will be as effective as and possibly synergistic with antimicrobial drugs.

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