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—infected especialists. In contrast, the emphasis or empirical therapy, combined with the lack of early microbiological diagnoses, made narrower-
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 tab­
lets) in his bag and thus be prepared to begin
treatment immediately upon diagnosis.

Merck & Co. Limited Montreal

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

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

The emphasis on a non-pathogen-specific antimicrobial stra­
egy in the design, selection, and implementation of antinfective
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 iso­
lates were resistant by the late 1940s [17]. Non-pathogen-spe­
cific 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 inci­
dence of gram-negative bacteremia associated with high mor­
tality, such that by 1965 the mortality due to bacteremic infec­
tions 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 infec­
tions 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 in­
fluenzae to resistant gram-negative bacteria like P. aeruginosa)
[21–23].

The Practice of Empiricism

The principle of early empirical therapy for infectious dis­

cases dates from the experience with serum therapy. The real­
ization that type-specific serum was most effective against
pneumococcal pneumonia when administered early in the

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 recog­
nition 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 antifungal 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 marke’s 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 formula 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.

References

31. Kollef MH. Antibiotic use and antibiotic resistance in the intensive care unit: are we curing or creating disease? Heart Lung 1994;23:363–7.