Disseminated Histoplasmosis and Human Immunodeficiency Virus Type 1 Infection: Risk Factors in Guatemala

Str—We read with interest the report by Hajjeh [1], which emphasizes the importance of determining risk factors for and effective strategies to prevent disseminated histoplasmosis in HIV-1–infected individuals. In Guatemala, where Histoplasma capsulatum is considered to be endemic (infected individuals commonly present with pulmonary histoplasmosis), we have noted a 6.7% incidence of progressive disseminated histoplasmosis (PDH) among HIV-1–infected patients. A retrospective review of the charts of 120 HIV-seropositive patients, admitted between 1984 and 1994 to the 800-bed San Juan de Dios Hospital in Guatemala City, revealed eight cases of PDH. All of the PDH cases occurred in male patients, who ranged in age from 17 years to 35 years. The clinical diagnosis was confirmed with a blood smear and bone marrow aspirate smear for six of the patients and from postmortem hepatic biopsy results for two of the patients who died within 48 hours after admission.

Limited medical resources in Guatemala make it difficult to distinguish between the similar clinical findings of disseminated histoplasmosis and disseminated tuberculosis in HIV-infected patients. Although common manifestations of disseminated tuberculosis [2] were observed at admission, as shown in table 1, all of the patients with PDH died within 10 days of hospital admission, underscoring the necessity of establishing possible risk factors for PDH and guidelines for rapid diagnosis.

Our assessment of possible risk factors indicated that the majority (6 of 8) of the patients with PDH were farmers, construction workers, or factory workers from Escuintla and Alta Verapaz, which are farming/cave regions where histoplasmosis is endemic. This finding suggests that presentation with disseminated disease may reflect reactivation resulting from prior exposure. Chest radiographs demonstrating perihilar adenopathy or calcifications in all (8 of 8) of the patients support this suggestion, as shown in table 1.

The presence of PDH in HIV-1–infected patients is of particular concern because of the high associated mortality rate and limited medical treatment available in Guatemala. Only itraconazole, a triazole derivative, is obtainable; amphotericin B, which is widely used in induction therapy, is generally unavailable. Routine determination of possible risk factors for PDH, including immunodepression, residence in farming/cave areas, and the presence of calcifications or perihilar adenopathy on chest radiographs, should enhance the ability to detect disseminated infection. An early confirmed diagnosis, made by using unsophisticated and available diagnostic methods (blood and bone marrow smears), would permit more rapid initiation of treatment that might alter the course of disease progression.

Table 1. Characteristics of HIV-1–infected patients with progressive disseminated histoplasmosis.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Clinical findings</th>
<th>Diagnosis at admission</th>
<th>Possible risk factors for PDH</th>
<th>Diagnostic test for PDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Hypotension, weight loss, splenomegaly, sensory alteration</td>
<td>Disseminated TB</td>
<td>HIV+, perihilar adenopathy, farm area resident</td>
<td>Blood and bone marrow smear</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>Fatigue, fever, weight loss, adenopathy, diarrhea</td>
<td>TB</td>
<td>HIV+, perihilar adenopathy</td>
<td>Blood and bone marrow smear</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>Cough, fever, fatigues, splenomegaly, hypotension</td>
<td>TB</td>
<td>HIV+, cave area resident, calcifications</td>
<td>Hepatic biopsy (postmortem)</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>Pallor, hepatomegaly, diarrhea, hypotension</td>
<td>Disseminated TB</td>
<td>HIV+ farm area resident calcifications</td>
<td>Blood and bone marrow smear</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>Cough, hypotension, weight loss, splenomegaly, pallor, fever, sensory alteration</td>
<td>Disseminated TB, PCP</td>
<td>HIV+, farm area resident, perihilar adenopathy</td>
<td>Hepatic biopsy (postmortem)</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>Fatigue, cough, diarrhea, pallor</td>
<td>TB</td>
<td>HIV+, cave area resident, perihilar adenopathy, calcifications</td>
<td>Blood and bone marrow smear</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>Fever, cough, pallor, hepatomegaly</td>
<td>TB</td>
<td>HIV+, calcifications</td>
<td>Bone marrow smear</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>Hypotension, fatigue, cough, fever, splenomegaly, adenopathy</td>
<td>Disseminated TB</td>
<td>HIV+, perihilar adenopathy, calcifications</td>
<td>Blood and bone marrow smear</td>
</tr>
</tbody>
</table>

Note. PCP = Pneumocystis carinii pneumonia; PDH = progressive pulmonary histoplasmosis; TB = tuberculosis; + = positive.

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References
Enterocytozoon bieneusi Infection in Patients Who Are Not Infected with Human Immunodeficiency Virus

Sir—We read with interest the article by Wanke et al. [1], who reported a case of Enterocytozoon bieneusi infection in a patient who was not infected with HIV. We had previously reported a case of E. bieneusi infection in an immunocompetent Turkish girl that the authors did not cite in their review of the literature [2]. Our case was noteworthy for a number of reasons. The affected girl had no signs of cellular or humoral immunodeficiency. Before getting ill, she had played with young goats and lambs in a rural area in Turkey. Because of her protracted diarrheal illness, stool samples were examined for ova and parasites. Dual infection with Cryptosporidium parvum, an established zoonotic parasite, and E. bieneusi was noted.

Concurrent cryptosporidiosis and microsporidiosis had previously been reported in HIV-infected adults and children [3] but had never before been diagnosed in an immunocompetent person. Microsporidial oocysts and E. bieneusi spores were repeatedly detected in several stool specimens. The microsporidial organism was identified as E. bieneusi with use of electron microscopy. Since our article was published, species identification was further confirmed by PCR with use of species-specific primers. Our patient received only symptomatic treatment. The diarrheal illness resolved without specific intervention after 6 weeks, and the patient did not have a relapse for more than 2 years. No cryptosporidial oocysts or microsporidial spores were detected in follow-up stool samples.

Our findings further confirm the necessity of considering E. bieneusi as well as C. parvum as a cause of otherwise unexplained traveler’s diarrhea in immunocompetent individuals. We agree with Wanke et al. that increased awareness of this potential agent of diarrheal illness is required to advance our understanding of the pathogenicity of this parasite, especially in patients who are not infected with HIV.

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References

Effect of Food Intake on the Bioavailability of Itraconazole

Sir—In an excellent review and commentary article in Clinical Infectious Diseases, Piscitelli et al. [1] discussed the many drug interactions of concern when caring for patients with AIDS. The recent introduction of the protease inhibitors compounds this problem even further. One specific interaction addressed by these investigators was the effects of pH on the absorption of the azole antifungal drugs itraconazole and ketoconazole.

The authors state that both of these drugs require a gastric pH of <3.0 for complete dissolution and absorption and that drugs that interfere with this acidity (antacids, didanosine, H₂-histamine blockers, and omeprazole) reduce the overall bioavailability of these azoles. While gastric acidity definitely plays an important role in the absorption of these two agents, the recommendation for administering itraconazole therapy can be somewhat confusing to the reader. Itraconazole, as opposed to ketoconazole, is best administered with food, and apparently the higher the fat content of the food, the better the bioavailability. Zimmerman et al. [2] demonstrated that the bioavailability of itraconazole in a fasting state relative to that when the drug is administered with a full meal was only 54%. Likewise, Barone et al. [3] concluded that the average peak concentration of itraconazole in a fasting state (140 ng/mL) was only 59% that of the concentration when the drug was taken after a standard meal (239 ng/mL).

This important point deserves mention here. Therapy with itraconazole can be enhanced significantly in patients with AIDS and in all other patients if the drug is taken with food. Gastric pH plays a major role if the stomach is empty, and therefore these drug interactions that raise gastric pH can become clinically significant; however, maximum absorption of itraconazole, unlike ketoconazole, requires food to enhance its solubility and transport into the bloodstream.

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References
Inadequate Use of Immunization to Prevent Severe Pneumococcal Infection

Sir—Although the Photo Quiz by Embil et al. [1] describes an interesting case of purpura fulminans due to Streptococcus pneumoniae, the authors missed the major teaching point of the case: that immunization can potentially prevent many severe pneumococcal infections such as the one they described. Although the authors do not mention whether their patient had been immunized, serotype 22F is included in the currently available 23-valent pneumococcal vaccine. Despite conflicting data, there is substantial evidence that the vaccine provides clinical protection for the groups for whom it is recommended. For example, a recent observational study suggested that the vaccine’s efficacy is 75% for immunocompetent adults >65 years old [2]. Another major benefit of the vaccine is that it includes most of the pneumococcal serotypes associated with drug resistance [3].

Pneumococcal vaccine coverage was recently estimated to be 27% in the United States [4] and appears to be dismal in Canada as well [5]. It is difficult to understand why the health care systems of two of the wealthiest nations do not use this simple and inexpensive, albeit imperfect, preventive tool. Cases such as the one described in the Photo Quiz should serve as a reminder that pneumococcal immunization should be provided to all individuals at high risk for pneumococcal infection [6].

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References

Reply

Sir—We appreciate the important comments by Drs. Feola and Rapp regarding the administration of itraconazole with food. While we did not specifically address drug-food interactions, there are several additional examples that are important for patients attempting to take their medications around their daily schedules. In addition to itraconazole, agents such as oral ganciclovir, saquinavir, and atovaquone require administration with a meal for optimal absorption. Conversely, didanosine must be taken on an empty stomach, and indinavir should be taken either on an empty stomach or with a light, low-fat meal.

Unfortunately, these opposing food restrictions may lead to rigid daily routines with small windows of time between eating and proper spacing of medications. These drug-food interactions further emphasize the importance of methodically reviewing with patients the precise schedule of drug administration and educating them to discuss any changes in the schedule or the drugs they are taking (whether or not those drugs have been prescribed) with their health care providers.

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Reply

Sir—We acknowledge Dr. Harrison’s point concerning the importance of the pneumococcal vaccine for preventing invasive Streptococcus pneumoniae infection, as was seen in our patient with symmetric peripheral gangrene [1]. Our patient was over the age of 65 years and was in a group for whom vaccination with the 23-valent vaccine is indicated [2, 3]. However, she had never received immunization with the pneumococcal vaccine, which contains the same serotype of S. pneumoniae (22F) that caused her fatal illness; her case thus represents a missed opportunity for pneumococcal vaccination.

We recently reviewed pneumococcal bacteremia at our teaching hospitals in Winnipeg, Manitoba, Canada [4]. In that study, we found that only 1.7% (9 of 534) of patients with pneumococcal
bacteremia had received the pneumococcal vaccine, although 89% (281 of 314) of the adults and 45% (99 of 220) of the children met the criteria for vaccination. In that paper, we emphasized the importance of pneumococcal vaccination.

Although the issue of pneumococcal vaccination is an important teaching point, our Photo Quiz was about symmetric peripheral gangrene, an uncommon condition that is caused by a variety of organisms in addition to S. pneumoniae.

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**References**


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**Fluoroquinolone Prophylaxis for the Prevention of Bacterial Infections in Patients with Cancer—Is It Justified?**

Sir—Since the relationship between granulocytopenia and life-threatening bacterial sepsis was highlighted by Bodey and colleagues more than 30 years ago [1], the prevention of bacterial infections in neutropenic patients with cancer has remained a seductive but elusive goal. However, elaborate strategies and chemoprophylactic regimens aimed at preventing bacterial infections in neutropenic patients have met with limited success and have had little impact on rates of response to chemotherapy and on overall survival [2]. Because of their broad spectrum of antimicrobial activity, their bioavailability, and their tolerability, fluoroquinolone antibiotics are widely used as prophylaxis for bacterial infections in neutropenic patients in Europe, and they are increasingly being used prophylactically in the United States. Is such a practice justified?

Cruciani and colleagues [3] recently reported two meta-analyses of controlled randomized trials on the use of fluoroquinolones for the prevention of bacterial infections in neutropenic patients. These authors confirm that prophylaxis with fluoroquinolones reduces the incidence of gram-negative infections, including bacteremias, in neutropenic patients. They found that the addition of antibiotics directed against gram-positive bacteria, such as vancomycin, to the fluoroquinolone appeared to reduce the frequency of gram-positive bacteremias. Nevertheless, these prophylactic measures had no effect on infection-related morbidity, as assessed by the rate of febrile episodes, and more important, these measures had no effect on mortality in this population. How are these apparent paradoxes explained?

First, the cause of fever cannot be identified in most febrile neutropenic patients; even among febrile patients with profound neutropenia (neutrophil count, <0.1 × 10⁹/L), <20% will have bacteremia [4]. Second, over the past two decades, there has been a change in the pattern of pathogenic bacterial isolates recovered from patients with microbiologically documented infections. Gram-negative sepsis, which was once the major cause of excess early morbidity and mortality among neutropenic patients, has declined in relative importance in recent years [5]. In many institutions, gram-positive bacteria, particularly coagulase-negative staphylococci, are now the most common cause of bacteremia in neutropenic patients. Given the intrinsic lack of activity of the currently available fluoroquinolones against many gram-positive bacteria, including coagulase-negative staphylococci, oral prophylactic regimens are unlikely to be effective. Last, the prompt initiation of broad-spectrum antibiotic therapy is the single most important factor influencing early mortality and remains the cornerstone of initial management of febrile neutropenic patients, regardless of antibiotic prophylaxis.

The issue of greatest concern regarding fluoroquinolone prophylaxis in neutropenic patients is the increasing evidence that the widespread use of these drugs is associated with the emergence of resistant isolates [6–9]. Patients with cancer who are receiving fluoroquinolone prophylaxis rapidly become colonized with fluoroquinolone-resistant strains of Escherichia coli and coagulase-negative staphylococci [6, 9], and cross-infection of other patients readily occurs in the nosocomial setting [6]. The emergence of fluoroquinolone-resistant clinical isolates has been observed among patients receiving prophylaxis with these agents in a variety of cancer treatment institutions in diverse countries, and clinically significant infections and bacteremic episodes due to fluoroquinolone-resistant isolates have been well documented [6–9]. It is likely that the increasing resistance to fluoroquinolones among isolates recovered from some cancer patients reflects repeated or prolonged selective pressure on endogenous flora over the course of several cycles of chemotherapy, rather than the possibility of dissemination of fluoroquinolone-resistant strains in the general population [10].

Until recently, the use of fluoroquinolone prophylaxis at Memorial Sloan-Kettering Cancer Center (MSKCC; New York) was not widespread. Between 1992 and 1995, >95% of the most frequent gram-negative blood isolates (E. coli, Klebsiella species, Pseudomonas aeruginosa, and Enterobacter species) from patients at MSKCC were susceptible to ciprofloxacin as determined with the National Committee for Clinical Laboratory Standards breakpoints (table 1). Over a 10-month period in 1994, 99% of 262 E. coli isolates from all sites were susceptible to ciprofloxacin. More than 50% of coagulase-negative staphylococci recovered at MSKCC have remained susceptible to ciprofloxacin. These data contrast with those reported from institutions participating in the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer [7, 8].

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Fluoroquinolone Prophylaxis for the Prevention of Bacterial Infections in Patients with Cancer—Is It Justified?
Table 1. Comparison of the frequency of ciprofloxacin-susceptible blood isolates at Memorial Sloan-Kettering Cancer Center (New York) from 1992 to 1995 and at participating institutions of the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer from 1991 to 1994 [7, 8].

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>100 (113)</td>
<td>99 (84)</td>
<td>99 (156)</td>
<td>100 (90)</td>
<td>72 (57)</td>
</tr>
<tr>
<td><em>Klebsiella species</em></td>
<td>96 (91)</td>
<td>100 (76)</td>
<td>96 (105)</td>
<td>98 (61)</td>
<td>92 (13)*</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>98 (55)</td>
<td>100 (46)</td>
<td>95 (66)</td>
<td>98 (48)</td>
<td>92 (13)*</td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td>96 (49)</td>
<td>96 (34)</td>
<td>100 (45)</td>
<td>93 (28)</td>
<td>NA</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>69 (285)</td>
<td>65 (355)</td>
<td>63 (378)</td>
<td>57 (266)</td>
<td>32 (79)</td>
</tr>
</tbody>
</table>

NOTE: Data are percentage (total number of isolates). EORTC = European Organization for Research and Treatment of Cancer; MSKCC = Memorial Sloan-Kettering Cancer Center; NA = data not available.
* Data gathered through end of 1993 only.

It is not surprising that ciprofloxacin is an important part of our therapeutic armamentarium for the empirical treatment of febrile neutropenic patients at MSKCC, particularly those with renal impairment or who are significantly hypersensitive to β-lactam antibiotics. In 1995 alone, our pharmacy dispensed >5,000 doses of intravenous ciprofloxacin to inpatients (these data are from the MSKCC Hospital Infection Committee Antibiotic Use Report—January 1996). While fluoroquinolone prophylaxis may decrease the incidence of gram-negative infections, we are concerned that more widespread use of prophylactic ciprofloxacin will almost certainly lead to the emergence of resistant strains and diminish the drug’s usefulness for the initial treatment of febrile neutropenic patients at our institution.

The headlong rush to embrace dubious strategies aimed at preventing bacterial infections in the granulocytopenic patient has a long and checkered history. The limitations of fluoroquinolone prophylaxis in the current management of neutropenic patients, together with the specter of the emergence of resistant clinical isolates, should give us pause for thought.

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References


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**Reply**

SIR—We appreciate the experience of Murphy and colleagues at Memorial Sloan-Kettering Cancer Center (New York), and we are grateful for their interest in our meta-analysis of fluoroquinolone prophylaxis for bacterial infections in neutropenic patients. Many of the issues raised by Murphy and colleagues are well addressed and important. We agree with their comments, but we also believe that prophylactic strategies aimed at reducing the occurrence of gram-negative infections are worth pursuing. Murphy and colleagues are correct in pointing out that prophylaxis with fluoroquinolones had no effect on mortality in our patient population.
However, the use of survival as the outcome variable for neutropenic patients poses several problems [1]. First of all, it is often difficult to assess the specific cause of death for patients in this population. Moreover, the considerable progress made in the management of fever and neutropenia has resulted in a remarkable decrease in the mortality rate, and this finding has rendered any further decrease impossible or impractical to detect unless several thousand patients are studied [1].

We agree with Murphy and colleagues that a clear beneficial effect of fluoroquinolone prophylaxis with respect to fever-related morbidity is not evident; however, in our main meta-analysis, we found a slight, albeit statistically insignificant, trend toward a reduction in the number of febrile episodes among fluoroquinolone recipients (overall OR, 0.76; 95% CI, 0.56–1.04; P = .09). We believe that this lack of correlation between the reduction in the number of specific infections and in the overall fever-related morbidity could be attributed to the possibility of an increase in the number of unexplained fevers in fluoroquinolone recipients, as has already been suggested [2]. In a recent prospective randomized study, Bow et al. [3] provided evidence for this discrepancy. They showed that the reduction in the number of microbiologically documented infections among recipients of ofloxacin and ofloxacin plus rifampin were offset by a concomitant increase in the number of fevers of unknown origin in the study population. As Murphy and colleagues point out, the cause of fever cannot be identified in a large proportion of febrile neutropenic patients. However, it has been shown that unexplained episodes of fever in granulocytopenic patients receiving fluoroquinolone prophylaxis can be safely managed with strategies that allow early discontinuation of parenteral antibacterial therapy or a reduction in the amount of antibiotic therapy directed against gram-negative organisms [4, 5].

Murphy and colleagues also mention that because of the fluoroquinolones’ intrinsic lack of activity against many gram-positive organisms, oral prophylaxis with the available compounds is unlikely to be effective. However, we would like to emphasize that the results of our analysis do not support a higher rate of gram-positive bacteraemias among fluoroquinolone recipients than among controls. In a subgroup analysis, we found that the risk of developing gram-positive bacteraemia was similar to that found in studies comparing fluoroquinolones with co-trimoxazole (overall OR, 1.22; 95% CI, 0.80–2.04) or with placebo (OR, 0.79; 95% CI, 0.41–1.54).

Apart from fluoroquinolone prophylaxis, other factors may be associated with the increased frequency of gram-positive infections observed at many cancer centers. For instance, in a recent report, Bochud et al. [6] demonstrated that the use of cytosine arabinoside, the presence of mucositis, and the lack of prior antibiotic therapy, but not fluoroquinolone prophylaxis, were independent risk factors for invasive streptococcal disease.

Overall, prophylaxis with fluoroquinolones has, until now, led to a decrease in the occurrence of gram-negative infections. Thus, we entirely agree with the concern expressed by Murphy and colleagues regarding the appearance of many reports of bacteraemia due to fluoroquinolone-resistant *Escherichia coli* among patients with cancer. Emergence of such resistance will likely undermine one (if not the only) of the most attractive features of fluoroquinolones for preventing bacterial infections in patients with cancer.

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**References**


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**Changing the Focus of Infectious Diseases to Pathogen-Specific Therapy**

**SIR**—Casadevall [1] makes a logical argument for changing the tools of infectious disease medicine from broad-spectrum antimicrobials to narrow-target drugs and immune modulators. These interventions, supplemented by improved diagnostic tests, are certainly our best scientific hope for curbing the current epidemics of drug-resistant organisms and tenacious opportunistic infections.

Unfortunately, however, neither logic nor science informs a great deal of clinical practice at present—instead, the alternate disciplines of economics, psychology, efficiency, and law predominate, and for this reason Casadevall’s essay must be seen as remarkably naive.

The fact is that careful microbiological diagnosis is to a great extent no longer possible in many hospitals in the United States because diagnosis without intervention is seen as a waste of time, money, and beds. The emphasis on prompt treatment and discharge is a pressure that is often almost impossible to withstand. Admission for “observation” is a relic of the past; endocarditis is treated for invasive streptococcal disease, and pneumonia is treated without a single sputum culture [2]; sepsis is treated with empirical broad-spectrum agents that are often continued even after a specific diagnosis is made for reasons of convenience and simplicity, not to mention the ease of once-a-day dosing at home. An entire generation of medical students and house officers now functions without easy access to materials for gram staining on the wards. The pace of hospital-based medicine has become too frenetic to support careful bacteriologic diagnostics of the kind Casadevall envisions, no matter how rapidly testing is performed in the future.
Similarly, in outpatient practice careful diagnosis and targeted treatment are difficult ideals to sustain. Time, money, and the physician’s instincts for self-preservation mitigate against them. Patients often cannot or will not return for the two, three, or four visits necessary to nail down a diagnosis. The result is antibiotic therapy for viral syndromes, for “just in case” syndromes, for “cover all bases” syndromes, and for those gray zones between prophylaxis and treatment. All are well-intentioned usages that rapidly promote drug resistance, are common in most outpatient medical practices, and cannot realistically be eradicated.

Most infectious disease clinicians wage a series of constant daily battles to preserve some vestige of reasoned diagnosis and narrow-spectrum therapy in their practices—and daily lose many of those battles. It seems to me that better diagnostics will not change our odds unless the present climate of medical practice changes first. In other words, even if the science to support Casadevall’s attractive vision of pathogen-specific agents is developed, the tide against broad-spectrum agents is unlikely to turn until the rest of the factors now informing medical decision-making—the economics, the psychology, and even the legalities—are addressed as well.

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References


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Reply

Sr:—The present paradigm of empirical therapy with broad-spectrum antimicrobial drugs dates back to the early days of the antibiotic era in the 1940s and 1950s, long before the rise of managed care, malpractice suits, and for-profit medicine. As suggested in my article, the present paradigm is a consequence of the fact that the first truly effective antimicrobial drugs were not pathogen specific and were perceived to have low toxicity.

The arguments presented by Dr. Zuger, although thoughtful and derived from observations on the current sociopolitical milieu of medical practice, are implicitly based on the assumption that present antinfecive practices are safe and cost-effective. There are few if any data to support the cost-effectiveness of empiricism in the treatment of infectious diseases. Cost-benefit analysis would have to include the costs to society of increased antimicrobial resistance and of superinfection to the individual. The concept of safe broad-spectrum antimicrobial therapy may be an oxymoron. It is difficult to argue that drugs that alter human commensal flora are safe when the function of these microorganisms is poorly understood. Hence, the use of the adjective “safe” when referring to broad-spectrum therapy is premature, since an appropriate case control study (i.e., broad-spectrum vs. pathogen-specific therapy) has never been done.

Infectious disease consultants frequently bemoan the fact that many physicians believe they can treat most infections without expert advice by simply giving broad-spectrum therapy. It is worth comparing the practice of infectious diseases to that of oncology. Nonspecific therapy is the mainstay of therapy for both infectious diseases and cancer. However, obtaining a specific diagnosis is fundamental to oncological practice. Empirical antineoplastic therapy is seldom, if ever, given. Diagnostic accuracy is emphasized in the practice of oncology because the toxicity of most antineoplastic drugs precludes their empirical use. The correct oncological diagnosis provides prognostic information and permits optimization of therapy.

In comparison to antineoplastic drugs, antibiotics have a much higher therapeutic index. In the practice of infectious diseases, this fact has facilitated and encouraged empirical antibiotic therapy and diminished the rationale for making a specific diagnosis. In this regard, it is noteworthy that the application of the more toxic antibiotic regimens, such as those that include amphotericin B, usually await a microbiological diagnosis, and such regimens are rarely used empirically.

Practitioners in the disciplines of infectious diseases and medical microbiology find themselves in a vicious cycle: empirical broad-spectrum therapy must be used because early microbiological diagnoses are impossible, but there is little perceived need for rapid diagnosis because pathogen-specific therapy is not available. In the few instances where narrower-spectrum therapy is available, it is frequently withheld because a firm diagnosis has not been made and because the possibility of a pathogen that is not susceptible to the narrow-spectrum drug looms heavily in the minds of practitioners. Unlike most other medical disciplines in which diagnostic information precedes and determines the therapeutic avenue that is pursued, in infectious diseases, diagnostic information is usually first available (even in the best-case scenario) after therapy has begun. This has produced an uncomfortable contradiction in how we train infectious disease consultants: on the one hand, we teach the virtues of narrow-spectrum therapy, but on the other, we do not want the consultants to miss a possible pathogen, especially one that is easily covered by a broad-spectrum regimen.

The discipline of infectious diseases has firm underpinnings in the scientific achievements of the 20th century in the areas of microbiology, cell culture, molecular biology, and immunology. In recent decades our discipline has been undermined by a combination of reduced reliance on scientific methodology, less emphasis on establishing a microbial diagnosis, and the acceptance of empirical broad-spectrum therapy. Dr. Zuger is right. To some degree, society has forced the adoption of empiricism in medical therapy. However, with the rise of resistant microorganisms and superinfection in immunocompromised hosts, we are beginning to experience the consequences of this antiscientific approach. The warning signs that our present approach cannot endure have arisen at a time when
we have an ever-increasing population of patients with impaired immunity who have infections for which we have neither acceptable therapy nor adequate diagnostic modalities. Making a specific diagnosis and administering pathogen-specific therapy would be good medicine and, in all likelihood, cost effective as well.

The idea that the infectious disease community cannot influence the manner in which infections are diagnosed and treated is dangerous and has the potential to uproot our discipline. The argument that we can do nothing to stem the tide of empiricism because of social, economic, and legal pressures reflects complacency and a degree of defeatism. Historically, physicians have been in the vanguard of their communities, frequently revered as the most learned individuals in society and sometimes reviled for their opinions before they could convince others that they were right. We of the infectious disease community have the power to change the therapeutic paradigm, but we must develop a vision and muster the will to implement it.

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