



This Week in the Journal

January 24, 2002

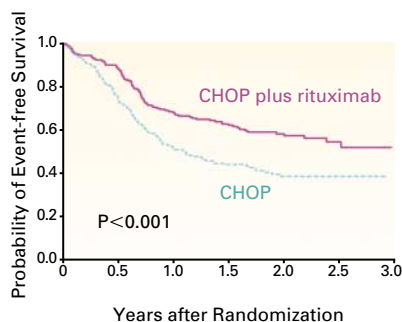
“Documented breakthrough fungal infections occurred in 8 patients receiving voriconazole and 21 patients receiving liposomal amphotericin B.”

Voriconazole as Empirical Antifungal Therapy in Patients with Neutropenia and Persistent Fever

This large, randomized, multicenter trial compared voriconazole, a second-generation triazole, with liposomal amphotericin B as empirical antifungal therapy for 837 patients with persistent fever and neutropenia. The success rates in terms of composite outcome were similar: 26.0 percent with voriconazole and 30.6 percent with amphotericin B. There were fewer breakthrough fungal infections among those treated with voriconazole (1.9 percent vs. 5.0 percent).

Voriconazole may be an acceptable alternative to amphotericin B preparations. There were fewer infusion-related reactions and less evidence of nephrotoxicity with voriconazole. However, many patients taking voriconazole reported transient visual changes or hallucinations.

see page 225 (Perspective, page 222; editorial, page 278; letter, page 289)



Rituximab in Combination with CHOP Chemotherapy for Diffuse Large-B-Cell Lymphoma in Elderly Patients

This trial compared a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with CHOP plus rituximab, a monoclonal antibody against a surface protein (CD20) on lymphoma cells, in elderly patients with diffuse large-B-cell lymphoma. As compared with CHOP alone, CHOP plus rituximab had superior results without an increase in toxicity.

The standard treatment for diffuse large-B-cell lymphoma is CHOP. Results in patients over 60 years old, however, have been unsatisfactory. In this rigorously conducted study, the benefit of adding rituximab was clear-cut. The results are likely to change the management of diffuse large-B-cell lymphoma, the most common form of non-Hodgkin's lymphoma.

see page 235 (editorial, page 280)

“Early detection of deafness is essential for the application of palliative treatments and special education.”

A Deletion Involving the Connexin 30 Gene in Nonsyndromic Prelingual Hearing Impairment

Up to half of patients with congenital autosomal recessive nonsyndromic deafness have mutations in the gene encoding the gap-junction protein connexin 26 (*GJB2*); the rest have had no identifiable mutations. In this study, patients with this form of deafness who had one mutant *GJB2* allele were found to have a novel 342-kb deletion that truncates the gene encoding another gap-junction protein, connexin 30 (*GJB6*). Twenty-two of the 33 subjects studied were heterozygous for both mutations and 2 were homozygous for the *GJB6* mutation.

These data extend our understanding of heritable causes of deafness. Homozygous mutations in either GJB2 or GJB6 or heterozygous mutations in both genes can result in prelingual deafness.

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PERSPECTIVE

Persistent Fever in Patients with Neutropenia

Organ transplantation and major cancer chemotherapy are often associated with prolonged neutropenia (defined as less than 500 polymorphonuclear neutrophils per cubic millimeter), alterations in phagocyte function and lymphopenia due to immunosuppressive agents, and disruption of mucosal defense barriers resulting from mucositis and the presence of indwelling catheters. All these changes can lead to colonization and to invasion by microorganisms — as signaled by fever. More than 30 years ago, the empirical use of broad-spectrum antimicrobial drugs was shown to reduce the frequency of bacteremia and sepsis among

such patients. In the 1980s, it was learned that persistent or relapsing fever during antibiotic treatment was associated with invasive fungal infections, especially with *Candida albicans*. The addition of empirical amphotericin therapy to the antimicrobial regimen reduced the incidence of this complication, and this approach has gained increasing favor.

The Choice of Therapy

Invasive fungal infections are difficult to diagnose, and cryptic foci of infection are common. Disseminated infection continues to be associated with high mortality rates, even with the best supportive care and appropriate antifungal chemotherapy, including the new echinocandins. The current clinical practice is to assume fungal infection may be present and to treat it empirically. A problem with this approach, however, is that empirical amphotericin therapy is frequently associated with infusion-related toxic

effects and commonly also has renal and occasionally pulmonary toxicity. In the past five years, there has been an incremental reduction in the morbidity associated with empirical amphotericin therapy. The new lipid amphotericin products are better tolerated but add substantially to the cost of care. The study by Walsh et al. in this issue of the *Journal* (see pages 225–34) extends this therapeutic approach to a new azole derivative, voriconazole, which compared favorably with liposomal amphotericin B, the lipid amphotericin product with the lowest level of infusion-related toxicity.

Response to Therapy

As in studies of prolonged febrile neutropenia 15 years ago, fever resolved in only about 35 percent of the patients with prolonged neutropenia in this study, indicating the importance of causes of fever other than fungal infections (Table 1). Indirect evidence



Frequency of Uterine Contractions and the Risk of Preterm Delivery

Although randomized clinical trials have failed to show that ambulatory monitoring of contractions is effective in reducing the risk of preterm delivery, such monitoring continues to be used in clinical practice. In this prospective study, 306 women (most of whom were considered to be at high risk for preterm delivery) used a home contraction monitor from 22 to 24 weeks of gestation until delivery or 37 weeks. No threshold frequency of contractions or other clinical measure effectively identified women who delivered before 35 weeks.

Measurement of the frequency of uterine contractions is not useful in clinical practice to predict preterm delivery.

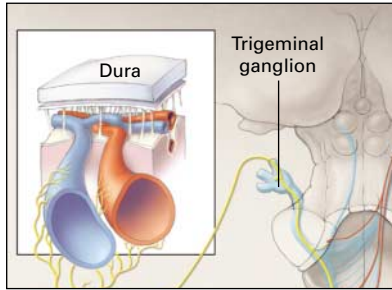
see page 250 (editorial, page 282)

| Possible Causes of Fever | Approximate Frequency in High-Risk Patients (%) |
|---|---|
| Fungal infections susceptible to empirical therapy | 40 |
| Fungal infections resistant to empirical antifungal therapy | 5 |
| Bacterial infections (with cryptic foci and resistant organisms) | 10 |
| <i>Toxoplasma gondii</i> , mycobacteria, or fastidious pathogens (legionella, mycoplasma, <i>Chlamydia pneumoniae</i> , bartonella) | 5 |
| Viral infections (herpesviruses, cytomegalovirus, Epstein–Barr virus, human herpesvirus 6, varicella–zoster virus, herpes simplex virus) and respiratory pathogens such as parainfluenza virus, respiratory syncytial virus, influenzaviruses | 5 |
| Graft-versus-host disease after hematopoietic stem-cell transplantation | 10 |
| Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens) | 25 |

suggests that many fevers in this group of patients are infectious in origin, since 30 to 50 percent of patients have defervescence with a change of antimicrobial therapy. Moreover, as documented in the report by Walsh et al., breakthrough fungal infections, especially with molds such as aspergillus and zygomycetes, also occur. Clinicians caring for immunocompromised patients with neutropenia who are receiving empirical antimicrobial and antifungal therapy must remain vigilant for occult sources of infection or inflammation. Some of the potential pathogens include viruses, especially herpesviruses and respiratory viruses; fastidious organisms

Table 1. Causes of Fever in Patients with Prolonged Neutropenia Who Are Receiving Broad-Spectrum Antibiotics.

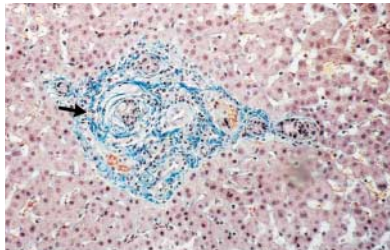
Patients who have received fluconazole prophylaxis have higher levels of resistant fungal infections and lower initial rates of response to empirical antifungal therapy.



Drug Therapy: **Migraine**

Migraine is a common and sometimes debilitating disorder. This review describes the epidemiology, pathophysiology, and preventive and symptomatic treatment of migraine, with special attention to drug therapy with the triptans.

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Case Records of the Massachusetts General Hospital: **Case 3-2002**

A 17-year-old boy was admitted to the hospital with abdominal pain exacerbated by eating and accompanied by nausea. The serum aspartate aminotransferase level was 119 U per liter.

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“Conflicts of interest that cannot be eliminated must be recognized, disclosed fully, and managed.”

Sounding Board:

Maintaining the Public Trust in Clinical Research

Financial conflicts of interest are present in many types of medical research. Until recently there has been no unified effort to address the many problems that arise because of such conflicts. The Association of American Medical Colleges recently approved guidelines for dealing with individual, as opposed to institutional, conflicts of interest. In this Sounding Board article, Kelch outlines the many features of the guidelines and urges their widespread adoption.

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such as legionella; and occasionally *Toxoplasma gondii* and mycobacteria. Defining the cause of the fever and finding the right therapeutic approach for those who do not respond to initial empirical antimicrobial and antifungal therapy remain major problems for clinical research (Table 1).

Use of Prophylactic Antifungal Agents

For patients at high risk for fungal infections, such as those undergoing stem-cell or bone marrow transplantation and preterm infants, prophylactic anti-

fungal therapy has proved to be more effective than preemptive therapy once fever occurs. Fluconazole prophylaxis reduces *C. albicans* infections and increases survival after hematopoietic stem-cell transplantation. A recent report (N Engl J Med 2001;345:1660-6) showed that fluconazole reduced colonization and invasive disease among preterm infants. However, since the advent of routine fluconazole prophylaxis, the frequency of azole-resistant infections has increased. Aspergillosis and zygo-

mycosis now constitute the majority of invasive fungal infections in many transplantation and cancer chemotherapy centers. Whether prophylaxis with the expanded-spectrum azole derivatives or the echinocandins can reduce the morbidity from aspergillus and other mold infections will be the next important part of the story.

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