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VRE Kills!

ABSTRACT & COMMENTARY

***Synopsis**: VRE bacteremia is an independent predictor of death, and appropriate antibiotic therapy is associated with improved survival.*

Source: Vergis E, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. A prospective multicenter study. *Ann Intern Med.* 2001;135:484-492.

VERGIS AND COLLEAGUES AT 4 US ACADEMIC MEDICAL CENTERS and one community hospital performed a prospective observational study of patients with enterococcal bacteremia in order to determine whether vancomycin resistance is an independent predictor of death as well as whether outcome is affected by appropriate antibiotic therapy.

Sixty percent of the 398 bloodstream isolates were *Enterococcus faecalis* and 37% *E faecium*; 35% of the 398 were vancomycin resistant (VRE; MIC ≥ 32 µg/mL), while 2% were intermediate (MIC 8–16 µg/mL). Eight percent of *E faecalis* and 80% of *E faecium* were vancomycin resistant. Eighty-seven percent of *E faecium* were resistant to ampicillin, 60% had high-level gentamicin resistance, and 22% had reduced susceptibility to quinupristin/dalfopristin; linezolid was not tested in this study that ended in March 1977.

Thirty-eight percent of the 147 patients with VRE bacteremia and 49% of those with susceptible enterococcal bacteremia had more than one organism recovered in blood culture ($P = 0.007$). Infection at an abdominal site other than the biliary tract was 4 times more common (20% vs 4%) in the patients with VRE bacteremia compared to those with susceptible isolates. Vascular catheters were the most common site of infection in the former group and the second most common site in the latter. Endocarditis was present in 3% of patients in each group.

Multivariate analysis found that the independent risk factors for VRE bacteremia were receipt of vancomycin within the previous 14

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days, receipt of glucocorticosteroids within the previous 14 days, and the severity of illness (APACHE II score). Risk factors for death within 14 days were the presence of an underlying hematologic malignancy, vancomycin resistance (odds ratio [OR], 2.10; 95% confidence interval [CI], 1.14-3.88; P = 0.02), and severity of illness.

Bacteriological failure was more common with VRE infection (12/16 vs 4/16; P = 0.001). In a multivariate analysis restricted to 208 patients with monomicrobial VRE bacteremia, APACHE II score was a risk factor for 14-day mortality, while receipt of appropriate antibiotic therapy within 48 hours of of the initial positive blood culture was protective (OR, 0.21; 95% CI, 0.06-0.80; P = 0.02).

COMMENT BY STAN DERESINSKI, MD, FACP

This study addresses a central question related to VRE, the answer to which had previously remained uncertain: Does VRE matter? Previous studies have resulted in varying answers. For instance, a case control study identified VRE bacteremia as being associated with greater all-cause mortality than was bacteremia with vancomycin-susceptible strains.[1] However, other studies have found that, although patients with VRE bacteremia do, indeed, have greater overall mortality, vancomycin resistance is not an independent predictor of mortality and is more likely simply a marker of the severity of comorbity.[2]

The paper under review—the senior author of which is Bob Muder, an editor and important contributor to *Infectious Disease Alert*—authoritatively answers the question of the relevance of VRE bacteremia in the affirmative. They have demonstrated that VRE bacteremia and lack of effective antibiotic therapy active against VRE in patients with bacteremia are each independent risk factors for mortality.

These observations have important implications. First, vigorous attempts to prevent patient acquisition of VRE are warranted. This means implementation of effective infection control practices to limit the spread of VRE and control of use of relevant antibiotics that predispose to colonization with VRE, especially vancomycin. It also means that strong consideration be given to screening of high-risk patients for colonization with VRE.

The results of this study also demonstrate that a low threshold for administration of antibiotics likely to be active against VRE must be maintained in the appropriate settings. Thus, in institutions in which VRE are prevalent, the presence of organisms morphologically compatible with enterococci observed on Gram staining of blood culture should trigger the use of an antibiotic likely to be effective against VRE, at least until definitive microbiological data are available. This is likely to be a policy unpopular with those responsible for the pharmacy budget, since the antibiotic most reliably active against VRE is linezolid—according to the *Medical Letter*, in 2000 the average wholesale cost of 600 mg vial was $72 and that of a 600 mg tablet was $53.[3] ❖

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Antibiotics in Acute Exacerbations of Chronic Bronchitis

ABSTRACT & COMMENTARY

Synopsis: *The administration of ofloxacin to patients requiring mechanical ventilation because of acute exacerbations of chronic bronchitis significantly improved outcomes.*

Source: Nouira S, et al. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: A radomised placebo-controlled trial. *Lancet*. 2001;358:2020-2025.

Nouira and colleagues randomized 93 patients with chronic obstructive lung disease admitted to 2 Tunisian hospitals because of acute respiratory failure necessitating mechanical ventilation to receive either ofloxacin or placebo for 10 days. Among the reasons for exclusion from the study were recent (within 10 days) antibiotic use and radiographic evidence of pneumonia. None were receiving corticosteroids. Culture of respiratory secretions yielded "no growth" in 34 patients, while cultures from the other 55 patients yielded a total of 67 organisms. *Haemophilus* spp. accounted for 63% of the Gram-negatives isolated, while streptococci, 38% of which were *Streptococcus pneumoniae*, accounted for all but 1 of the Gram-positives. Two of 8 (25%) of the *S pneumoniae* were resistant to ofloxacin.

There was a decreased number of patients requiring treatment for pneumonia (presumably community acquired) in the first 3 days of hospitalization among the ofloxacin recipients. Nosocomial pneumonia developed after the third hospital day in 10 of 46 (21.7%) patients receiving placebo and 3 of 47 (96.4%) given ofloxacin (P = 0.03). The pathogens isolated from these patients were *A baumanii* (5), *P aeruginosa* (5), *E cloacae* (2), and *K pneumoniae* (1). The duration of both mechanical ventilation and of hospital stay was significantly reduced in the ofloxacin recipients. Finally, the in-hospital mortality was 4% in those randomized to receive ofloxacin and 22% in those assigned placebo (absolute risk reduction 17.5%; 95% CI 4.3-30.7%; P = 0.01).

COMMENT BY STAN DERESINSKI, MD, FACP

Despite their widespread use for this purpose in the United States, the role of bacteria and of antibiotic therapy in acute bacterial exacerbations of chronic bronchitis has remained controversial. In one study, protected brush specimens obtained by bronchoscopy in 54 patients with acute exacerbation of chronic bronchitis requiring intubation obtained within 24 hours after admission yielded no growth in one half.[1] Furthermore, with the exception of fever, the severity of exacerbation was the same in those with and without positive cultures and, among those with positive cultures, the administration of appropriate antibiotic therapy did not affect outcome.

However, a meta-analysis of placebo-controlled trials found a small but statistically significant improvement due to antibiotic therapy in patients with exacerbations of COPD.[2] The authors of that study pointed out that, although the benefit appeared small, it may be of clinical significance, especially in patients with severe underlying airways disease. It should also be noted that these studies examined were performed prior to the availability of the "respiratory quinolones." The fluoroquinolone used in the trial reviewed here is also not among the most potent against respiratory pathogens. In fact, although the number of pneumococcal isolates in this study was only 8, 2 of these were resistant to ofloxacin.

It is possible that antibiotics may provide benefit by mechanisms independent of their antibacterial effect. Thus, both macrolides and fluoroquinolones have been reported to have immunomodulatory activity.[3-5] Most likely, these are not independent benefits; the presence of bacterial pathogens in the sputum of patients with exacerbations is associated with increased sputum concentrations of proinflammatory cytokines.[6]

Among the apparent benefits from antibiotic therapy in the study reviewed here were a reduced number of both early (first 3 days) and late pneumonia. The pneumonias occurring in the first 3 days were presumably community acquired and the administration of ofloxacin most likely prevented the progression of early inapparent pneumonia to a stage at which it became apparent on plain chest radiography. This interpretation is consistent with a previous study demonstrating that plain radiography missed almost one third of pneumonias detectable by high resolution computerized tomography.[7] More extensive reporting of microbiological data may have helped to assess this hypothesis. In contrast, the reduction in incidence of later pneumonias was most likely the result of effective prophylaxis.

This trial appears to clearly demonstrate that antibi-

otic administration is beneficial to patients with ABECB who are ill enough to require assisted ventilation. Further studies are necessary to confirm this observation and to more clearly define the role of antibiotic therapy in patients with less severe illness. ❖

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How Often Should Ventilator Circuits be Changed?

ABSTRACT & COMMENTARY

Synopsis: *A circuit-change interval of 7 days was associated with a lower risk of ventilator-associated pneumonia than a 2-day change interval.*

Source: Han JN, et al. Effects of decreasing the frequency of ventilator circuit changes to every 7 days on the rate of ventilator-associated pneumonia in a Beijing hospital. *Respir Care*. 2001;46:891-896.

HAN AND COLLEAGUES INVESTIGATED WHETHER decreasing the interval between ventilator circuit changes from every 2 days to every 7 days would impact ventilator-associated pneumonia (VAP) rates. All mechanically ventilated patients at Peking Union Medical College Hospital in China were studied over a 21-month period. From March 1998 to February 1999, ventilator circuits were changed every 2 days, and from June 1999 through December 1999, ventilator circuits were changed every 7 days. Nosocomial pneumonia was identified using the criteria of the Centers for Disease Control. In the 2-day-change group, there were 2277 ventilator-patient days and 38 patients developed pneumonia, resulting in a pneumonia rate of 16.7 cases per 1000 ventilator days. The 7-day-change group accumulated 972 ventilator days and 8 patients contracted pneumonia, resulting in a pneumonia rate of 8.2 cases per 1000 ventilator days. The pneumonia rate was significantly lower in the 7-day-change group ($P = 0.007$). To standardize for seasonal variability, results were compared from the same seasonal time frames (June 1998 to December 1998 for the 2-day-change group, and June 1999 to December 1999 for the 7-day-change group), and obtained similar findings; during those periods, pneumonia rates were 24.2 cases per 1000 ventilator days for the 2-day-change group and 8.9 cases per 1000 ventilator days for the 7-day-change group ($P = 0.001$). It is concluded that a circuit-change interval of 7 days was associated with a lower risk of VAP than a 2-day change interval.

COMMENT BY DEAN R. HESS, PhD, RRT

It has become increasing recognized that VAP is unlikely to be related to the ventilator or the ventilator circuit per se. Patients are more likely to develop VAP from secretions aspirated past the cuff of the endotracheal tube than by what is breathed through the endotracheal tube. It is not surprising, then, that the rate of VAP has been reported to be decreased if subglottic secretions are aspirated so that they cannot be aspirated into the trachea. Moreover, reduced rates of VAP have been reported when noninvasive ventilation is used (therefore, no endotracheal tube) compared to invasive ventilatory support.

Over the past 15 years, there have been both observational studies[1-5] and randomized, controlled trials[6-9] reporting the effects of less frequent ventilator circuit changes. As individual studies, no significant differences in VAP have been reported when circuit change intervals have been lengthened. Several studies have now reported no change in VAP rates when circuits are only changed on an at-needed basis. It is interesting to note that no change in VAP rate occurred when inline suction catheters are changed on an as-needed basis rather than on a daily basis.[10] For nearly 5 years, it has been the practice at the Massachusetts General Hospital to change ventilator circuits and inline suction catheters on an as-needed basis (and, of course, between patients).

I recently used the tools of evidence-based medicine and meta-analysis to explore the effects of less frequent ventilator circuit changes on the development of VAP. For the observational studies, the risk of VAP is significantly reduced ($P = 0.04$) for less frequent circuit changes (odds ratio, 0.79, 95% CI, 0.63-0.99). For the randomized controlled trials,6-9 the risk of VAP is also significantly reduced ($P = 0.03$) for less frequent circuit changes (relative risk, 0.70, 95% CI, 0.51-0.96).[1-5] This analysis suggests that there might be a reduction of about 25% in the

risk of VAP with less frequent circuit changes.

The available evidence suggests that ventilator circuits do not need to be changed at frequent intervals. In fact, the evidence suggests that ventilator circuits do not need to be changed at any regular intervals. Adoption of this practice results in important health care cost savings, and might actually decrease the risk for VAP. ❖

Dean Hess is Assistant Professor of Anesthesia, Harvard Medical School; Assistant Director of Respiratory Care, Massachusetts General Hospital, Cambridge, Mass.

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HIV Update

By Carol A. Kemper, MD, FACP

HAART: How Good is Good Enough?

Synopsis: *The "decay" in HIV viremia during the first week of therapy can predict longer-term response and is similar for all responders.*

Source: Polis MA, et al. Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy. *Lancet*. 2001; 358:1760-1765.

The measurement of plasma HIV-1 RNA has provided a useful marker of the risk of HIV progression and response to antiretroviral therapy. The current US Department of Health Human Services guidelines suggest that consideration be given to augmentation of therapy or a change in the regimen if there has not been at least a 0.5-0.75 log reduction by 4 weeks of therapy or at least a 1.0 log reduction by 8 weeks.[1] Polis and colleagues examined the relationship between the kinetics of the virologic response to therapy as early as 1 week after initiation of treatment and virologic outcome, as defined by the DHHS guidelines, at 4 and 8 weeks. Three groups of patients were examined, including 52 children who were protease inhibitor-naïve who received indinavir monotherapy, 38 children who were protease inhibitor-naïve who received ritonavir monotherapy, and 34 adults who received a 4-drug combination regimen of AZT, 3TC, indinavir, and nevirapine. There were no significant differences between the groups with regard to CD4 cell counts and plasma viral load.

A one-exponential model was used to determine the coefficient of decay (k) for each of the 3 groups. All 34 patients receiving HAART had a good response to therapy, as defined by the current guidelines, with a mean decay constant = 0.26 at 1 week. Far fewer patients had a good response to ritonavir monotherapy (34%) or indinavir monotherapy (7.7%). However, for those that were considered responders, the average decay constants were 0.24 and 0.21, respectively, after 1 week of ritonavir or indinavir monotherapy, which were similar to that for patients receiving HAART. In other words, the dynamics of the HIV decay in response to 1 week of treatment was similar for all responders, irrespective of the specific agent, or agents, received.

A cut-off value of $k \geq 0.21$ per day was predictive of a good response to therapy at 8 weeks with a sensitivity of 0.85, a specificity of 0.82, and a predictive value of 0.87. Using the decay constant as a predictive model, there was a 95% or greater chance of virologic failure at week 8 with a viral load response < 0.96 at 1 week of therapy, and a 95% or better chance of success with a viral load response > 1.68 at 1 week of therapy.

Because this analysis was only performed in patients naïve to the type of therapy received, these results may not apply to more ART experienced patients or those who have pre-existing mutations. Theoretically, the initial HIV dynamics for patients with archived mutations who have a predominance of circulating wild-type virus following a treatment interruption may show a similarly immediate response to therapy. However, the decay constant during the first week of therapy may fail to predict the emergence of drug resistant mutants in response to selective pressure by as early as 8 weeks of therapy. Nonetheless, this data may be very useful in patients

who are treatment naïve or who are naïve to the class of drugs received. —CAK

Hepatic Injury to HAART

Synopsis: *Liver function test abnormalities are frequent in HAART but should not lead to discontinuation of therapy in most patients.*

Source: Nuñez M, et al. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2001;27:426-431.

NUÑEZ AND COLLEAGUES IN MADRID, SPAIN, DETERmined the frequency of hepatic injury in 222 HIV-infected treatment-naïve patients beginning their first HAART regimen. Elevations in hepatic transaminases that were considered significant were ≥ 5 times the upper limit of normal, or ≥ 3.5-fold rise above abnormal baseline values. Patients received a variety of antiretroviral regimens either containing a protease inhibitor (43%), an NNRTI (40.5%), or both (15.8%). The groups were similar with respect to stage of HIV, CD4 cell counts, frequency of abnormalities in transaminases, and prevalence of hepatitis C (38%), chronic hepatitis B (5%), or D (2%).

Overall, 21 of 222 (9%) patients experienced severe elevations in hepatic transaminases, the frequency of which was similar for patients receiving a PI, an NNRTI, or both. In patients receiving either a single PI or an NNRTI, severe hepatic injury occurred, in decreasing order of frequency, with ritonavir (18%), saquinavir (14%), nevirapine (11%), nelfinavir (10%), indinavir (9%), and efavirenz (6%). Fortunately, most of these more severe laboratory test abnormalities were transient, and had resolved within 1 to 2 months in 75% of patients despite continuation of therapy. Only 6% of subjects discontinued or changed their regimen because of hepatic toxicity.

In multivariate analysis, the presence of chronic hepatitis C infection was the most significant factor predictive of hepatic injury, followed by alcohol abuse and older age. Elevations in hepatic enzymes were 3 times as frequent in patients with underlying HCV infection vs. HCV-negative patients (16% vs 5%). They were also 3 times more frequent in patients with chronic HBV infection. The shift in the paradigm for initiating HAART at lower CD4 cell counts provides a window of opportunity to first treat chronic HCV infection, thereby possibly reducing the potential for subsequent HAART treatment toxicity. In addition, Nuñez et al point out that more attention to alcohol consumption when starting HAART, and more aggressive alcohol counseling, may further reduce the potential for toxicity. Although more severe liver function test abnormalities are frequent (6-18%) in patients initiating HAART, they do not often require a change in therapy, and are resolved in most patients without serious sequelae. —CAK

Enhanced Susceptibility to Amprenavir

Synopsis: *"Hypersusceptibilty" and enhanced virologic response to amprenavir-based antiretroviral therapy may be associated with the presence of an N885 mutation in the protease gene.*

Source: Zachary KC, et al. Human immunodeficiency virus type 1 hypersusceptibility to amprenavir in vitro can be associated with virus load response to treatment in vivo. *Clin Infect Dis*. 2001;33:2075-2077.

SEQUENCING OF PROTEASE INHIBITOR THERAPY IN response to the emergence of resistant HIV virus is critical to the success of an overall treatment strategy for patients with HIV infection. Recognized patterns of cross-resistance in patients failing a protease inhibitor are helpful in estimating the likelihood of response to therapy, although the specific pattern of susceptibility for any one individual is difficult to predict from treatment history alone without the benefit of genotypic and phenotypic resistance assays. Phenotypic resistance data also provide important information on the magnitude of susceptibility, including whether an isolate may have enhanced susceptibility to a particular agent ("hypersusceptibility"), which may have important therapeutic implications.

Data suggest that the N88S protease gene mutation, which is occasionally observed in patients failing indinavir and nelfinavir, may confer enhanced susceptibility to amprenavir.[2] Zachary and colleagues report a case of an HIV-positive man who had previously failed first indinavir and then nelfinavir for 2 years, with evidence of amprenavir hypersusceptibility and a remarkably sustained virologic response to an amprenavir-containing regimen. Following failure to nelfinavir, a genotypic resistance assay revealed multiple thymioine associated mutations (TAMs) plus several protease mutations (L10I, I64V, V77I, and N88S). The corresponding phenotype indicated the following fold changes: abacavir (2.1), D4T (1.7), amprenavir (0.1),

ritonavir (0.6), and nelfinavir (14.6). [Fold change = the concentration of drug required to inhibit viral replication by 50% (IC50) compared with control (wild type virus) (IC50 patient/IC50 control), (PhenoSense™ HIV Assay, ViroLogic Inc., South San Francisco, Calif)]. Based on this information, the patient received a combination of D4T, abacavir, amprenavir 750 mg b.i.d., and ritonavir 400 mg b.i.d. with a resulting sustained virologic response for more than 2 years (HIV RNA < 50 copies/mL).

Based on this individual's history of failure to first indinavir and then nelfinavir, he was likely to have significant cross-resistance among the protease inhibitors, although prior mutations as the result of indinavir failure may have been "archived" and not phenotypically evident. In our study of patients failing ART therapy who had mostly been treated with nelfinavir- or indinavir-containing regimens,[3] the majority retained virus with a drug-sensitive phenotype (FC ≤ 2.5) to amprenavir or saquinavir (lobucavir susceptibility was not assessed at that time). HIV isolates from 55 patients failing nelfinavir commonly remained susceptible (FC < 2.5) to ritonavir (84%) and amprenavir (93%), whereas HIV isolates obtained from 22 patients failing indinavir less often remained susceptible to ritonavir (36%) and amprenavir (54%). Furthermore, we found that in patients failing nelfinavir, the mean fold change in IC50 to ritonavir was 2.3, and to amprenavir was 1.1.

A cut-off fold change smaller than 0.4 is believed to confer hypersusceptibility, although the clinical significance of this finding is still being explored. In addition, based on an increasing amount of data, a fold change of > 1.7 has been proposed for D4T resistance. Therefore, this man had evidence of significantly enhanced susceptibility to amprenavir but reduced susceptibility to D4T. Although the contribution of each PI to the regimen in this case is not known, the administration of ritonavir-boosted amprenavir in the presence of known hypersusceptibility, possibly associated with the N88S mutation, may have been important to the long-term success of this regimen. ❖

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CME Questions

6. Which of the following was an independent protective factor for mortality in patients with monomicrobial VRE bacteremia in the report by Vergis and colleagues?

a. Receipt of appropriate antibiotic therapy within 48 hours of the initial positive blood culture
b. High APACHE II score
c. Underlying hematologic malignancy
d. Receipt of corticosteroids

7. Which one of the following statements is correct?

a. Daily ventilator circuit changes are associated with a reduced risk of pneumonia when compared to weekly changes.
b. Every other day ventilator circuit changes are associated with a reduced risk of pneumonia when compared to weekly changes.
c. The development of pneumonia during mechanical ventilation is most often the result of inhalation of bacteria inhaled through the breathing circuity.
d. Weekly ventilator circuit changes are associated with a reduced risk of pneumonia when compared to every other day changes.

8. Which one of the following statements is correct?

a. The rate of decrease in viral load measured 1 week after the initiation of HAART in treatment-naive patients is predictive of more sustained virological response.
b. The rate of decrease in viral load measured 1 week after the initiation of HAART in treatment-experienced patients has been demonstrated to be predictive of more sustained virological response.
c. US guidelines recommend a change in antiretroviral therapy if, after 4 weeks of therapy, the decrease in HIV viral load is less than 0.1 $\log_{10}$.

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to Infectious Disease Alert. Send your questions to: Rob Kimball—Reader Questions, *Infectious Disease Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374, or via the Internet by sending e-mail to robert.kimball@ahcpub.com. We look forward to hearing from you. ❖

In Future Issues:

Computer Decision Support for Antibiotic Prescribing

UPDATES

By Carol A. Kemper, MD, FACP

Anthrax Vaccine Program Bombs

Source: ProMED mail post, Jan. 9, 2002. www.promedmail.org.

The federally sponsored effort to provide postexposure anthrax vaccine to more than 5100 individuals potentially exposed to the deadly organism last fall has met with significant resistance and disinterest. Lacking union support, postal workers uniformly eschewed vaccination, including those workers at the New Jersey facility that experienced 2 deaths and 2 non-fatal cases of infection. Only 152 people, many of whom are congressional staffers, agreed to participate in the program. The controversial program was intended to thwart concerns regarding the possible risk of "reactivation" of anthrax despite receipt of prophylactic antimicrobials. In addition, adherence to the prophylactic regimen was amazingly poor. Reports suggest that half of those receiving prophylaxis did not complete their course of therapy. ❖

Voriconazole vs. Liposomal Ampho in Neutropenic Fever

Source: Walsh TJ, et al. *N Engl J Med.* 2002;346:225-234.

Voriconazole, an experimental second-generation azole with a broader spectrum of in vitro activity than fluconazole, is likely to be available for use in the United States within the next couple of months. This open-label, international multicenter study by the Mycoses Study Group compared the efficacy of voriconazole vs. liposomal amphotericin B (LA-B) in patients with neutropenia and fever. A total of 837 patients were randomly assigned (1:1) to voriconazole or LA-B. Eligible patients were at least 12 years old, had received chemotherapy for various malignacies (mostly leukemia and lymphoma) or bone marrow transplants, were neutropenic and had persisting fever (> 38 C), despite at least 4 days of systemic antibacterial therapy. Patients with active fungal infection at the time of enrollment were excluded, although 13 patients in the voriconazole group and 6 patients in the LA-B group were diagnosed with fungal infection within 24 hours of randomization. Voriconazole was administered as a loading dose (6 mg/kg Q12 hrs) and then 3 mg/kg Q12 hrs; LA-B was administered 3 mg/kg daily. The dosages of both drugs could be increased as needed in the event of fungal infection, and were continued for at least 3 days beyond neutrophil recovery or up to 12 weeks.

Success was measured by the use of a composite score based on 5 different outcomes, including resolution of fever, prevention of breakthrough fungal infection, response to treatment in those with documented fungal infection at entry, premature discontinuation of therapy for toxicity or lack of response, and survival. Based on these 5 measures, the overall success of voriconazole vs. LA-B therapy was 26.0% vs. 30.6% (P = NS). Breakthrough fungal infection was significantly less frequent in patients receiving voriconazole (1.9%) vs. LA-B (5%) (P = .02). In patients at especially high risk for fungal infection (relapsed leukemia or allogeneic transplants), breakthrough fungal infection occurred in only 1.2% of voriconazole patients and 9.2% of LA-B patients. However, in patients with documented fungal infection at entry to study, there was a trend toward better response in patients receiving LA-B than voriconazole (4 of 6 vs 6 of 13;P = .63). There was no difference in mortality between the 2 treatment groups.

Patients receiving LA-B were more likely to experience infusion reactions and renal insufficiency, whereas patients receiving voriconazole more commonly experienced abnormal vision and visual hallucinations (4.3%), most of which were transient. In addition, 22% of patients receiving voriconazole were able to switch over to the oral formulation, allowing quicker discharges from the hospital in some patients. Voriconazole appears to be an excellent alternative to LA-B for the empiric treatment of fever and neutropenia. In addition, the availability of an oral formulation will greatly add to our ability to treat many fungal infections without the need for parenteral access or hospitalization. ❖

Ebola Spreads to the Congo

Source: ProMED-mail post, Jan. 24, 2002. www.promedmail.org.

An outbreak of ebola hemorrhagic fever, which has been brewing for weeks in Eastern Gabon near Mekambo, has spread into the adjacent Republic of Congo. As of January 20, at least 42 cases have been confirmed, resulting in 34 deaths—11 of which have occurred in the Congolese villages bordering Gambon. Officials admit that the situation was initially not well contained as angry villagers in Mekambo scared off international medical workers. This part of the French Equatorial Africa is rich in oil, timber, and minerals, but political turmoil and graft continue to hamper access to medical care. ❖