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Tropical Pulmonary Eosinophilia

ABSTRACT & COMMENTARY

Synopsis: *Tropical pulmonary eosinophilia must be considered in patients with asthma-like symptoms and significant eosinophilia, who have resided in areas endemic for lymphatic filariasis.*

Source: Boggild AK, et al. Tropical Pulmonary Eosinophilia: A Case Series in a Setting of Nonendemicity. *Clin Infect Dis.* 2004;39:1123-1128.

BOGGILD AND COLLEAGUES DESCRIBE 17 PATIENTS WITH TROPICAL pulmonary eosinophilia seen at Toronto General Hospital Tropical Disease Unit over a 13-year period. All were of South Asian ancestry, with approximately half having emigrated to Canada, where they had resided for a median of 18 months, from the Indian subcontinent, while the other half had lived in Guyana. They had resided in Canada for a median of 18 months.

The patients had been ill for as long as 60 months (median, 6 months), and had seen a median of 2 physicians each prior to referral to the Tropical Disease Unit. Shortness of breath, nocturnal cough, and wheezing were present in 88%. Three-fourths had received a diagnosis of asthma, and 15 patients received treatment for presumed asthma, including prednisone in 41%, with little or no improvement.

Chest X-ray was performed in 14 patients; 4 were normal and 10 showed interstitial patterning. Eleven of 12 had abnormal pulmonary function studies. All had eosinophilia, ranging from 2.8 x 109 to 53.3 x 109 eosinophils/L, and all had elevated serum IgE levels. Anti-filaria antibody titer, performed at the NIH in Bethesda, MD ranged from 1:4096 to1:32,678.

All patients were treated with diethylcarbamazine (DEC) for a minimum of 21 days, and follow-up information was available in 15; all but one of whom had resolution of symptoms. However, pulmonary function abnormalities returned to normal in only 1 of 4 patients.

COMMENT BY STAN DERESINSKI, MD, FACP

Tropical pulmonary eosinophilia (TPE) occurs in < 0.5% of

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individuals infected with the agents of lymphatic filariasis, *Wucheria bancrofti*, and *Brugia malayi*.[1] In contrast to other forms of filariasis, microfilariae cannot be detected in peripheral blood, although they have been found in lymph nodes and other tissue. This is consistent with TPE being the result of a hypersensitivity reaction to filarial antigens, with parasitic gamma-glutamyl transpeptidase being a likely allergen.[2] Lung histopathology in the early stages of the illness are characterized by an eosinophilic alveolitis. With chronicity, however, this is gradually replaced by a fibrotic reaction.

Up to one-fifth of patients have a normal chest X-ray. Pulmonary function studies within the first month of onset of symptoms may demonstrate abnormalities dominated by obstruction to airflow, but as the disease continues, a restrictive pattern emerges, frequently leading to a mixed testing pattern.

Table 1

Diagnostic Criteria—Tropical Pulmonary Eosinophilia.

- History of residence in an area endemic for lymphatic filariasis.
- Peripheral blood eosinophilia of > 3000/mm^3.
- Elevated serum IgE levels of > 1000 IU/mL.
- Increased anti-filaria antibody titer.
- Absence of detectable microfilaria in peripheral blood.
- Clinical response to diethylcarbamazine.

The diagnosis of TPE depends on residence in areas endemic for lymphatic filariasis, which include many tropical and subtropical regions of South America, Africa, Asia, and Oceania. Additional criteria are listed in *Table 1*. In addition to the examinations indicated there, all patients should have stool examination for helminthes, and a sensitive test for chronic strongyloidiasis, such as an antibody test.

The differential diagnosis includes other causes of eosinophilic lung disease, including migrating intestinal parasites, such as *Ascaris*, *Strongyloides*, and *Ancylostoma*, as well as zoonootic infestations, such as dirofilariasis and toxocariasis. Other diagnostic considerations include drug reactions, allergic bronchopulmonary aspergillosis, vasculitides (especially Churg-Strauss syndrome, Wegener's granulomatosis, and polyarteritis nodosa), chronic eosinophilic pneumonia, and idiopathic hypereosinophilic syndrome.

Because of the progressive fibrosis that may occur in the absence of treatment, early diagnosis and intervention is critical to assuring an optimal outcome. The treatment of choice remains DEC. ■

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S. aureus, Erythrocyte Hemolysins, and Heme Iron—A Nice Little Package

ABSTRACT & COMMENTARY

Synopsis: S. aureus *preferentially utilizes iron of heme origin, whose availability is the consequence of erythrocyte hemolysins produced by the organism.*

Source: Skaar EP, et al. Iron-Source Preference of *Staphylococcus aureus* Infections. *Science.* 2004;1626-1628.

SKAAR AND COLLEAGUES AT THE UNIVERSITY OF Chicago subcultured iron-starved *S. aureus* into a chemically-defined medium supplement with equimolar amounts of [5^4Fe] hemin and [5^7Fe] transferrin, in order to determine which iron source was preferred by this pathogen. Analysis of organisms sampled over time demonstrated a significant (up to 5-fold) enrichment in the ratio of heme Fe to transferrin Fe, as compared to the ratio in the nutrient medium. Skaar et al also identified a heme transport system in *S. aureus* consisting of 3 genes with homology to known heme transporter genes of *Yersinia enterocolitica* and *Corynebacterium diphtheriae*.

COMMENT BY STAN DERESINSKI, MD, FACP

Sequestration of iron is an important element of the host defense against bacterial infection, for the very reason that infecting pathogens require iron for growth and virulence. Since free iron is present in almost non-existent concentrations in plasma, the 2 major potential host sources of iron are heme and transferrin, the transporter protein. Bacteria acquire iron from their environment by expression of receptors specific for heme or transferrin iron, and/or by secretion of siderophores that can remove iron from transferrin with subsequent importation of the iron-siderophore complex into the bacterium. Heme, on the other hand, is itself sequestered within erythrocytes, and is not directly available. *S. aureus*, however, produces a number of hemolysins that disrupt function of the erythrocyte membrane, leading to cellular lysis and release of hemoglobin. Although the mechanisms are not strictly defined, heme is then released from its globin partner, allowing its importation into the bacterial pathogen, with release of iron from heme.

Further analysis by Skaar et al found that this iron of heme origin is critical to the virulence of experimental *S. aureus* infection during its early phase. ■

Treatment of Invasive Aspergillosis: To Combine or Not to Combine?

ABSTRACT & COMMENTARY

***Synopsis**: A retrospective review found evidence indicating improved survival when voriconazole was used in combination with caspofungin than when voriconazole was used alone in the treatment of patients with invasive aspergillos failing therapy with amphotericin B.*

Source: Marr KA, et al. Combination Antifungal Therapy For Invasive Aspergillosis. *Clin Infect Dis.* 2004; 39:797-802.

MARR AND COLLEAGUES RETROSPECTIVELY EVALUATED the outcomes of salvage therapy in 47 patients with probable or proven invasive aspergillosis who failed treatment with amphotericin B. Eighty-seven percent had received a hematopoietic stem cell transplant, most of which were allogeneic. Seventeen patients had received amphotericin B deoxycholate as primary therapy, while 30 received either amphotericin B lipid complex or liposomal amphotericin B. Salvage therapy was initiated either because of progressive infection, intolerance, or renal dysfunction. From 1997 until February 2001, voriconazole alone was used for salvage (31 patients), while after that date, caspofungin was given together with voriconazole (16 patients). Progressive infection was the reason for salvage in 71% of the monotherapy group and in 93% of those given combination therapy.

Overall, 3-month mortality after the diagnosis of aspergillosis, as well as after initiation of salvage therapy, was greater in those who received the combination with a hazard ratio (HR) of 0.43 (95% CI, 0.17-1.1; P = 0.50). Multivariate analysis also found that combination therapy was associated with lesser mortality than monotherapy (HR, 0.27; 95% CI, 0.09-0.78; *P* = .008). This apparent benefit was also present when only allogeneic stem cell recipients were considered. There was no evidence of greater toxicity with combination therapy.

COMMENT BY STAN DERESINSKI, MD, FACP

Voriconazole has become the antifungal agent of choice for patients with invasive aspergillosis on the basis of a randomized trial demonstrating its association with improved survival, when compared to treatment with amphotericin B deoxycholate.[1] Caspofungin has been demonstrated in a non-randomized trial to have efficacy as salvage therapy with this high lethality infection. In vitro evidence has demonstrated no antagonism, but has found frequent synergy between caspofungin and several other antifungals, including voriconazole.[2] Caspofungin and voriconazole demonstrated apparent antimicrobial synergy in a rodent model of invasive aspergillosis, although the 100% survival with voriconazole alone could not be improved upon.[3] Synergy has been demonstrated in experimental pulmonary aspergillosis between caspofungin and ravuconazole.[4] In addition, there are no pharmacokinetic interactions between azole voriconazole and caspofungin, and no increase in toxicity appears to result from their use in combination. These characteristics have made the use of these drugs in combination in an attempt to improve survival in invasive aspergillosis a tempting prospect.

Others have reported their experience with the use of caspofungin with either voriconazole or amphotericin in patients with variable, and often, difficult to interpret results.[2] In a retrospective study of patients with hematologic malignancy who had received salvage therapy for definite or probable invasive aspergillosis, the response rates for 38 patients who received an amphotericin B lipid formulation was 5%, while it was 20% for caspofungin recipients (n = 15), and 14% for those who received both drugs (n = 42) ($P > 0.1$).[5] A review by the same group of patients who had received either posaconazole or caspofungin plus an amphotericin B lipid formulation for salvage therapy, found no significant difference in outcome.[6]

This single center study evaluated a very small number of patients and was retrospective, non-randomized, and non-concurrent. As indicated above, the limited experience reported from some other centers is not confirmatory of these results. Nonetheless, the study is highly provocative, and most of all, provides the rationale for a randomized clinical trial. Such a trial, however, is likely to be prohibitively costly in dollars and time because of the very large sample size required.

It must be remembered that the only thing we know about the treatment of invasive aspergillosis from randomized clinical trials, is that voriconazole is superior to amphotericin B deoxycholate as primary therapy. We do not know the relative efficacy of voriconazole vis a vis lipid formulations of amphotericin B, caspofungin, or even itraconazole. It is possible that one or the other of these are superior to voriconazole. Thus, there remains a great

deal of work to be done.

The story, however, does not end at the issue of 2 drug combinations. In vitro synergy with caspofungin against *Aspergillus* spp. has been reported with sulfamethoxazole,[7] flucytosine, flucytosine plus amphotericin, and with flucytosine plus voriconazole.[8] Subinhibitory concentrations of amphotericin B have an additive effect against *Aspergillus* spp., when added to caspofungin together with either voriconazole or ravuconazole in vitro.[9]

The major downside to combination therapy of caspofungin with voriconazole is increased cost. We may never, unfortunately, have the randomized trial data necessary to conclusively resolve the issue of combination therapy for invasive aspergillosis. In the meantime, it is undeniable that the use of these drugs in combination should be considered in the therapy of patients with invasive aspergillosis failing amphotericin B. The data, however, provide us no insight with regard to the currently more common situation, salvage therapy in patients failing voriconazole monotherapy. To complicate matters further, some clinicians are using the combination of voriconazole and caspofungin for primary therapy as well. All of this is a demonstration that much current decision making in the management of patients with life-threatening fungal infections remains more an art than a science. ■

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Corticosteroids in Tuberculous Meningitis

ABSTRACT & COMMENTARY

Synopsis: *Adjunctive dexamethasone therapy of adolescents and adults with tuberculous meningitis was associated with improved survival, but not with reduced severe disability among those who did survive.*

Source: Thwaites GE, et al. Dexamethasone For the Treatment of Tuberculous Meningitis in Adolescents and Adults. *N Engl J Med.* 2004;351:1741-1751.

THWAITES AND COLLEAGUES RANDOMIZED 545 adults and adolescents with tuberculous meningitis to receive, in addition to standard antituberculous therapy for 9 months, either dexamethasone (4 weeks for mild disease, 8 weeks for more severe illness) or placebo. HIV coinfection was present in 16.1% of the placebo and 19.9% of the dexamethasone group. Of the 170 *M. tuberculous* isolates tested, 58.2% were susceptible to all first line drugs, and 5.9% were resistant to at least isoniazid and rifampin; resistant isolates were approximately equally distributed between the treatment groups.

Adjunctive dexamethasone administration was associated with a significantly reduced risk of death (31.8% vs 41.3%) RR, 0.69; 95% CI, 0.52-0.92; $P = 0.01$). There was, however, no significant intergroup difference

with regard to the development of severe disability among survivors, which was observed in 18.2% in the corticosteroid and 13.8% in the placebo arms. Relapse occurred in 15% of dexamethasone recipients and 17.7% of placebo recipients ($P = 0.42$). The 98 patients who were HIV infected had higher mortality than the rest of the study participants, but without a significant difference between treatment groups.

Adverse events occurred more frequently among placebo recipients than those assigned dexamethasone (79% vs 68%; $P = 0.005$), but with similar rates of discontinuation. Eight placebo recipients, one of whom died, developed severe hepatitis, while no dexamethasone recipient did so ($P = 0.004$).

COMMENT BY STAN DERESINSKI, MD, FACP

The results of this study present a mixed bag—adjunctive dexamethasone was associated with improved survival in this study of adolescents and adults, but no reduction in the proportion of survivors with severe disability. A metaanalysis of previous randomized, controlled trials had found evidence of improved survival in children but not adults given adjunctive corticosteroids, and also pointed out the many limitations of those studies.[1] The reduction in severe adverse events seen with corticosteroid administration has been previously observed in patients with pulmonary tuberculosis.

The lack of benefit observed in the HIV-infected patients is confounded by the small number enrolled and the fact that, in contrast to the rest of the study population, deaths were spread throughout the 9 months of observation. The latter suggests that many of the deaths were not directly related to the tuberculous infection. It is likely that few of these patients in Vietnam had access to effective antiretroviral therapy.

The relapse rate of approximately 16% in this study was quite high, raising questions about the therapy, including compliance. In a recently reported study, none of 591 patients who received more than 6 months of treatment relapsed, although 2 of 131 (1.5%) of those treated for only 6 months did so.[2]

The unequivocal diagnosis of tuberculous meningitis remains difficult. In this study, at study entry, only approximately one-sixth had definite (positive acid fast smear) or probable tuberculosis (one or more of: compatible chest X-ray, positive smear at site other than CSF, or clinical evidence of other extrapulmonary tuberculosis). When culture is also taken into account, however, 34% had microbiologic evidence of tuberculous meningitis. Furthermore, in a high prevalence setting such as Vietnam, it is likely that most of the rest also had *M. tuberculosis* as the etiology of their meningitis. While nucleic acid amplifications tests such as PCR were not used for diagnosis in this study, their use would likely have been only of somewhat marginal benefit, given their reported overall sensitivity with CSF of only 56%.[3]

At least one other agent with putative anti-inflammatory properties has been evaluated in patients with tuberculous meningitis. A placebo-controlled, randomized trial in children was aborted because of excess toxicity and mortality in those given thalidomide.[4]

This study provides clear evidence of survival benefit in adolescents and adults with tuberculous meningitis, as well as for a reduction in antituberculous drug related adverse events. The lack of benefit with regard to severe disability among survivors, however, gives one pause. Nonetheless, adjunctive corticosteroids will remain part of the therapeutic recommendations for treatment of tuberculous meningitis in children, adolescents, and adults. ■

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Chemotherapy-Induced Hepatitis B Reactivation—A Preventable Complication

ABSTRACT & COMMENTARY

Synopsis: *Chronic carriers of hepatitis B receiving immunosuppressive chemotherapy have about a 30-50% risk of reactivation of their HBV infection, which is associated with significant morbidity and mortality.*

Source: Idilman R, et al. *J Viral Hepat.* 2004;11:141-147.

I WAS RECENTLY ASKED TO EVALUATE A 53-YEAR-OLD man diagnosed with Stage IV follicular lymphoma,

who had just completed 4 cycles of chemotherapy with prednisone, vincristine, cyclophosphamide, and rituxan in September. He presented to the hospital in late October with progressive hepatitis. He was originally from Ethiopia, and had emigrated to the United States 23 years ago. He was married, had a 13-year old son, and his last trip to Africa was about 5 years ago.

On admission, laboratory studies showed a total bilirubin 1.6, AST 1544, ALT 2578, INR 1.6, and a PTT of 19.5. His bilirubin peaked during hospitalization at 23.3, with an AST 1603 and ALT 2537. Laboratory studies were also remarkable for 22% eosinophilia, a positive HBs antigen, a positive schistosomiasis IgG titer, and evidence of *Strongyloides stercoralis* larvae in stool specimens. He was known to be PPD positive, but had not received INH for latent TB. A chest radiograph was negative. Biopsy of the liver showed acute hepatitis with bridging necrosis, and prominent eosinophils and lymphocytes. Of note, he had not previously been tested for hepatitis B, although had complained of intermittent right upper quadrant discomfort for 4 years, with previously normal LFTs.

What was the cause of this man's hepatitis?

COMMENT BY CAROL A. KEMPER, MD

Perhaps 2 things: Although the evidence for disseminated strongyloidiosis is at least suggestive, it is unlikely to result in severe hepatocellular necrosis, the prominent eosinophilia seen on hepatic biopsy suggests that either the strongyloides or a drug reaction may have at least contributed to the acute hepatocellular dysfunction. More likely, however, he has acute reactivation of occult hepatitis B infection.

Chronic carriers of hepatitis B receiving immunosuppressive chemotherapy, have about a 30-50% risk of reactivation of their HBV infection, which is associated with significant morbidity and mortality. It is now recommended that patients be screened for HBV surface antigen prior to receipt of immunosuppressive chemotherapy. However, this may not be sufficient in some patients: One report described reactivation HBV leading to hepatic failure in a man receiving immunosuppressive therapy for a hematologic malignancy; HBs Ag was initially negative, but gradually became positive during the course of chemotherapy.[1] Idilman and colleagues suggested that studies for HBs Ag may not be sufficient, and HBc Ab may be additionally used for screening patients.

Two studies have demonstrated the value of prophylactic lamivudine (3TC) in the prevention of chemotherapy-induced HBV reactivation. Idilman et al used 3TC vs no therapy in patients with hemato/oncological malignancy receiving chemotherapy. None of 8 patients receiving 3TC for 1 year following completion of chemotherapy developed reactivation HBV infection. In contrast, 5 of 10 patients receiving no antiviral prophylaxis developed reactivation of HBV infection (one 12 months after receipt of chemotherapy). No significant morbidity or mortality was observed in either group, and the 3TC was well tolerated. In a second study, retrospective review of 35 HBs Ag-positive patients receiving chemotherapy found that none of the 16 patients who received 1 year of prophylactic antiviral therapy with 3TC developed reactivation hepatitis, compared with 7 of 19 patients (37%) who did not. Five of these latter patients later died of complications of hepatitis, despite administration of antiviral therapy for acute hepatitis.

Prophylactic antiviral therapy with 3TC can prevent reactivation of HBV in patients receiving immunosuppressive chemotherapy. Anecdotal evidence suggests that patients with reactivation hepatitis should receive antiviral therapy, especially if they are immunocompromised. We elected to treat our patients with adefovir and ivermectin, and he had prompt improvement in his liver function studies within 1 day. ■

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Does Tuberculosis Increase HIV Load?

ABSTRACT & COMMENTARY

Synopsis: *Poor prognosis for HIV-infected individuals after TB may be due to preexisting high HIV load, rather than to the TB event itself.*

Source: Day JH, et al. Does Tuberculosis Increase HIV Load? *J Infect Dis.* 2004;190:1677-1684.

THIS IS AN OBSERVATIONAL COHORT STUDY THAT compared HIV patients who acquired TB or bacterial pneumonia with comparison of those 2 groups of patients without TB or bacterial pneumonia, respective-

ly. The site of the study was Free State, South Africa between 1999-2002. The regional hospital was the sole source of secondary care. Patients were prophlylaxed for PCP using cotrimoxazole, with CD4 cell counts that were < 200cells/uL. Antiretroviral therapy was not used in the clinic for these patients.

Pneumonia or TB was diagnosed either at hospital admission by a study team or at subsequent clinic visits. TB was diagnosed by culture or by response at 2 month to anti-TB therapy. The bacterial pneumonia group were diagnosed as having a chest film typical of bacterial pneumonia and had "culture of bacteria that typically cause pneumonia."

The control group was diagnosed with HIV without TB 3 months before study entry or 3 months after the final samples of the study had been drawn, and the same was true for bacterial pneumonia, except with a 1 month window before study entry and final blood draws.

The results compared 2 relatively small groups. The TB group had 30 TB patients, with 56 controls, and the pneumonia group had 14 patients and 35 controls. The TB group, but not the pneumonia group, showed a significant HIV load rise, however, both groups started with viral loads around log (10) = 4.5. The TB group increased from log (10) 4.73 to 5.02, and the pneumonia group from 4.47 to 4.51.

The most interesting finding was a CD4 cell decrease per year of 53.0 for the TB group, versus 6.7 for the control group. Amazingly, 778 other participants enrolled in the study for a minimum of 6 months, and actually had a CD4 decrease of only a 17.4/yr. On the other hand, the HIV load difference was not different in patients who were stratified by CD4 count above and below 200.

COMMENT JOSEPH F. JOHN, Jr., MD

The impression that TB, like some other opportunistic infections, accelerates the progression of HIV disease, is not supported by this study. From this study, it is more likely to conclude that higher viral loads, at the outset of TB disease, are more attributable to poor outcome. These data also show that HIV viral load is likely independent of CD4 count as a risk factor for TB. Day and colleagues further extrapolate that a difference, as seen in this study, though small, of 0.25 log (10), would amount to a difference of about 1 year in the time to progression of severe HIV disease or death. This extrapolation is based on pre-ART data, but is interesting, and stresses the fact that these patients have NO antiretroviral therapy on board, and thus, are susceptible to the full effect of unabated and uncontrolled viral loads.

The implication of this study, especially for the developing world and South Africa where there are high rates of HIV and TB, is that treatment of HIV should be paramount. By intervening in the natural history of HIV using ART, whatever role TB plays in hastening severe disease and death, can be minimized. The world waits as countries like South Africa, with some outside help, mobilize to make ART a reality for many of their HIV-infected population. ■

Increase in the Reservoir of Community-Acquired MRSA, With Implications for Hospital-Acquired Infection

ABSTRACT & COMMENTARY

Synopsis: *Over a 7-year period, there was a dramatic increase in the isolation of community-acquired MRSA in the San Francisco area. Molecular typing showed movement of community-acquired strains into hospitals.*

Source: Carleton HA, et al. Community-Adapted Methicillin-Resistant *Staphylococcus aureus* (MRSA): Population Dynamics of an Expanding Community Reservoir of MRSA. *J Infect Dis*. 2004;190:1730-1738.

COMMUNITY-ACQUIRED MRSA (CO-MRSA) HAVE BEEN isolated with increasing frequency over the past decade. One possible explanation is that many strains of CO-MRSA are in fact nosocomial MRSA (NO-MRSA) that have entered into the community. However, a number of strains of CO-MRSA have genetic and phenotypic characteristics that differentiate them from NO-MRSA. True CO-MRSA typically carry the type IV staphylococcal chromosomal cassette (SCC) mec element that confers beta-lactam resistance. NO-MRSA usually carry the type II SCCmec element which encodes beta-lactam resistance, but typically carries resistance to other unrelated antimicrobials as well. Thus, CO-MRSA tend to be susceptible to multiple non-beta-lactam agents, whereas NO-MRSA are multi-resistant.

Carleton and colleagues studied the molecular epidemiology of MRSA in the hospital and community over a 7-year period. They collected isolates from a university hospital in San Francisco, as well as affiliated long-term care, correctional, and outpatient facilities. They performed molecular typing, including SCCmec typing, pulsed field gel electrophoresis (PFGE), multilocus restriction-fragment typing (MLRFT), and multilo-

cus sequence typing (MLST) on a random sample of nearly 500 isolates. Between the years 1998 and 2002, they found a 4-fold increase in the incidence of MRSA. The incidence of NO-MRSA (defined as isolation of MRSA > hours after hospital admission) during the period was relatively stable. There was a large and statistically significant increase in the incidence of CO-MRSA, however. Concomitantly, there was a parallel increase in the rate of isolation of type IV SCCmec-bearing strains, with most of these belonging to 4 predominant genotypes. These 4 genotypes were predominantly associated with community-acquired disease (76.9%), rather than disease acquired in the hospital (19.4%) or long-term care facility (3.7%). One of these strains accounted for 30% of CO-MRSA; after it became established in the community it was isolated from cases of NO-MRSA. By the end of the survey period, it accounted for 14% of NO-MRSA.

Carleton et al noted that some of the isolates from NO-MRSA cases belonged to genotypes associated with community-acquired disease, but bore type II SCCmec, and were resistant to multiple non beta-lactam antimicrobials. Type II SCCmec isolates were largely confined to the hospital, indicating limited ability to spread in the community.

COMMENT BY ROBERT MUDER, MD

CO-MRSA appears to be increasing in frequency in numerous geographic areas. A number of epidemiologists have identified prior admission to a hospital, or other contact with the healthcare system as a risk factor for CO-MRSA. Such infections are not truly community- acquired, but rather community onset. Carelton et al took advantage of a major genetic difference between nosocomial and community-acquired strains. Strains of nosocomial origin in the United States usually contain type II SCCmec, which typically encodes resistance to multiple antimicrobials in addition to beta-lactam resistance. Strains of community origin typically contain SCCmec IV which does not. One explanation is that the genetic cost of carrying these additional determinants makes type II SCCmec poorly adapted to the community setting, in which multiple antimicrobials are less likely to be encountered. Thus, they tend to stay within healthcare facilities, where heavy antibiotic pressure confers on them a survival advantage.

Carelton et al were able to show that the increase in MRSA noted in their community was largely due to an increase in community-acquired strains. Further, the community strains were able to enter the hospital and displace strains of nosocomial origin. Some of these community strains appeared to adapt to the hospital environment by acquiring the SCCmec II genotype, conferring additional resistance determinants.

These findings have important implications for both public health and for control of nosocomial infection. CO-MRSA is clearly an emerging public health problem that is occurring independently of what is happening in hospitals. The expected spread of NO-MRSA into the community does not seem to have materialized. On the contrary, CO-MRSA strains appear to be moving into the hospital and acquiring additional resistance determinants. This is likely to complicate attempts at control of NO-MRSA to a considerable degree. ■

CME Questions

22. Which of the following is correct?

a. Tropical pulmonary eosinophilia is caused by the agent of loa loa.
b. The diagnosis of tropical pulmonary eosinophilia requires the detection of microfilariae in peripheral blood smears.
c. Patients with tropical pulmonary eosinophilia may have normal chest X-rays.
d. The treatment of choice of tropical pulmonary eosinophilia is etanercept.

23. Which of the following is correct?

a. Caspofungin and voriconazole are antagonistic against *Aspergillus* spp.
b. The toxicity of caspofungin and voriconazole is synergistic.
c. Marr and colleagues reported that the combination of voriconazole and caspofungin was associated with improved survival, when compared to voriconazole alone in patients receiving salvage therapy for invasive aspergillosis.
d. Caspofungin and voriconazole have important pharmacokinetic interactions.

24. Which of the following is correct?

a. Thalidomide reduces mortality in children with tuberculous meningitis.
b. Adjunctive dexamethasone reduces mortality in adolescents and adults with tuberculous meningitis.
c. Adjunctive dexamethasone recuses the incidence of severe disability in adolescent and adult survivors of tuberculous meningitis.
d. Nucleic acid amplification tests, such as PCR, have an almost 100% sensitivity in the diagnosis of tuberculous meningitis.

25. Which of the following is correct?

a. Most malaria deaths in the United States are due to *P. vivax*.
b. Patients with suspected *P. falciparum* malaria must be given intravenous quinine sulfate.
c. Malaria smears should only be examined in reference laboratories for initial examination in order to avoid the unnecessary administration of antimalarial therapy.
d. Quinidine is effective in the treatment of *P. falciparum* infection.

26. Which of the following statements is true?

a. Community-acquired MRSA infection is usually the result of strains that originated in hospitals.
b. Community-acquired MRSA strains do not circulate in hospitals.
c. Community-acquired MRSA isolates are usually susceptible to non-beta lactam anti-staphylococcal agents.
d. Community and hospital isolates of MRSA are genetically identical.

27. In individuals who have HIV what major factor determines the effect of TB on disease progression?

a. Other opportunistic infections
b. HIV viral load at the time of acquisition of TB
c. Severity of TB
d. CD4 cell count at baseline

Answers: 22. (b); 23. (c); 24. (c); 25. (d); 26. (c); 27. (b)

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In Future Issues:

HPV Vaccine

UPDATES

By Carol A. Kemper, MD, FACP

Flu Shortage—Who Cares?

Isn't it amazing how people don't want something until they cannot have it. This year's nationwide shortage of flu vaccine, caused by manufacturing problems at the Chiron facility in England, has generated more bellyaching, finger pointing, and outright panic than is justified—it makes one almost wonder if the shortage was just an attempt to get people to want the flu shot. Let's put this in perspective. Every year, hundreds of thousands of doses of flu vaccine go unused and are destroyed, as the Public Health Service and healthcare providers urge patients to get vaccinated. At best, ~65% of the elderly and at risk patients receive the flu vaccine. Last year, when flu vaccine was offered free of charge to patients in our hospital, about 30% refused.

People need to understand some basic information about the flu shot: vaccination against the flu offers only partial (~70%) and temporary protection against a few flu viruses. In contrast, the natural immunity one develops from actual infection is much broader and more durable, lasting an estimated 3 to 5 years following infection. Every year, influenza experts meet to determine the composition of the following year's influenza vaccine, which amounts to little more than a crapshoot. The vaccine usually contains 3 strains of virus: 2 type A strains and 1 type B strain. For the 2003-2004 flu season, the trivalent influenza vaccine included A/Panama/2007/99 (H3N2)-like antigen, A/New Caledonia/20/99(H1N1)-like antigen, and B/Hong Kong/330/2001-like antigen. Last year, it was estimated that only 10-14% of those who received the flu vaccine were protected against the strain of flu they were exposed to. This year's vaccine is identical.

I've overheard perfectly healthy 30-year olds complaining they cannot get vaccine—although they look puzzled when you ask them if they've ever received one before. One mother was furious that her 4- year-old was denied a vaccine by her pediatrician—until I pointed out to her that that was a good thing; it meant her child was healthy and not at high risk for complications of the flu. Interestingly, the mother desperately explained the child really need the vaccine because she'd had the flu last year—and did not understand the child probably already had much better immunity than any vaccine could provide.

Most likely, there will be enough vaccine for those high-risk patients who may benefit the most from vaccination. The print and mogul media have a responsibility to quell peoples' fears of epidemics and shortages, provide the public with accurate information about the flu shot, and encourage healthy people to pass on vaccination. ■

Can Cutaneous Zoster Result in Airborne Transmission?

Source: Suzuki K, et al. *Clin Infect Dis*. 2004:189:1009-1012.

A frequent question, when a patient with localized cutaneous zoster is admitted to hospital, is the appropriate infection control precautions. Are standard and contact precautions sufficient? Which immunosuppressed patient requires respiratory isolation? Do patients with AIDS and zoster require respiratory isolation? And, can a floor nurse make this assessment?

Using a highly sensitive PCR, Suzuki and colleagues assessed the presence of VZV DNA in swab specimens from cutaneous dressings, throat swabs, and from air purifiers in 13 patients hospitalized with cutaneous zoster, who were placed in respiratory isolation with air purifiers. Nine of the patients had moderate cutaneous involvement, and one had severe disease with extensive dermatomal involvement. At least 4 of the patients were considered immunosuppressed, 2 of whom were receiving steroids. All of the patients received parenterally administered acyclovir, beginning anywhere from day 1 to day 5 of hospitalization.

Patients were randomly assigned to conventional gauze bandages or a hydrocolloid dressing (Duoactive, Bristol Meyer Squibb). Specimens were obtained every day between day 4 and day 7 of their outbreak. In the gauze group, VZV DNA was detected in 22 of 23 samples taken from the surface of dressings, in throat specimens of 4 patients (11 of 23 specimens), and in the air filters from all 6 patient rooms (13 of 23 samples). Interestingly, air filter specimens were positive in 2 of the patients with negative throat swabs. In contrast,

in patients whose lesions were covered with hydrocolloid dressing, none of the specimens from dressings or the air filters were positive, although 2 patients had positive throat swabs.

These data suggest that even localized cutaneous zoster, in immune competent hosts, can result in airborne spread of virus, although whether the viral particles detected by these molecular means is sufficiently viable to cause infection, is not known. Hydrocolloid dressings appear much more effective than standard gauze dressings in preventing passage of viral DNA particles through dressings, and may reduce the risk of airborne spread of virus. ■

If It Was a Bear. . . Part II

ProMED-mail post November 5 and November 8, 2004; www.promedmial.org

Last month, it was postulated in this column that brown bears, which rarely attack people, are less likely to harbor oral anaerobes than their meat-eating counterparts, possibly because their diet consists mainly of berries, grasses, and seeds.

Anaerobes aside—authorities in central Romania have declared a rabies alert, and sealed off a forested area, following a brown bear that savaged 11 people in the area. Several people were just out foraging in the woods that day, one of whom was gathering mushrooms. Seven people were severely injured, and one has died. The bear was shot and killed by hunters several hours following the attack, and tests confirmed the bear had rabies the next day. A total of 97 persons who had contact with the victims have been vaccinated and/or received immune globulin. The area is currently sealed off for 15 km around the radius of the attack, with a 3rd degree quarantine—meaning that all animals in the zone are being monitored and vaccinated for rabies—including oral vaccine for all foxes.

Breakthrough Fungal Infection With Voriconazole

Source: Imhof A, et al. *Clin Infect Dis.* 2004;39:743-744.

Over the years, we've seen sequentially more resistant breakthrough fungal infections in immunosuppressed patients receiving prophylactic antifungal therapy. When fluconazole became available, the rate of breakthrough *Aspergillus* infection increased. With the increased use of itraconazole, and now voriconazole in immunosuppressed patients, we are just beginning to see an increase in azole-resistant yeasts and zygometes infection.

During a 5-year period, 13 of 139 patients (9%) who had undergone stem cell transplantation, who were receiving voriconazole at the Fred Hutchinson Cancer Research Center, developed breakthrough fungal infections. Four patients developed fungemia due to *Candida glabrata* resistant to voriconazole (MICs > 1 mcg/mL), 6 patients had zygomycetes, and 2 patients developed infection from either *Aspergillus ustus* or *A. terreus*. The patients were generally receiving voriconazole for suspected or documented Aspergillus infection, although a few were receiving it for primary prophylaxis. Caspofungin was used in combination with voriconazole in 2 of the patients, one of whom developed infection with both *C. glabrata* and rhizopus.

The emergence of voriconazole-resistant yeasts has been increasingly documented. Many of these infections tend to be *C. glabrata*, which has lower rates of response to salvage treatment with voriconazole. In addition, voriconazole has limited activity against the pathogenic zygomycetes. As more immunocompromised patients receive voriconazole, fewer infections due to *Aspergillus* are likely to occur, but the rate of breakthrough infection with some of the nastier zygomycetes, for which there is often little effective therapy, will increase. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

ACE Inhibitors and Receptor Blockers: Which is Inferior?

The first head-to-head comparison study of an ACE inhibitor and an angiotensin receptor blocker, to assess renoprotective effects in type 2 diabetes, has shown that the drugs are comparable in their benefit. It has been known for more than a decade that ACE inhibitors prevent progression of microalbuminuria in type 2 diabetes, out of proportion to their blood pressure lowering effects. It has also been shown that angiotensin receptor blockers are renoprotective, but it has not been shown that the drug classes are equivalent in their benefit. The Diabetics Exposed to Telmisartan and Enalapril Study Group (DETAIL study) was designed in 1996 to compare the 2 drugs in 250 patients with type 2 diabetes and early nephropathy. Patients were randomized to 80 mg of telmisartan or 20 mg enalapril daily. The primary end point was the change in Glomerular Filtration Rate (GFR) during 5 years of the study. Secondary end points included annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; the rates of end stage renal disease and cardiovascular events; and all-cause mortality. After 5 years, the change in GFR was -17.9 mL/min with telmisartan and -14.9 mL/min with enalapril (the 95% CI, -7.6- 1.6 mL/min). The data suggest that telmisartan is not inferior to enalapril in providing long-term renotection in patients with type 2 diabetes (*N Engl J Med*. 2004;351:1952-1961). In the same issue of the *Journal*, researchers in Italy compared the ACE inhibitor trandolapril plus verapamil, trandolapril alone, verapamil alone, or placebo in patients with hypertension and type 2 diabetes, and normal urinary albumin excretion. The end point was the development of persistent microalbuminuria. Over 3 years of treatment, the percentage of those patients developing microalbuminuria were: trandolapril 6%, trandolapril plus verapamil 5.7%, verapamil alone 11.9%, and placebo 10%. The authors conclude that trandolapril plus verapamil and trandolapril alone decrease the incidence of microalbuminuria to similar extent, whereas the effectiveness of verapamil alone was similar to that of placebo (*N Engl J Med*. 2004; 351:1941-1951).

The Infection Risk of Acid-Suppressing Drugs

Ever since cimetadine was first marketed in 1977, physicians have been concerned about the risk of infection associated with acid-suppressing drugs. Now researchers from the Netherlands have shown that concern is warranted, by demonstrating a link between acid-suppressing drugs and community-acquired pneumonia (CAP). Utilizing the Integrated Primary Care Information database in the Netherlands between 1995 and 2002, incidence rates for pneumonia were calculated for those exposed to acid-suppressive drugs and those who were unexposed. A case control analysis was conducted, nested in a cohort of incident users of acid-suppressive drugs, with up to 10 controls matched to each case for practice, year of birth, sex, and index date.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com.

The main outcome was CAP. The incidence rates for pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 in 2.45 per hundred person-years, respectively. The adjusted relative risk for pneumonia among persons currently using a proton pump inhibitor (PPI), compared with those who stopped using a PPI, was 1.89 (95% CI, 1.36-2.62). The risk for current users of H2 antagonists was 1.63 (95% CI, 1.07-2.48). The authors conclude that acid-suppressive drugs, especially proton pump inhibitors (PPIs), are associated with an increased risk of pneumonia, and suggest that these drugs should be used with caution, and at the lowest possible doses in patients who are at risk for pneumonia (*JAMA.* 2004;292:1955-1960). An accompanying editorial points out the biological plausibility of the findings and suggest that, while acid-suppressive drugs are indicated for a wide variety GI conditions, long-term, chronic use of these drugs should always be balanced with patient safety (*JAMA.* 2004;292:2012-2013).

Is Rosuvastatin As Safe As Other Statins?

Rosuvastatin (Crestor), AstraZeneca's entry into the high potency statin market, has not achieved marketshare comparable to Pfizer's atorvastatin (Lipitor) or Merck's simvastatin (Zocor). This, despite the facts that the drug is very potent and AstraZeneca has priced the drug 15-20% lower than Lipitor. Some physicians remember the cerivistatin (Baycol) withdrawal from the market, and may be concerned regarding the highest doses of rosuvastatin, especially since European regulators issued a warning earlier this year about the drug. New postmarketing data suggest, however, that rosuvastatin is as safe and well-tolerated as other statins. The records of 12,400 patients who received 5-40 mg/day were reviewed, representing 12,212 continuous patient years. In fixed dose trials with comparator statins, 5-40 mg of rosuvastatin showed an adverse event profile similar to those for 10-80 mg of atorvastatin, 10-80 mg of simvastatin, and 10-40 mg of pravastatin. Clinically significant increases in liver transaminases were uncommon (≤ 0.2%) in all groups. Myopathy with creatine kinase increases > 10 times the upper limit of normal, with muscle symptoms occurring in ≤ 0.03 % of patients who took rosuvastatin at doses of 40 mg or less. Proteinuria, at the same doses, was comparable to the rate seen with other statins as well. There were no deaths and no cases of rhabdomyolysis in patients on 40 mg or less of rosuvastatin. The authors conclude that rosuvastatin was well-tolerated, and out of safety profile similar to other commonly statins (*Am J Cardiol.* 2004;94:882-888).

Which Estrogen Preparation is the Safest?

Is esterified estrogen safer than conjugated equine estrogen? At least with regard to venous thrombosis, the answer may be yes, according to a recent study. Group Health Cooperative in Washington State, a large HMO, switched their patients from conjugated equine estrogen (CEE) to esterified estrogens (EE) in 1999. Records of perimenopausal and postmenopausal women were studied between January 1995 and the end of 2001. The primary outcome was the risk of first venous thrombosis, in relation to current use of either estrogen with or without a progestin. There were 586 cases of venous thrombosis identified. Compared with women not currently using hormones, current users of EE had no increase in venous thrombotic risk (odds ratio, 0.92; 95% CI, 0.69-1.22). Women taking CEE however, had an elevated risk (OR, 1.65; 95% CI, 1.24-2.19). Comparing users of the 2 estrogens, current users of CEE had an odds ratio of 1.78 for venous thrombosis, compared to users of EE (95% CI, 1.11-2.84), and higher doses of CEE were associated with a higher risk. Among all estrogen users, concomitant use of progestin was associated with an increased risk, compared to use with estrogen alone (OR, 1.60; 95% CI, 1.13-2.26). The authors conclude that conjugated equine estrogen, but not esterified estrogen, is associated with an increased risk of venous thrombosis (*JAMA.* 2004; 292:1581-1587). While the authors acknowledge that these data need to be replicated, the study raises the interesting question of the differences between various estrogen preparations and the potential risks associated with them, especially when noting that conjugated equine estrogen was the only estrogen preparation used in the Women's Health Initiative.

FDA Actions

Serono has been given approval to market recombinant human luteinizing hormone (Luveris) for the treatment of infertility in women. The drug, which was granted orphan status, has been available in more than 60 countries for several years.

The FDA and Centocor have issued a warning to health care professionals about the increase risk of lymphoma associated with inflixamab (Remicade) in patients with rheumatoid arthritis and Crohn's disease. The warning applies to all tumor necrosis factor blocking agents. The drugs are associated with a 1 in 1400 risk of lymphoma, according to MedWatch, the FDA's safety information program.