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'Mad Deer Disease': Another Reason to Become a Vegetarian?

ABSTRACTS & COMMENTARY

Synopsis: *The emergence of chronic wasting disease, a transmissible spongiform encephalopathy in North American cervids, raises concern about potential transmission to humans, as has occurred elsewhere with bovine spongiform encephalopathy and vCJD.*

Sources: Wisconsin deaths may be first instance of 'mad deer' disease transmission to humans. Reuters Medical News. July 31, 2002; Antonio Regalado. Spreading 'mad deer' plague leaves US scientists baffled. *The New York Times*. May 2002; http://www.maddeer.org/plague.html; http://www.madison.com/captimes/opinion/column/guest/23628.php; Brian McCombie. Who is to blame for mad deer? *The Progressive*. August 2002; www.progressive.org/August%202002/mcco0802.html; Mad deer disease spreads across the USA—Hunters are starting to worry. *Outdoor Life*. Oct 1999; http://www.organicconsumers.org/Meat/maddeerusa.cfm; Brian McCombie. Stop the madness. Malady threatens Wisconsin's elk, deer and, ultimately, people. *Isthmus Newspaper*. Madison, WI, July 2000. http://www.madison.com/captimes/opinion/column/guest/23628.php.

THREE DEER HUNTERS, AGED 30 AND YOUNGER, FROM UTAH, Oklahoma, and Maine died of Creutzfeldt-Jakob disease (CJD) during the period of 1997-2000. This raised an alarm since the national occurrence of CJD is approximately 1 per million and generally affects older people. Because of the common variable of consuming deer meat, autopsies were performed to confirm the diagnoses. The results of the autopsies demonstrated that the 3 had died of sporadic CJD and not the more "virulent" form of variant CJD (vCJD). More recently, the Centers for Disease Control and Prevention (CDC) is helping the Wisconsin health department review the cases of 3 hunting partners who died in the 1990s (2 in 1993 and 1 in 1999) of rare brain disorders.

vCJD, also known as "mad cow disease," is responsible for somewhere between 43 to more than 100 deaths in Europe; numbers vary depending on the source of information that is reviewed. Concern over vCJD is that it has a shorter incubation period and affects peo-

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INSIDE

ple at an earlier age.

Chronic wasting disease (CWD) is a variant of the mad cow disease that has been reported in deer and elk. CJD and CWD are classified as transmissible spongiform encephalopathy (TSE). The "infectious" agent associated with TSE is a small, relatively stable protein known as a prion. Prions are normally folded in a loopy pattern resembling a corkscrew, but when they unfold, they can cause other prions to change shape. This triggers the chain reaction that ultimately results in destruction of tissue, typically in the brain.

CWD was first noticed in a Colorado research facility in 1967 and slowly spread among wild deer and elk in Nebraska and Wyoming. It has also been found in captive elk in Colorado, Kansas, Montana, Nebraska, Oklahoma, Saskatchewan, and South Dakota. In Colorado at least 15% of some wild herds are affected. Because it has also been found in animals imported into Wisconsin, authorities there recommend following the lead of Montana which placed a moratorium on the importation of all game farm animals. Testing of animals in Wisconsin was negative in 1999, but in 2001, 3 animals tested positive for CWD.

The Food and Drug Administration has gone on record saying that mad deer disease is not a threat in the United States. Dr. Ermias Belay of the CDC told a panel investigating this that the cases "suggest a possible relationship with CWD," but investigations found "no strong evidence of a causal link" with the patients' illnesses. The FDA has now suggested, however, that significant efforts be undertaken to remove the CWD from the US deer and elk populations.

COMMENT BY THOMAS G. SCHLEIS, MS, RPh

Tom Thorn, a Wyoming state veterinarian, when discussing CWD stated that "You cannot say with 100 percent certainty that it won't transmit to people, but there is no evidence that it will transmit to people." That essentially sums up the wealth of knowledge we have about mad deer disease—maybe it's a threat, maybe it's not.

The list of TSEs is becoming extensive. We have scrapie in sheep, mad cow, mad deer, mad elk, CWD, CJD, and vCJD.

Having grown up in Wisconsin where the 4 favorite pastimes are eating, drinking, watching television, and hunting, I can only imagine the effect this information has had in that state. Wisconsin has approximately 100 deer and elk farms, and it is big business with elk calves selling for around $1,500 and bull breeding garnering as much as $20,000. Farms sell venison; and the velvet that peels from new elk antlers are considered an aphrodisiac in Asia, selling for $17.00 an ounce. Hunting guides can also package tours that cost from $1,000 to $10,000 depending on the ultimate "prize." This is a billion dollar industry with hunters killing close to half a million deer annually. With no mandatory reporting required for animals suspected of CWD, the disease could go unchecked for years.

What is important here is that this phenomenon be thoroughly investigated. Lab studies have suggested that CWD could theoretically infect humans by converting human prion proteins into their deadly form in a lab dish after exposure to CWD prions. If we have learned anything from mad cow disease, it is that denial can be deadly. With mad cow disease, it was years before British officials were convinced that there was a causal link and appropriate action was taken. It is vital that we do not allow the same mistake to happen here. ■

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Clostridium neontale: A New Nosocomial Pathogen

ABSTRACT & COMMENTARY

Synopsis: *A clonal outbreak of a newly identified organism, Clostridium neonatale, occurred in association with necrotizing enterocolitis in a neonatal ICU.*

Source: Alfa MJ, et al. An outbreak of necrotizing enterocolitis associated with a novel clostridium species in a neonatal intensive care unit. *Clin Infect Dis*. 2002; 35(Suppl 1): S101-S105.

An outbreak of 8 cases of necrotizing enterocolitis occurred over a 2-month period in a Canadian neonatal intensive care unit. All affected infants had bloody stool, and 6 of 8 had typical x-ray findings of gas in the bowel wall (pneumatosis intestinalis). Seven of the infants were receiving parenteral antibiotics at the time of onset. Blood cultures from 3 infants and stool cultures from 2 infants grew a bacillis identified as *Clostridium clostridioforme* by a rapid anaerobe identification panel. Because the facility had never isolated this species of Clostridia previously, and because *C clostridioforme* has not been previously associated with necrotizing enterocolitis, the isolate was sent to a national reference laboratory. It appeared to be a previously unidentified species and was given the tentative name "*Clostridium neonatale*." Alfa and colleagues performed a point-prevalence study in the NICU and adjacent intermediate care nursery. Five of 24 neonates had rectal swabs positive for *C neonatale*. Pulsed field gel electrophoresis analysis of bacterial DNA demonstrated clonality among blood, stool, and rectal swab isolates.

COMMENT BY ROBERT MUDER, MD

Necrotizing enterocolitis is a disorder that primarily affects low birthweight neonates (< 1500 g). Intestinal perforation, peritonitis, and bacteremia are frequent; the mortality rate is 20-40%. The pathogenesis of necrotizing enterocolitis is incompletely understood. Mucosal ischemia due to hypoxemia, hypotension, or endotoxemia is thought to be a major contributing factor. The disease may occur in outbreaks; these have been associated with a variety of bacterial species including staphylococci, several *Clostridium* species, *E coli*, *Klebsiella*, and *Pseudomonas*. Some investigators postulate a role for both ischemia and bacterial pathogens.

The outbreak reported by Alfa et al is distinctive first for the association with a previously unidentified bacterial species, and the occurrence of disease in relatively mature neonates; 6 of 8 were > 35 weeks gestation. There was a fairly significant reservoir of asymptomatic intestinal carriage of *C neonatale*. Patient-to-patient transmission was highly likely based on the finding of clonal identity among isolates. Clostridia species are spore formers; the spores are highly resistant to a variety of disinfectants and can persist in the environment for prolonged periods of time. Clostridia spores are not killed by the waterless alcohol-based hand disinfectants that are being used with increasing frequency. Thus, if *C neonatale* is indeed a causative agent of necrotizing enterocolitis, it has characteristics favoring its persistence and spread in the hospital environment. ■

And the Best PI is . . . ?

ABSTRACT & COMMENTARY

Synopsis: *A protease-inhibitor-based regimen containing lopinavir-ritonavir provided more durable antiviral efficacy than a similar regimen containing nelfinavir in treatment-naïve HIV-infected patients.*

Source: Walmsley S, et al. *N Engl J Med*. 2002;346: 2039-2046.

Walmsley and colleagues conducted a double-blind, placebo-controlled, randomized, clinical trial comparing standard-dose nelfinavir (750 mg thrice daily) with one of the newer protease inhibitors, lopinavir-ritonavir (400-100 mg twice daily), in combination with d4T and 3TC, in 653 treatment-naïve HIV-infected patients. The major study end points included the proportion of patients with undetectable plasma viral load (HIV PCR < 400 copies) at 24 weeks of therapy, and the loss of virologic efficacy at 48 weeks of therapy. The 2 groups were remarkably similar at entry to the study, with an average HIV viral load of about 4.9 logs and an average CD4 count of about 260. About 20% of the study participants were female. Both regimens were surprisingly well tolerated and only 3.4% of those randomized to receive lopinavir-ritonavir and 3.7% of those receiving nelfinavir discontinued the study drug because of intolerance.

At week 24 of therapy, a greater proportion of patients treated with lopinavir-ritonavir (79%) had undetectable viral loads (< 400 copies) compared with those receiving the nelfinavir-based regimen (71%) ($P < .05$). By week 48 of study, the proportion of patients with undetectable viral loads (< 400 copies) in the lopinavir-ritonavir vs. nelfinavir groups was less (75% vs 63% respectively; $P <$

.001). Similarly, by week 48, the proportion of patients with < 50 copies HIV RNA in the lopinavir-ritonavir vs. nelfinavir groups was only 67% vs. 52%, respectively (P < .001). The Kaplan Meier estimates of the sustained virologic response at week 48 for the 2 groups were, respectively, 84% vs. 66% (hazard ratio of 2.0).

COMMENT BY CAROL A. KEMPER, MD, FACP

HIV clinicians have long debated the virologic potency and durability of nelfinavir relative to the other protease inhibitors, although head-to-head comparative studies are few. Walmsley et al found a statistically significant virologic benefit of an initial regimen containing lopinavir, boosted with ritonavir, over a similar regimen containing nelfinavir. This difference was observed despite the fact that both drugs were similarly well tolerated and overall adherence to each of the regimens was better than 90%. However, examined in a harsher light, one third of treatment-naïve patients receiving lopinavir-ritonavir and one half of those receiving nelfinavir failed to achieve complete suppression of viremia (< 50 copies HIV RNA) at 48 weeks of study despite maximal compliance with the regimens and optimal tolerability. Although it may have proved more effective than nelfinavir, the combination of lopinavir-ritonavir still fell short of that hoped for in a PI. The reasons provided for "treatment failure" at 48 weeks of therapy for patients receiving lopinavir-ritonavir vs. nelfinavir were viral rebound (21 vs 62 patients), failure to achieve initial viral suppression (22 vs 38 patients), discontinuation of the regimen (7 vs 5 patients), and the addition of other antivirals (1 vs 3 patients).

Among patients with detectable viremia (> 400 copies) occurring between weeks 24 and 48 of the study, HIV protease mutations were observed in 25 of 76 patients receiving nelfinavir vs. none of 37 patients "failing" lopinavir-ritonavir. Mutations associated with resistance to 3TC, were also twice as frequent among patients receiving nelfinavir compared with those receiving lopinavir-ritonavir.

Of concern on reviewing these data was the possibility of pre-existing mutations associated with resistance to protease inhibitors in patients receiving nelfinavir—an agent that has been around for much longer than lopinavir but an agent whose use does not commonly confer cross-resistance to this agent. However, none of the 24 patients with baseline virus isolates available for genotype resistance testing have evidence of protease mutations. Nonetheless, the possibility of archived resistance in these subjects cannot be ruled-out, especially in patients who never achieved virologic suppression. Genotype or phenotype resistance testing during the initial few months of therapy may have proved interesting.

The high degree of drug tolerability observed in this study is nothing short of remarkable, in my experience. Diarrhea (15-17%) and other gastrointestinal symptoms were the most frequent side effects of both agents. Unfortunately, fasting lipid levels were not assessed during this trial. Assessment of nonfasting cholesterol and triglyceride levels suggested that lopinavir-ritonavir resulted in higher cholesterol levels and was significantly more likely to cause severe hypertriglyceridemia > 750 mg/dL (9.3% vs 1.3%; P < .001), but this was apparently not believed to be dose-limiting.

The longer-term assessment of lipid effects, the occurrence of lipodystrophy, as well as the addition of therapeutic drug monitoring would have greatly added to this study. Nonetheless, the use of small amounts of ritonavir to pharmacologically boost lopinavir blood levels was more effective as initial therapy than nelfinavir administered as a single agent.

Murine Typhus in Hawaii: When the Mice Come Into Play

CASE STUDY

By Alan Tice, MD

Synopsis: *Life in paradise is still not without risk.*

It seems this year was a good one for rodents. An unusually wet winter and spring in Hawaii led to exuberant growth of grasses and vegetation that support the replication and survival of mice and rats on several of the Hawaiian islands. It was not until late summer when the fields began to dry out that the explosion of the vermin population was recognized. They headed into town to look for food—and brought their fleas with them. There were reports of mice brazenly moving into homes and of traps being filled or overflowing nightly. Terminex was overwhelmed. Some swimming pools had to be cleaned daily to get rid of the dozens or sometimes hundreds of mice trapped in them. The situation seemed the worst on Maui, where there have been problems before but not as bad.

The mice and rats created a special problem for my patient, a young man in prior excellent health, who lives on Molokai but works on Kahoolawe 4 days a week

cleaning up debris on the island which was used as a practice bombing run since World War II. Goats primarily populate it at this point. After returning from work on the island, he noted myalgias and malaise and a headache along with a chill. His symptoms gradually got worse over the next few days and he began to run a fever. He visited a local urgent care center but was told he had a viral syndrome and was sent home without therapy. When his headaches worsened and his fevers persisted for a week, he came to Honolulu for more advice. Evaluation found a well-nourished and developed man who was miserable and had a temperature of 103°. He had mild meningismus and a little photophobia but no conjunctival hemorrhages. His chest was clear but his liver was enlarged and tender. No rash was noted. Labs showed a WBC of 13,000 and liver function studies 5 times upper limit of normal. On specific questioning, he had noted an increase in the number of mice around his home and at work. He even remembered being bitten by one on Kahoolawe. He was given a prescription for doxycycline and began to feel better within a day and was able to go back to work in 4 days.

His serologies for leptospirosis were negative, but when other cases of murine typhus were reported from Maui, his blood was tested for murine typhus and was found to be strongly positive with a more than 4-fold increase in IgG titers over 3 weeks.

Murine typhus is an unusual infection and probably often overlooked. There were up to 5000 cases reported per year in Hawaii during World War II but it almost disappeared after a DDT campaign was instituted. Only a few dozen cases are now reported to the health department each year, and those are mainly from Maui, where the endemic focus was established before. An endemic focus has also been identified in Kauai with a report of 5 cases in 1998.[1] The risk continues with exposure to rats and mice, but the outbreaks occur when there is migration of the pests into the residential areas. The primary carrier is *Rattus rattus*. The vector is usually *Xenopsylla cheopis* but the cat flea, *Ctenocephalides felis*, can carry the pathogen as well. Either flea spreads the infection to humans through bite wounds contaminated with flea feces, although dried feces can apparently cause an inhalation form as well. The flea is a life-long host of the rickettsia once it is infected.

Rickettsia typhus commonly presents with myalgias, a severe headache, persistent fevers, and often a fine macular rash. Pneumonitis and meningoencephalitis may also occur, sometimes with devastating results if the appropriate antibiotic is not used early. Hepatitis is common. Mild thrombocytopenia and leukocytosis are often present but seldom a clinical problem. Infections may occur in many places, often in port cities and tropical areas. Outbreaks have been reported in Texas and California but it can be found almost any place in the world where a population of rats can exist.

Mice were certainly a problem in Hawaii this year but a fall overflow has been reported in California as well, although no specific diseases have been attributed to it. There is also an apparent increase in hantavirus infections in Peru, again likely related to a rise in the rodent population. The differential diagnosis for murine typhus in Hawaii is primarily leptospirosis, which is endemic in most of the fresh water in Hawaii and even contaminates the seawater on occasion when there is a lot of rainfall. Dengue is also of concern in Hawaii but the recent epidemic seems to be over. The differential in the rest of the world is very great and includes meningococcemia, measles, typhoid fever, syphilis, toxic shock syndrome, Kawasaki disease, Rocky Mountain Spotted Fever, Colorado Tick fever, and various viral infections. A careful and detailed history plus knowledge of the local disease epidemiology may be extremely useful.

Local measures such as rat traps, pesticides, and exterminators have all been advocated by the health department and have apparently been effective over the last few weeks. No further cases have been reported and the rodent population seems to be declining. ■

Reference

1. Manea SJ, et al. Clinical and epidemiological observations regarding the 1998 Kauai murine typhus outbreak. *Hawaii Med J*. 2001;60:7-11.

Mosquito Repellents: What Works?

ABSTRACT & COMMENTARY

Synopsis: *The efficacy of several commercially available insect repellents was compared. The topical application of compounds containing DEET was far more protective against mosquito bites than was application of products containing soybean oil or citronella. With the resurgence of West Nile virus in the southern United States this summer, and the potential for spread of infections, mosquito protection assumes even greater relevance at this time.*

Source: Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med*. 2002;347: 13-18.

IN A LABORATORY SETTING, ADULT LABORATORY workers exposed an arm to caged, hungry female

Aedes mosquitoes while using a variety of commercially available insect repellents. Sixteen separate repellent formulations were evaluated in a total of 270 test episodes on the 15 volunteer subjects. The time elapsed until the first bite was noted as the end point of "complete protection time."

The Table highlights a few of the relevant results. Topically applied products were generally more effective than were impregnated wristbands. DEET-containing products varied in efficacy with longer protection noted with higher concentration formulations. Citronella-containing products provided a maximum of 30 minutes of protection.

Table

Protective Efficacy of Various Insect Repellents

Product	Active Ingredient	Mean Complete Protection Time (min)
OFF! Deep Woods	DEET, 23.8%	302
Sawyer Controlled Release	DEET, 20%	234
OFF! Skintastic	DEET, 6.65%	112
Bite Blocker for Kids	Soybean Oil, 2%	95
OFF! Skintastic for Kids	DEET, 4.75%	88
Skin-So-Soft Bug Guard Plus	IR3535, 7.5%	23
Natrapel	Citronella, 10%	20
Skin-So-Soft Bug Guard	Citronella, 0.1%	10
Skin-So-Soft Moisturizing Suncare	Citronella, 0.05%	3
Various wristbands	DEET or Citronella	< 0.5

Adapted from: N Engl J Med. 2002;347:16.

■ COMMENT BY PHILIP R. FISCHER, MD, DTM&H

Travel medicine practitioners are well aware of the importance of insect repellents in preventing mosquito-transmitted infections such as malaria, yellow fever, and Japanese encephalitis. In addition, the use of insect repellents is also protective against many tick-borne diseases. With the westward and southward expansion of the endemic region of West Nile virus in North America, even nontravelers are increasingly interested in avoiding insect bites.

Advertisements, anecdotes, and the lay literature include many claims about the effectiveness and safety of various insect repellents. Fradin and Day, in a recent issue of the *New England Journal of Medicine*, have provided practically useful information about the relative efficacy of various readily available repellents.

For approximately 4 decades, DEET (also known as N, N-diethyl-meta-toluamide or N, N-diethyl-3-methylbenzamide) has been the most widely used insect repellent.[1] With questions about the safety of DEET for human usage, alternative products have been developed. Fradin and Day have now clearly shown that DEET-containing repellents are markedly more effective than other common repellent preparations. Under standardized conditions, DEET protected against mosquito bites for much longer than any of the other preparations. As suggested in previous studies, the duration of DEET's protection depends on the DEET concentration; peak protection is conferred by products containing about 30% DEET. Though not specifically studied in this investigation, it is not clear that high concentrations of DEET (such as the 90+% products available in some camping stores) are more effective than products containing "only" 20-30% DEET. Interestingly, a "long-acting" formulation of DEET did not seem to protect for any longer than did a similarly concentrated standard formulation. Botanical preparations containing citronella protected only for a few brief minutes. Of note, repellents were not significantly protective when applied only to a nearby wristband. The message should be clear to travelers and to domestic residents at risk of exposure to mosquitoes carrying disease: **DEET is the most effective mosquito repellent**.

But, is laboratory testing using caged *Aedes* mosquitoes relevant to the conditions faced by travelers? It is impossible to perfectly replicate any individual traveler's situation in an artificial environment. Different individuals are differentially attractive to mosquitoes [with pregnant women being particularly appealing[2]], and insect repellents are not always applied in a completely careful manner. Repellent efficacy varies somewhat between different genera and species of mosquitoes as well. These factors should make us cautious about guaranteeing any specific repellent's duration of protection for a particular traveler, but the relative efficacy for the different products tested would not be expected to change between individuals and settings.

What about safety? When ingested, DEET can have neurotoxic effects. It can also cause irritation when rubbed into eyes or, in some individuals, when rubbed vigorously (such as in elbow creases) on the skin in high concentrations. Clearly, oral and ocular applications of DEET (such as can occur inadvertently in children who rub their faces with DEET-laden hands or lick their DEET-treated forearms) should be avoided.

However, there have been a few, albeit rare, reports of serious and even fatal episodes in children who used DEET. In those cases, inappropriately frequent application (up to 10 times in a day) and oral ingestion (licking

of arms) were sometimes reported, and there is no good evidence linking DEET concentration to the risk of toxicity. Of course, no product is perfectly safe. Citronella toxicity has also been reported.[3]

Since 1998, the American Environmental Protection Agency has removed restrictions on the concentration of DEET used in children. The American Academy of Pediatrics has acknowledged that lower concentrations of DEET are not safer than higher concentrations and that higher concentrations of DEET are more effective in repelling insects than are formulations with lower concentrations.[4] Each organization does stress the importance of *appropriate* use of DEET with care: 1) not to apply the repellent on or near the eyes or mouth; 2) to apply the repellent only on exposed skin (not skin covered by clothes); and 3) to wash remaining DEET off the skin when leaving an area of risk for insect bites. In Canada, where recent safety concerns have limited DEET concentrations, the use of products containing up to 30% DEET is still accepted and advocated.

The editorial accompanying the report by Fradin and Day[5] wisely summarizes DEET safety when writing that DEET is far less toxic than many people believe. Adverse effects, though documented, are infrequent and are generally associated with gross overuse of the product. The risk of DEET-related adverse effects pales in comparison with the risk of acquiring vector-borne infection in places where such diseases are endemic.

This summer, Fradin and Day have provided a great service though their *New England Journal of Medicine* paper. Their solidly scientific study reminds us that DEET-containing insect repellents are much more effective than other products and that DEET efficacy increases with increasing DEET concentration. Appropriate use of DEET, both at home and in travelers, should result in improved health for many people. ■

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1. Fradin MS. *Ann Intern Med*. 1998;128:931-940.
2. Ansell JJ, et al. *Trans R Soc Trop Med Hyg*. 2002;96:113-116.
3. Temple WA, et al. *J Toxicol Clin Toxicol*. 1991;29: 257-262.
4. AAP News pages 52-53, August 2001.
5. Pollack RJ, et al. *N Engl J Med*. 2002;347:2-3.

CME Questions

15, Insect repellents containing 20-30% DEET are:

a. dangerous in young children, due to excessive absorption through skin.
b. more effective than citronella-containing repellents.
c. equally effective as repellents containing 10% citronella for mosquitoes.
d. clearly useful when applied only to wristbands in attempts to avoid toxicity.

16. Which of the following is correct?

a. Chronic wasting disease is caused by neonatal infection with SV40.
b. Chronic wasting disease predominalty affects skunks and racoons.
c. Chronic wasting disease is a transmissible spongiform encephalopathy.
d. Chronic wasting disease has been reported to be readily transmissible to humans, and hundreds of cases have been reported in the Middle East.

17. Which of the following is correct?

a. The etiologic agent of murine typhus can be transmitted by cat fleas.
b. Murine typhus is caused by a virus closely related to hantaviruses.
c. Only imported cases of murine typhus have been identified in the Hawaiian islands.
d. Because of antigenic cross-reactivity, serologic tests are unable to distinguish a case of leptospirosis from that of murine typhus.

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In Future Issues:

Caspofungins

UPDATES

By Carol A. Kemper, MD, FACP

Antibiotic Allergy: To Dose or Not to Dose?

Source: Robinson JL, et al. *Clin Infect Dis*. 2002;35:26-31.

THIS THOUGHTFUL ARTICLE nicely summarizes the "practical aspects" of choosing an antibiotic in a patient with a reported drug allergy. Although penicillin skin testing is very useful for predicting a serious allergic reaction to the beta-lactam ring of the penicillins, a careful history is probably the most useful tool at the clinician's disposal. However, I am finding (unfortunately, more often) with the use of computer-based templates and problem lists, that the nature of most allergic reactions is not being well characterized. Often, the important task of collecting this information is left to hospital nursing staff, who cannot be expected to differentiate between mild or more severe reactions, or even simple drug intolerance. The importance of the accuracy of this information is underscored by data suggesting that anywhere from 5-20% of patients believe they are "allergic" to penicillins.

The first challenge is the appropriate characterization of the allergy, as follows: 1) IgE mediated reactions, including diffuse erythema, urticaria, angioedema, bronchospasm, and hypotension; 2) delayed hypersensitivity reactions, including nonurticarial rashes, such as commonly observed with the aminopenicillins; 3) immune-complex mediated reactions or "serum sickness," a rare phenomenon; 4) antibody-mediated reactions, including, most commonly, neutropenia to the cephalosporins, but also hemolysis, thrombocytopenia, and interstitial nephritis; and 5) unknown mechanisms, such as Stevens Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis, but also fixed drug eruptions, drug fever, and autoimmune phenomenon.

In general, Robinson and colleagues believe that the cross-reactivity between penicillins and the second- and third-generation cephalosporins is significantly less than commonly believed, and probably no greater than reactions to drugs in other classes. Most patients with a history of penicillin allergy can safely be administered penicillins, especially with a negative skin test. In clinical trials, 8.1% of patients with and 4.5% of patients without a reported penicillin allergy had possible allergy to cephalosporins. Most cephalosporin reactions are to the various side-chains and not the beta-lactam ring. Overall, the risk of a serious reaction to cephalosporins is < 0.02% in the population, and may be 3 times more common in patients with a penicillin allergy.

For those in need of a specific antibiotic but with a history of IgE-mediated allergy to that agent, Robinson et al recommend skin testing and desensitization. The one notable exception: skin testing should not be performed in patients with a history of suspected Stevens Johnson Syndrome or toxic epidermal necrolysis and the use of cephalosporins should be avoided. Non-beta-lactam antibiotics seldom cause severe or life-threatening reactions. Most of these antibiotics can safely be administered even in patients with a history of allergy. ■

Resistance Mutations in HIV: Discordance Between CSF & Plasma

Source: Tashima KT, et al. *Clin Infect Dis*. 2002;35:82-83.

ALTHOUGH DISCORDANCE BETween drug-resistant HIV mutations found in CSF and plasma has been previously reported, this report was interesting because it was the first to describe the presence of K103 resistant virus in CSF but not in plasma. The patient had received a combination of efavirenz and indinavir, with subsequent virologic failure with a plasma viral load of 23, 648, and a CSF viral load of 242 copies/mL. While there was evidence of a protease gene mutation in both CSF and plasma virus (A71V), only the virus found in CSF had evidence of K103N and K70R mutations, which are associated with resistance to the non-nucleoside reverse transcriptase drugs. If the development of drug resistance occurs as the result of exposure of replicating virus to subtherapeutic concentrations of drug, Tashima and colleagues point out that differences in drug levels between CSF and plasma may result in varying risk of drug resistance in the separate compartments. Several antiviral agents, including efavirenz, poorly penetrate the CSF. Virus replicating in CSF would, therefore, be exposed to smaller concentrations of drug, thus increasing the risk of drug resistant mutations. ■

PHARMACOLOGY WATCH

Forgot Your Ginkgo? Forget About It, Study Shows

The $15 billion dietary supplement industry took a bruising in the last month with reports that some of the most popular over-the-counter treatments are little more than expensive placebo. Ginkgo, the commonly used memory enhancing agent, was evaluated in 230 men and women older than the age of 60 who had normal memory and were in good health. Patients were randomly assigned to receive ginkgo 40 mg 3 times a day or matching placebo for 6 weeks. Neuropsychological tests were administered at the end of the study, which revealed no significant differences between treatment groups on any of the outcome measures including verbal and nonverbal learning and memory, attention and concentration, naming and expressive language, self-reported memory, and companion scoring. The study concluded that ginkgo did not facilitate learning memory tension or concentration in adults older than the age of 60 (*JAMA*. 2002;288:835-840). In a separate study from The Netherlands, 652 adults older than age 60 were given a multivitamin/mineral supplement, 200 mg of vitamin E, both, or placebo in a study to evaluate whether the supplements would reduce the incidence and severity of acute respiratory tract infections. Patients were followed for nearly 1.5 years. No difference was found among any of the groups with regard to incidence or severity of acute respiratory infections, except for the finding of worsening severity of disease in the vitamin E group (19 days illness with vitamin E vs 14 days illness with placebo; $P = 0.2$). (*JAMA*. 2002;288:715-721.)

On the other hand, a homocysteine-lowering therapy with a combination of B vitamins effectively improves clinical outcomes after percutaneous coronary interventions. Folic acid, vitamin B_{12}, and vitamin B_6 were tested in a randomized, double-blind, placebo-controlled trial involving more than 550 patients in Switzerland who had undergone successful angioplasty. The participants received a combination of folic acid 1 mg/d, vitamin B_{12} 400 µ/d, and vitamin B_6 10 mg/d, or placebo. The main outcome measure was the composite outcome of major adverse events including death, nonfatal myocardial infarction, and the need for repeat revascularization evaluated at 6 months and 1 year. The composite end point was significantly lower at 1 year in the vitamin-treated patients (15.4%) compared to the placebo group (22.8%) (RR, 0.68; 95% CI, 0.48-0.96; $P = .03$) primarily due to reduce rate of revascularization. (*JAMA*. 2002;288:973-979).

Celebrex OK for Asthma Patients

Celecoxib (Celebrex®) may be safe to use in patients with a history of aspirin-induced asthma. Patients with known aspirin sensitivity, or aspirin-exacerbated respiratory disease (AERD), are generally unable to take aspirin or any NSAID. In a study from San Diego, 60 patients with AERD were challenged with celecoxib, a COX-2 inhibitor, or placebo over 48

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hours. During the study period, none of the 60 patients experienced any symptoms or changes in nasal examinations or declines in FEV_1. The following day, all 60 patients were exposed to aspirin and all showed sensitivity. The study concluded that inhibition of COX-1 is the critical initiating event in respiratory reactions in patients with AERD (*Arthritis Rheum*. 2002;46:2201-2206).

Losartan Not Superior to Captopril

The angiotensin II receptor blocker losartan is not superior to the ace inhibitor captopril after complicated acute myocardial infarction. The large OPTIMAAL trial (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) looked at 5477 patients in 7 European countries with confirmed acute myocardial infarction and heart failure. Patients were randomly assigned and titrated to target dose of losartan 50 mg once daily or captopril 50 mg 3 times daily. The primary end point was all-cause mortality. During a mean follow-up of 2.7 years, there were 499 (18%) deaths in losartan group and 447 (16%) in the captopril group (RR 1.13; 95% CI, 0.99-1.28; $P = 0.07$). Because of this nonsignificant trend in total mortality in favor of captopril, the study suggests that losartan cannot be generally recommended in this population. It is noted however that losartan was better tolerated than captopril, and associated with significantly fewer discontinuations (*Lancet*. 2002;360:752-760).

Alfa-Interferon Could Help Fight West Nile

The number of West Nile virus cases is mounting in the United States, Canada, and Mexico where 37 deaths have been attributed to the virus, now the first case has been reported in California, and other cases are the result of organ donation from infected donor. Researchers are hoping that alfa-interferon may be of help. The drug has been effective against St. Louis encephalitis, a similar virus, and is the drug of choice for treatment of hepatitis C. Researchers are enrolling patients in the New York area where the virus first appeared 3 years ago. Although infection with the mosquito-borne virus rarely causes serious illness (< 1%), the elderly and chronically ill are particularly prone to encephalitis. alfa-interferon will be given for 2 weeks and should be started within the first few days of illness, prior to the onset of encephalitis. Research is also progressing on 3 West Nile virus vaccines, which should be in human trials by 2003.

Sertraline Effective Against Depression

Depression is common in patients with coronary artery disease and represents a significant independent risk factor for both first myocardial infarction and cardiovascular mortality. A new study shows that the selective serotonin reuptake inhibitor sertraline is safe and effective for treating major depression in patients with recent myocardial infarction or unstable angina. A total of 369 patients on 3 continents with major depressive disorder were enrolled and randomized to sertraline 50-200 mg/d or placebo in a double-blind fashion for 24 weeks. The main outcome was change in left ventricular ejection fraction (LVEF) while other outcomes included surrogate cardiac measures and cardiovascular adverse events. Sertraline had no significant effect on LVEF, and also did not increase ventricular premature complex runs, QTc intervals, or other cardiac measures. The incidence of severe cardiovascular adverse events was 14.5% with sertraline and 22.4% with placebo. Depression scores were better in the sertraline group. The authors conclude that sertraline is safe and effective for trading depression in patients with recent MI or unstable angina (*JAMA*. 2002;288:701-709).

FDA Actions

Procter & Gamble has announced that it expects an over-the-counter form of omeprazole (Prilosec) to be available by early 2003. The company has received an approval letter from the FDA but needs to clarify language on the package label so that consumers will clearly understand how to use the drug. Procter & Gamble is planning a study to make sure consumers understand the drug labeling, a process which will take several months. The FDA has approved fluoxetine (Prozac) for the treatment of panic disorder. The indication was previously only granted to paroxetine (Paxil) and sertraline (Zoloft), and it has been heavily promoted by the manufacturers of these drugs. Fluoxetine is also recently approved for long-term treatment of bulimia. The drug has been been available as a generic for more than a year, and as such represents a lower cost alternative for patients with these conditions. ■