TRAVEL MEDICINE ADVISOR

This Month's Compendium of Articles from Other Thomson American Health Consultants Publications

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INSIDE

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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 10^9 to 53.3 x 10^9 eosinophils/L, and all had elevated serum IgE levels. Anti-filaria antibody titers, performed at the NIH in Bethesda, MD, ranged from 1:4096 to 1:32,678.

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 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 eosionphilic alveolitis. With chronicity, however, this is gradually

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.

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.

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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Lassa Fever

ABSTRACTS & COMMENTARY

Synopsis: *Importation of Lassa fever remains a continuing danger.*

Sources: Lassa Fever, Imported-USA (New Jersey) ex Liberia. CDC. *M MWR*. 2004:53:894-897; United Kingdom: Probable Lassa Fever in Traveler Returning From West Africa. www.promedmail.org.

A 38-YEAR-OLD MAN RETURNED TO THE UNITED States from west Africa. He had spent the last 4 months in Liberia and Sierra Leone where he owned farms. Two days before his August 2004 return, he developed fever, chills, and severe sore throat, and shortly after his arrival, he was hospitalized with, in addition to these complaints, diarrhea and back pain. He deteriorated, developing ARDS and requiring mechanical ventilation, despite receipt of antibacterials and antimalarials. Lassa fever was considered, and administration of ribavirin was planned, but the patient died before receiving this antiviral medication. The diagnosis of Lassa fever was confirmed by serum antigen detection, immunohistochemical staining of postmortem liver tissue, virus isolation in cell culture, and genome sequencing.

A man returned to the United Kingdom in September 2004 after traveling for a month in Chad and Cote d'Ivoire, becoming febrile the following day. He sought care 2 days later and was admitted to the hospital and transferred to a medium security facility. After preliminary tests suggested Lassa fever, ribavirin therapy was initiated and he was transferred to a high security infectious disease facility. He became afebrile and was discharged from the hospital. Confirmatory tests are pending.

In both cases, extensive contact investigations were performed, including health care and laboratory workers, household contacts, and in the first case in which the patient traveled while symptomatic, airline passengers seated within 6 feet.

COMMENT BY STAN DERESINSKI, MD, FACP

Lassa fever, named after the Nigerian town where it was first identified, should be considered in any patient who has a negative malaria smear with fever, who's recently returning from west Africa. It is caused by a single-stranded RNA virus of the arenavirus family, and is known to be endemic in Sierra Leone, Guinea, and Nigeria. In addition, seropositivity has been detected in a number of other countries of the region, including Mali, Senegal, the Central African Republic, and the Democratic Republic of Congo.[1]

Lassa fever is a zoonosis, transmitted by rats of the genus Mastomys, that are distributed throughout west, central, and eastern Africa. Infection of the rodents is persistent, and the virus is shed in urine and feces. Humans are infected by contact with rats, which may be actively sought since they serve as a protein source in many areas. Human-to-human transmission may also occur, including in the health care setting. As a consequence, patients with suspected Lassa fever require careful infection control. Excretion of the virus in urine persists for 3 to 9 weeks, and for 3 months in semen.[1]

Approximately 80% of those infected remain asymptomatic or develop only mild illness after an incubation period of 6 to 21 days. The onset is usually gradual, and the presenting signs and symptoms are largely nonspecific. The complex of fever, retrosternal pain, and proteinuria, with the development of severe pharyngitis with white tonsillar patches, is suggestive. Progression may lead to the development of a hemorrhagic fever syndrome. Sensorineural hearing loss is a frequent complication. Ribavirin administration within the first 6 days of illness is reported to be associated with reduced mortality.[2] Ribavirin has also been used, in the absence of evidence of benefit, as prophylaxis in contacts. The virus is also inhibited in vitro by both interferon alpha and interferon gamma.[3] The differential diagnosis includes malaria, bacterial sepsis, and other viral hemorrhagic fevers, such as Ebola.

Only approximately 20 cases of imported infection have been reported. The United Kingdom patient is only the 7th case imported there. Nonetheless, its timely recognition is important because of the potential for human-to-human transmission. ■

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Reptile-Associated *Salmonellosis* in Children

ABSTRACT & COMMENTARY

Synopsis: *A retrospective review of 1387 cases of salmonellosis revealed that almost half of cases in children younger than 5 years of age were associated with reptile-contact.*

Source: Wells EV, et al. Reptile-Associated Salmonellosis in Preschool-Aged Children in Michigan, January 2001-June 2003. *Clin Infect Dis.* 2004;39:687-691.

A RETROSPECTIVE STUDY OF 1387 CASES OF *Salmonellosis*, representing about 88% of all cases reported through a comprehensive system to the Michigan Department of Community Health from January 2001 through June 2003, found that 106 cases reported exposure to a reptile. Analysis of the age distribution revealed that 50 of these cases occurred in children younger than 5 years of age, representing 13.9% of the 360 cases among children in this age group. Of these 50 cases, 35 (70%) occurred in infants, and 14 (28%) occurred in infants younger than 2 months of age. In contrast, the remaining 56 cases represented only 5.5% of cases that occurred in patients > 5 years of age.

The most common serotypes were *Salmonella typhimurium* (7 cases; 14%), *Salmonella poona* (6 cases; 12%), *Salmonella enteritidis* (5 cases; 10%), and *Salmonella typhimurium* (var 5-) (3 cases; 6%).

COMMENT BY HAL B. JENSON, MD, FAAP

The major source of salmonellosis is contaminated food, but reptile-associated Salmonella infection is a re-emerging disease that now accounts for about 6% of the estimated 1.2 million sporadic Salmonella infections that occur in the United States each year. Turtles were a major source of reptile-associate salmonellosis until FDA legislation in 1975 banned the commercial distribution of small (< 4 inches long) turtles. Most states subsequently prohibited the sale of small turtles. However, exotic reptile pets such as iguanas, lizards, and snakes (including boas) have become very popular, with a parallel increase in the incidence of reptile-related Salmonella serotypes isolated from humans. It is estimated that more than 1 million farm-bred baby iguanas have been imported into the United States from Central and South America, becoming the most popular reptile pet. The American Veterinary Medical Association estimates that there are now as many as 2.8 million pet reptiles in 1.5-2.5 million households in the United States. Approximately 90% of all reptiles carry, and intermittently shed, Salmonella in their feces, which survives for prolonged periods on environmental surfaces. Salmonellosis has also been associated with African pygmy hedgehogs, which are mammals.

The increased risk of salmonellosis among children is important not only as a cause gastrointestinal illness, but especially for the greater risk in this age group of progression to septicemia, meningitis, and death. The risk is highest among infants, especially those younger than 3 months of age, which is the basis for the recommendation for treatment of all gastrointestinal Salmonella infections in infants younger than 3 months of age.

The results of this study indicate that despite awareness of the confirmed association and the heightened risk to young children, many reptile owners remain unaware of the risk for salmonellosis from reptile contact. The CDC has published recommendations to prevent transmission of Salmonella from reptiles and amphibians to humans,[1] but only a few states require point-of-sale information to persons purchasing a pet reptile. The CDC recommendations include:

- Pet store owners, health care providers, and vet erinarians should inform reptile and amphibian pet owners of the risk of salmonellosis.
- Children < 5 years of age and immunocompromised persons should avoid contact with reptiles and amphibians and any items that have been in contact with reptiles and amphibians.
- Reptiles and amphibians should not be kept in households with children younger than 5 years of age. Expectant parents should be instructed to remove these pets before the child's birth.
- Reptiles and amphibians should not be allowed in daycare centers.
- Persons should always wash their hands thoroughly after handling reptiles and amphibians.
- Reptiles and amphibians should not be allowed to roam through living areas, or to enter kitchens or food-preparation areas.
- Reptiles and amphibians in zoos and exhibits should not have direct or indirect contact with patrons, except in designated areas with ade quate handwashing and exclusion of food items. ■

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1. Centers for Disease Control and Prevention: Reptile-Associate Salmonellosis-Selected States, 1998-2002. *MMWR.* 2003;52:1206-1209.

PHARMACOLOGY WATCH

Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

GEMINI Trial

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

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.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.