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INSIDE

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Highlights from the ASTMH Meeting in Puerto Rico: Cancelled, but Not Forgotten

SPECIAL COVERAGE

As we noted in the november/december 1998 issue of *Travel Medicine Advisor Update*, the clinical sessions that had been a planned part of the American Society of Tropical Medicine and Hygiene meetings had been replete with abstracts of potential interest to our readers. When those meetings were cancelled due to hurricane damage in Puerto Rico, we attempted to retrieve and highlight clinical information that would have been presented at those annual meetings. This issue continues our reviews and highlighting of several additional clinical abstracts by the associate editors. Once again, for those who wish to obtain copies of the abstract book, it is officially designated as the Program and Abstracts of the 47th Annual Meeting of the American Society of Tropical Medicine and Hygiene (a supplement to *Am J Trop Med Hyg* 1998;59:no. 3 for September). Additional copies of the abstract book can be obtained from the Society (telephone: 847-480-9592). **—fjb**

Loa loa Infections

Diethylcarbamazine (DEC) is the current pharmacological standard of care for treatment of *Loa loa* infections. It is curative for approximately 60% of non-endemic patients with loiasis, yet some individuals continue to have signs and symptoms of infection despite multiple courses of DEC. In this abstract, Klion AD and Nutman TB, who are experienced with this disease, report successful treatment of loiasis with albendazole. Three patients with refractory loiasis, defined as persistent symptoms of monthly Calabar swellings (2 patients) or malaise, myalgias, and arthralgias (1 patient) were given albendazole 200 mg by mouth, twice a day, for 21 days. Following therapy, symptoms resolved in all three patients, and, in two of them with Calabar swellings, symptoms have not recurred in seven years.

Loa loa is a filarial parasite commonly found in West and Central Africa. It is commonly known as the "eye worm" since adult worms are occasionally seen moving across the eyes of patients. It does not result in disfiguring lymphatic filariasis, yet it may cause serious complications when the organism invades the central nervous system or other vital organs. An epidemiological correlation has been observed between loiasis and the occurrence of endomyocardial fibrosis, suggesting that the hypereosinophilia induced by loiasis may lead to cardiac damage. Nephropathy and encephalopathy are far less common. Nodules in the conjunctiva, swelling of the eyelids, and proptosis have each been reported from

Uganda as ocular complications of loiasis. Adult worms may be obvious when they pass under the conjunctiva of the eye or under the skin. They usually appear, but then disappear without a trace. Hypereosinophilia, especially in expatriates from nonendemic regions, is common. Clinical manifestations of loiasis include calabar swellings that are most often observed on the wrists and ankles but can appear anywhere on the body. They are usually painless, nonpitting swellings, 5-20 cm in diameter, and last hours to days. One swelling occurs at a time, and it may recur at irregular intervals for years after the patient has left an endemic area. Other common symptoms include fatigue, generalized malaise, pruritus, and arthralgias. Death of an adult worm may cause a localized abscess, or they can sometimes calcify, making them radiographically detectable.

Albendazole has been used more broadly since its introduction—for more than just FDA-approved indications of neurocysticercosis and hydatid disease. It has had a good track record in terms of safety, and adverse events were described generally as mild, resolving without treatment. Abnormal liver function tests, abdominal pain, nausea, vomiting, headache, dizziness, meningeal signs, reversible alopecia, and fever have all been reported, but at a low incidence rate. Fewer than 1% of patients may develop leukopenia. Albendazole has been shown to be teratogenic in pregnant rats and rabbits and should be avoided in pregnant women at this time.

Although this report describes a small number of cases, each had a remarkable response with prolonged follow-up. Albendazole shows promise as an alternative agent for the treatment of loiasis. It may be an important macrofilaricidal drug addition for treatment of this disease, as well as for the treatment of strongyloidiasis. (*Abstract 77.*)

Strongyloidiasis

A retrospective analysis of patients attending the Tropical Disease Unit at the University of Toronto between 1990 and 1996 assessed those who received strongyloides serological evaluation by enzyme-linked immunosorbent assay (EIA). Fifty-six of 94 subjects demonstrated strongyloides on stool examinations or culture. Strongyloides serology was positive in 95% of those with documented infections. In 46 treated cases, the mean time for 50% reduction of antibody titer was six months. Within that time period, 34% of those with documented infections and 45% of those without parasites detected developed a negative serological test. Eosinophilia was present in 70% of those with documented infection and in 81% of those who only showed a positive strongyloides seropositivity. Return to normal occurred in 66% of those with documented strongyloidiasis and in 45% of those without documented parasites. Strongyloides serology appeared to be a sensitive test in this group for predicting successful treatment, with more specificity than following eosinophilia alone.

Unpublished data from our own hospital in Rhode Island support the use of serum antibodies against *Strongyloides stercoralis* to follow patients treated for strongyloidiasis. One family practice physician, who has become popular with the Cambodian community in Rhode Island, has followed approximately 40 asymptomatic patients who had eosinophilia and positive strongyloides antibody titers and treated them with thiabendazole. Nearly all tended toward lower antibody titers, although not all were done by the same lab using the same methods. Reference labs had changed hands and altered methodologies, but his findings support the data reported in this abstract from another "real-life" clinical care setting. (*Abstract 78.*) **—maria d. mileno, md**

Leptospirosis

Following a 1996 hurricane, the incidence of leptospirosis rose in Puerto Rico and Nicaragua (*TMA Update* 1998;8:2). Now, following Hurricane Mitch, leptospirosis is being increasingly identified in Central America. In addition to prompting cancellation of the 1998 ASTMH meeting, a hurricane can also increase flooding and stimulate increased contact between humans and spirochete-contaminated fresh water.

Had the 1998 ASTMH meeting taken place, DA Person from the Tripler Army Medical Center in Hawaii would have presented a report of nine children from Kosrae State, Federated States of Micronesia, who were diagnosed with severe leptospirosis. Infection is usually acquired through contact of mucus membranes or broken skin with contaminated fresh water, soil, vegetation, or infected animals. Each of these nine children had a history of exposure to a potential source of leptospirosis, and the majority were boys. Pancreatitis and acute renal failure, with anuria lasting 3-6 days, were common; pulmonary findings and a large pleural effusion were noted in one child. In the more recently treated patients, a "pulse" dose of corticosteroids was associated with reversal of renal failure and avoidance of dialysis. (There have been other anecdotal reports of the usefulness of steroids in leptospirosis, but controlled studies are lacking.) Leptospirosis is a common zoonosis. The diagnosis should be considered in individuals with febrile illnesses after potential spirochete exposure. Severe disease with liver and kidney involvement is still treatable. Antibiotic and, perhaps, corticosteroid therapy should be initiated for potentially affected individuals. For a review of the leptospirosis symposium presented at the 1997 ASTMH meetings, see *TMA Update* 1998;8:1-3. (*Abstract 404.*)

Praziquantel Chemotherapy

For years, praziquantel has been a mainstay of therapy for schistosomiasis. In 1995, reduced schistosomiasis cure rates were noted in Senegal, and decreased effectiveness of praziquantel was confirmed in the laboratory (*Am J Trop Med Hyg* 1995;53:61-62). Then, in 1996, a report from the Nile delta region of Egypt noted tolerance of some schistosome strains to repeated treatments with praziquantel (*Am J Trop Med Hyg* 1996;55:214-218).

Morshedy and colleagues from Alexandria University were slated to discuss an area of reduced praziquantel susceptibility in the Nile delta that is hyperendemic for schistosomiasis. In the studied village, 58% of people were infected. Eight weeks following treatment with praziquantel (40 mg/kg), only 53% of previously infected individuals showed parasitologic cure; in children, only about one-third were cured with treatment. Morshedy et al question whether this village is a site of a tolerant or resistant schistosome strain.

Further studies of praziquantel sensitivity in different areas will help confirm if, indeed, this agent is losing effectiveness. In the meantime, further anti-schistosomal drug development efforts must continue. Practitioners of travel medicine might consider follow-up parasitological testing after praziquantel therapy to confirm cure, especially in travelers who have been to Senegal or Egypt. (*Abstract 81.*)

Malaria

The combination of atovaquone and proguanil (Malarone) has been demonstrated to be effective in the prophylaxis and treatment of malaria. (See *TMA Update* 1998;8:35-36.) Is it safe in subjects who are glucose-6-phosphate dehydrogenase (G6PD) deficient?

Researchers evaluated the use of atovaquone-proguanil in 31 G6PD deficient individuals with uncomplicated falciparum malaria who were enrolled in clinical trials at several sites, and they compared the safety and efficacy of treatment between these patients and "normal" subjects. Similar adverse effects occurred in the two groups, and no G6PD deficient subject was withdrawn due to side effects. Measures of hemolysis were not different when compared in the two groups. Each G6PD deficient patient achieved clinical and parasitologic cure with a three-day course of treatment.

Atovaquone-proguanil appears to be safe in G6PD deficient subjects. It also provides effective cure of falciparum malaria. As resistance to antimalarials increases around the world, this combination therapy holds great potential for increasing usefulness. (*Abstract 75.*) **—philip r. fischer, md, dtm&h**

Which of the following is *not* true about leptospirosis?

a. Leptospirosis is more common following hurricane-induced flooding.
b. Leptospirosis is often contracted from animal urine-contaminated fresh water.
c. Antibiotic therapy is helpful for individuals with acute leptospirosis.
d. Corticosteroids are the mainstay of therapy for severe, life-threatening leptospirosis.
e. Leptospirosis is not associated with severe renal insufficiency unless treated with corticosteroids during the acute phase of the disease.

High-Altitude Cerebral Edema

ABSTRACT & COMMENTARY

Synopsis: *A recent publication that appeared in December in JAMA addresses the pathophysiology of high-altitude cerebral edema and its etiology, as demonstrated on magnetic resonance imaging. Before prevention and treatment of this disorder can be approached effectively, studies such as this are necessary to gain a better understanding of the basis for the disorder and to define its earliest manifestations.*

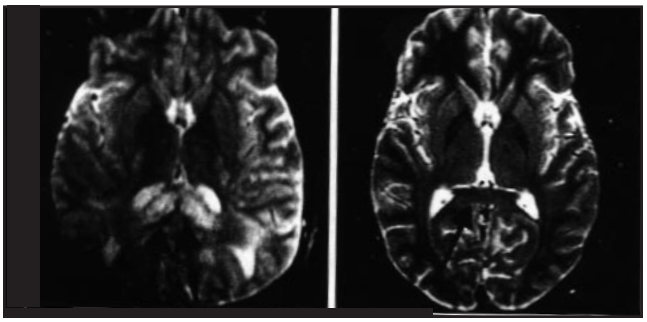
Source: Hackett PH, et al. *JAMA* 1998;280:1920-1925.

At the far end of the spectrum we call acute mountain sickness, often following the onset of high-altitude pulmonary edema (HAPE), lies the realm of reversible hypoxia induced high-altitude cerebral edema (HACE). Brain edema justifiably has been considered the pathophysiologic basis for this disorder, but, based upon limited animal data obtained in sheep, a single brain biopsy performed at autopsy and previous computerized tomographic (CT) imaging studies. The latter clearly demonstrated cerebral edema *in vivo*, but could not elucidate either the mechanisms or regional differences within brain tissue for this slowly resolving process. Magnetic resonance imaging (MRI) has demonstrated white matter changes following climbs to extreme altitude in subjects who apparently did not demonstrate HACE.[1,2] However, the deep lesions of white matter that were shown in such climbers may not be specifically related to HACE and were not considered reversible.

For the purposes of both this study and others that preceded it, a clear distinction has been made by Hackett and associates between two general types of cerebral edema. *Cytotoxic* cerebral edema is intracellular in origin

Figure

MRI Imaging During, and Five Weeks Following, High-Altitude Cerebral Edema (HACE)



Left, Azial T_2-weighted magnetic resonance image of patient showing markedly increased signal in corpus callosum (arrows), including both the genu and the splenium, as well as increased signal of periventricular and subcortical white matter. Right, Axial T_2-weighted magnetic resonance image of the same patient five weeks after original presentation, demonstrating no residual abnormality in splenium (arrow). Reprinted with permission from *JAMA* 1998;280:1924.

and dependent upon cellular swelling in response to insult or injury. *Vasogenic* cerebral edema is extracellular and ascribed to leaks in the blood-brain barrier. White matter is less dense than gray matter and is more prone to vasogenic edema, since its orderly array of extracellular channels offers less resistance than gray matter to invasion and spread of edema fluid. Any combination of these mechanisms could also account for the acute changes observed in patients with HACE. The objective of this study was to determine whether a clinical imaging correlate for HACE could be identified using MRI and, in the investigative process, to determine to what extent either vasogenic or cytotoxic cerebral edema contributed to the process. This distinction is extremely important if both prevention and therapy of HACE are to have a rational basis, given the large number of potential interventions that could be applied to the problem.

This study was designed as a case-comparison investigation performed in hospitals, which were accessed by helicopter and located in either Alaska or Colorado. Brain MRIs were performed during acute, convalescent, and recovery phases of HACE in consecutive study subjects and once in matched controls, immediately following high-altitude exposures. Study patients consisted of nine men, either climbers or skiers between ages 18 and 35, eight of whom also had HAPE, and had been evacuated from high-altitude locations. None had a history of previous HACE. Prior to hospitalization, study patients received initial treatment in the field with oxygen. Five had also received dexamethasone. Two received acetazolamide and nifedipine, and one was treated in a portable hyperbaric bag. All had mental status changes and/or ataxia in association with acute mountain sickness (AMS). Anoxic encephalopathy and toxic drug effects were excluded. Five study patients received repeat MRI scans during recovery, and four were also available for follow-up MRI *after* complete recovery. Six age-matched men who served as controls were equally divided between those who had been entirely well at altitude and three who had experienced HAPE without HACE. Their MRI scans were performed within 24 hours of returning to sea level, and they also matched the patient study group in their length of altitude exposures, which for all control subjects had occurred on Denali (Mt. McKinley).

Seven of nine study patients demonstrated intense white matter abnormalities suggesting vasogenic cerebral edema. Two patients with moderate illness had normal MRI findings. These appeared as intense T_2 signals exclusively in white matter, particularly in the posterior rounded end of the corpus callosum, known as the splenium, and in the centrum semiovale, but no changes were observed in gray matter. (*See Figure.*) All study patients recovered completely and their MRI changes resolved entirely on follow-up evaluations, although MRI resolution lagged behind clinical improvement. Control subjects showed no abnormalities on MRI. Hackett et al demonstrated what may be a useful diagnostic MRI correlate (i.e., reversible white matter edema and an early predilection for the posterior region of the splenium of the corpus callosum in patients with acute clinical HACE). The predominant mechanism was likely to be vasogenic edema, which primarily spreads along white matter tracts and involves a breakdown in the blood-brain barrier with movement of fluid and protein out of the vascular compartment. Hackett et al point out that this form of edema, although it cannot be entirely explained as yet, tends to respond to corticosteroid treatment and to resolve slowly, with preservation of brain tissue.

COMMENT BY FRANK J. BIA, MD, MPH

Hackett et al address several concerns in their own discussion of this work. Is white matter edema an incidental finding at high altitude? Three of their asymptomatic control climbers who were evaluated within 24 hours of returning from high altitude had no MRI abnormalities. This study also does confirm previous work indicating that brain edema does not seem to be caused by HAPE; however, a greater number of controls in both groups (climbers and skiers) would be of importance to truly exclude such causal associations. It is also not clear why two of four skiers with HACE in the study group did not demonstrate MRI changes. Hackett et al speculate this may be related to the increased effort, at higher altitudes, for more prolonged periods, among the climbers with HACE. One should

also be aware that this study cannot be generalized to all those who experience HACE at high altitude since both study subjects and controls were all men. Whether there are gender differences in the cerebral manifestations of HACE on MRI scanning will have to await further study, but it should not be assumed that future results that might be obtained in women at high altitude will be the same as those obtained here.

In reviewing this informative work, it brought to mind a series of three unusual cases reported by Schlim and Meijer earlier this decade.[3] They described acute manifestations of previously unsuspected brain tumors, which suddenly became symptomatic during acute exposure to high altitudes. Their symptoms might have easily been attributed solely to AMS, had they not persisted and been carefully evaluated. These included the onset of progressive right-sided hemiparesis in a 69-year-old woman after she had first experienced headaches upon arrival in Lhasa, Tibet. Subsequently, CT scanning revealed a left frontoparietal meningioma, later removed in Sweden. They also reported a 20-year-old woman with an unsuspected right frontal lobe meningioma who experienced left hemiparesis, fever, and seizures on arrival in Cusco, Peru, and a 16-year-old boy on a ski vacation in the Dolomites, who developed symptoms of headache, vomiting, and ataxia, later found due to a unsuspected malignant astrocytoma obstructing the third ventricle. Perhaps these lesions became clinically evident as acute exposures to high altitude induced acute cerebral edema in white matter that would have resolved, as described in the current study by Hackett et al, had they not occurred in patients who already had underlying lesions of the CNS? The current study contributes further to our understanding of both pathogenesis and natural history of HACE. When HACE fails to resolve or presents with atypical features, then we have to recognize such episodes as potentially representing more than HACE alone. It is studies such as these which will permit clinicians to do so with a greater degree of certainty in the future. ❖

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High-altitude cerebral edema (HACE) is characterized by each of the following except one. Which of the following statements is *not* characteristic of HACE?

a. HACE is often found in association with high altitude pulmonary edema (HAPE) even though it is not entirely explained by HAPE.

b. Cerebral edema associated with early HACE is cytotoxic and largely affects gray matter including regions such as the corpus callosum.

c. HACE may not always be manifest on brain MRI, even when there is clear-cut clinical evidence for its presence.

d. The cerebral edema associated with HACE is generally responsive to corticosteroid (dexamethasone) therapy.

e. The cerebral edema associated with HACE has been shown by brain MRI to have a predilection for the splenium of the corpus callosum.

Intradermal Rabies Vaccination

ABSTRACT & COMMENTARY

Synopsis: *Children who received intradermal vaccination had lower rabies-neutralizing antibody levels than children intramuscularly immunized.*

Source: Sabchareon A, et al. *Pediatr Infect Dis J* 1998; 17:1001-1007.

Concerned about the high cost of intramuscular rabies vaccine in developing countries, researchers in Thailand compared intradermal (lower volume and, hence, lower cost) and intramuscular use of purified Vero cell rabies vaccine as pre-exposure prophylaxis in children. Three doses of vaccine were given during a 28-day period to each of 190 children, and a booster dose was given a year later. Follow-up data were available from 82% of children one year after the primary series and from 62% of children two years following the booster dose. Children who received intradermal vaccination had lower rabies-neutralizing antibody levels than children intramuscularly immunized. Nonetheless, "adequate" protective titers were achieved in nearly all (94-100% at the different times tested) children whether they received intradermal or intramuscular vaccine. Side effects were generally minor and were similar in each treatment group.

COMMENT BY PHILIP R. FISCHER, MD

Rabies is still a uniformly fatal illness, and there are more than 50,000 human deaths due to rabies each year. Most fatalities occur in children in Asia, South America, and Africa, and exposure to rabid dogs is responsible for more than 99% of human rabies deaths worldwide. Human rabies is almost always associated with an actual bite wound, though other more subtle exposures have been reported. Control of animal rabies depends on vac-

cination of domestic dogs and elimination of stray dogs. Sadly, however, such control programs require heavy, ongoing expenditures.

Effective rabies vaccines are available. Pre-exposure vaccination provides significant protection and simplifies the post-exposure therapy by obviating the need for rabies immune globulin following exposure to rabies and by decreasing the number of needed post-exposure vaccine doses to two.

There are still, however, several controversial issues in regard to rabies vaccination. Who should be vaccinated? Which vaccine should be used? By which route should vaccine be administered? Cost is a significant factor in determining responses to these questions, and this study from Thailand is, therefore, helpful in identifying a lower cost means of effectively administering rabies vaccine to masses of children at risk of rabies in areas of limited financial resources.

The decision about whether to vaccinate a traveler depends on several individualized factors: age (more risk in children), planned activity (more risk in veterinary workers and spelunkers), destination (most risk in Latin America and Asia, only a few countries risk-free), duration of travel, access during travel to emergent administration of rabies immune globulin, and financial resources (as well as local cost of the pre-exposure vaccine that varies markedly from place to place). Whether immunized before the exposure, additional treatment is necessary following actual or presumed rabies exposure.

Until recently, there were two rabies vaccines available in the United States. Imovax is a human diploid cell rabies vaccine manufactured by Pasteur Merieux Connaught and has forms approved for intradermal and intramuscular use. Rabies Vaccine Adsorbed, produced by SmithKline Beecham, is available for intramuscular use. The FDA recently approved for marketing a new inactivated rabies vaccine (RabAvert, Chiron Corp.) that is grown in primary cultures of chicken fibroblasts. It is the first new vaccine against rabies to be introduced in almost 10 years and has been approved for both pre-exposure prophylaxis and post-exposure vaccination (see *TMA Update* 1998;8:23-24). A purified Vero cell rabies vaccine from Pasteur Merieux Connaught was used in the Thai study but is not currently available in the United States.

How high an antibody level is "protective" against rabies? The CDC and the WHO consider the lower limit of "protective" to be at different levels. By the higher WHO minimum protective titer, fewer Thai children achieved "adequate" levels, and the intramuscularly treated children were more likely to have "adequate" protection. By the CDC criterion, "protection" was almost always achieved, and there was no difference in efficacy between the two routes of administration. The Thai study provides evidence that the intradermal route will be widely effective and could find generalized use in developing country areas with limited financial resources. It is doubtful, however, that wealthier travelers would choose a route of administration that clearly prompts lower antibody levels that are not uniformly considered to be protective. If cost factors lead travelers to consider the intradermal route of this purified Vero cell rabies vaccine when it becomes available, travel medicine practitioners might, nonetheless, advise intramuscular use in travelers at risk of blunted anti-rabies immune responses (immunosuppressed individuals and individuals who must take chloroquine or similar antimalarials during the course of the rabies vaccination).

Children in the Thai study responded well to a booster dose regardless of their pre-booster antibody titer, and side effects were more common after the booster doses. It could be, as Sabchareon and colleagues point out, that repeated pre-exposure booster doses will not be needed in individuals who can have reasonable access to the two-dose post-exposure vaccination in the event of an animal bite.

This report is useful in leading the way to more affordable rabies prevention in financially challenged areas of the world. ❖

Effective pre-exposure rabies vaccination:

a. is currently available by both intradermal and intramuscular routes.
b. obviates the need for post-exposure rabies vaccination.
c. may be given by either intradermal or intramuscular routes using each of the vaccine preparations available in the United States.
d. is routinely given to children in developing countries.

Salmonella bacteremia in Southern Viet Nam

ABSTRACT & COMMENTARY

Synopsis: *Multidrug-resistant Salmonella typhi is a frequent cause of community-acquired septicemia in southern Viet Nam. As tourism to this part of southeast Asia increases, typhoid fever should be carefully considered in the differential diagnosis of febrile patients returning from the area. Multidrug resistant strains and potentially high mortality rates associated with them should be of concern to travel medicine practitioners.*

Source: Hoa NTT, et al. *Trans Royal Soc Trop Med Hyg* 1998;92:503-508.

A prospective study of community-acquired septicemia was conducted from mid-1993 to 1994 in southern Viet Nam. Patients were evaluated at the Centre for Tropical Diseases, Cho Quan Hospital, in Ho Chi Minh City. The microbiology, clinical features, and outcome were compared with studies from other developing countries. During this one-year study period, 3783 blood culture sets were obtained from 3365 patients. Five hundred eighteen had positive cultures (15.3%) and the isolate was considered a community-acquired, clinically significant non-contaminant in 437 patients (13%). Anaerobic blood cultures were not performed as a part of this study. The incidence of septicemia detected was 20.4 episodes per 1000 admissions. Gram-negative aerobes (facultative organisms) accounted for 90% of all isolates in documented cases of bacteremia. *Salmonella typhi* caused 67% (309 cases) and *Salmonella paratyphi* A accounted for 3%. Seventy percent of *S. typhi* were multidrug-resistant (MDR-resistant to chloramphenicol, co-trimoxazole, ampicillin, and tetracycline), and 4% were resistant to nalidixic acid. Three patients were co-infected with both *S. typhi* and *Plasmodium falciparum*.

The clinical features and outcomes for those patients with Salmonella-associated enteric fever were compared with those of patients with other types of septicemia. The patients with enteric fever were younger than patients with non-enteric fever (median age of 16 years vs 43 years). The median duration of illness before admission was 10 days for enteric fevers, which was longer than the duration of illness for other types of Gram-negative and Gram-positive bacteremia (4-5 days). Thirty-five percent of patients with enteric fever had diarrhea. Severe disease (with shock, impaired consciousness, gastrointestinal bleeding, intestinal perforation, renal failure, or jaundice) developed in 9% of the patients with enteric fever. However, severely ill patients were often admitted to other hospitals in the city. The mortality rate was lower in the patients with enteric fever than the patients with other forms of bacteremia (0.3% vs 23%).

The proportion of community-acquired septicemia due to *Salmonella sp*. was compared with studies from other developing countries. *Salmonella sp*. caused an unusually high (72%) proportion of septicemia in Viet Nam. In contrast to the current study, Hoa and associates cited a report on enteric fever in Thai children that had shown a decline of typhoid fever. This trend was attributed to improved hygiene and sanitation as well as the parenteral typhoid vaccination program for children that began in Thailand in 1977.[1]

COMMENT BY LIN H. CHEN, MD

Enteric fever is a major health problem in many developing countries and refers to both typhoid fever and paratyphoid fever. The current study of mostly urban patients from southern Viet Nam shows a strikingly high proportion of *Salmonella sp*., especially *S. typhi*, causing community-acquired septicemia. By comparison, a report from Hong Kong showed *Salmonella sp*. caused 27% of community-acquired septicemia in children, and *S. typhi* accounted for only one-third of these infections.[2] Travelers to southern Viet Nam appear to have a significant higher risk of potentially returning with typhoid fever, particularly given the median duration of illness of 10 days ensuing prior to admission. This is an area of the world where HIV is just beginning to emerge and the proportion of Salmonella-associated bacteremia due to non-typhoidal strains may increase as it has in Africa with the AIDS pandemic.

Epidemics of MDR *S. typhi* have been reported from numerous countries.[3,4] MDR *S. typhi* has unfortunately been associated with a higher mortality than infection with susceptible strains,[3] and it is alarming that a majority of the strains in the current report (70%) were MDR strains. It is also of concern that nalidixic acid-resistance is emerging, since the quinolone antibiotics have been widely and effectively used to treat multidrug-resistant typhoid fever.[5]

Given the high proportion of septicemia caused by *S. typhi*, the high percentage of MDR strains, and the emergence of quinolone resistance, travelers to southern Viet Nam should be particularly cautious regarding typhoid fever. Although food and water precautions are the most important preventive measures, an aggressive approach toward typhoid vaccination appears to be warranted for travelers to southern Viet Nam. Unfortunately, even a large inoculum of *S. typhi* can overcome the protective effects of typhoid vaccines, and typhoid fever should remain high in the differential diagnosis of febrile travelers returning from Viet Nam, even if they have received typhoid vaccine. ❖

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Which one of the following statements is correct?

a. *Salmonella typhi* is still universally susceptible to fluoroquinolone antibiotics.

b. Vaccination programs and improved hygiene have decreased the incidence of typhoid fever in some developing countries.
c. Fluoroquinolones should be used to treat multidrug-resistant and nalidixic acid-resistant *Salmonella typhi* infections.
d. Typhoid vaccines would generally eliminate all possibility of clinical infections associated with *Salmonella typhi*.
e. The prevalence of *Salmonella typhi*, as opposed to non-typhoidal Salmonella, infections increases in association with HIV-incidence.

Brief Report

Lariam or Lamasil?

By Carol A. Kemper, MD

Source: Lobel HO, et al. *JAMA* 1998;280:1483.

This letter to the editor describes three cases of drug overdose with antimalarials, two of which resulted from dispensing errors for patients prescribed terbenafine (Lamasil) for onychomyosis. The first patient mistakenly received mefloquine 250 mg daily for three weeks, and then 2-3 times weekly for six months. He became increasingly weak, depressed, disoriented, and developed parathesias for three months before the error was discovered. He had not fully recovered one year later. The second patient similarly received mefloquine 250 mg daily instead of Lamasil. Within 10 days, she developed ataxia, confusion, speech impairment, and high-frequency hearing loss. She continued to receive the incorrect drug for a total of 61 days before the error was detected. Only hearing loss remained one year later.

The third case, which was much more frightening, involved a patient in a California hospital with Plasmodium vivax infection. She received 1250 mg of mefloquine on day 1, and 1260 mg of primaquine on day 2, at which time she became acutely jaundiced. She continued to receive primaquine 15 mg per day for five days. She developed acute hepatic necrosis, and was temporarily placed on the liver transplant list, but fortunately recovered.

In contrast to mefloquine, which has a high toxicity margin, primaquine has a fairly narrow margin of toxicity. The usual adult dose is 15-30 mg daily, but the probable lethal oral dose is 5-50 mg/kg (about 350-3500 mg for this patient). Not only does the treatment of malaria require expert knowledge (or advice), but these cases demonstrate why it's better to write prescriptions using the generic name of drugs in most cases. We should all be aware of the potential for confusion of Lariam and Lamasil. (*Dr. Kemper is Clinical Assistant Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center, San Jose, CA.*) ❖

Primaquine has a fairly narrow margin of toxicity, while mefloquine has a high toxicity margin.
a. True
b. False