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INSIDE

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Presentations at the 49th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Houston, Texas, Oct/Nov 2000

CONFERENCE COVERAGE

Kids and Controversy

By Philip R. Fischer, MD, DTM&H

At work as at home, children often seem to stimulate controversy. During the 49th Annual Meeting of the American Society of Tropical Medicine and Hygiene in Houston, Texas, conference participants overloaded a large meeting room to hear a discussion of "Controversies in Pediatric Travel Medicine." With chairs full, some participants sat on the floor while others stood. Three expert speakers guided participants through consideration of the pediatric aspects of malaria prevention, air travel and altitude, and diarrhea management.

Malaria Prevention

Sheila Mackell, a pediatrician who cares for travelers within the Kaiser Permanente system in northern California, reminded conference goers about the proper use of clothes, nets, and permethrin to avoid mosquito bites. She then reviewed the history of the diethyltoluamide (DEET) controversy.

For decades, DEET has been used for millions of children with few side effects. In fact, it is estimated that approximately 30% of the population of the United States uses DEET each year. Among the millions who use DEET, 14 serious adverse reactions have been reported, and 13 of these were in children. There are, however, no data clearly linking the concentration of DEET to the risk of poor outcomes. The U.S. Environmental Protection Agency (EPA) rescinded their safety limits for the use of DEET in children a few years ago; the EPA now suggests only that DEET be used carefully (not on hands and only on exposed skin rather than under clothes).[1] Nonetheless, some pediatricians still suggest that children in the United States not use DEET during the first year of life and that they not use DEET in concentrations greater than 10%. Reviewing the data as well as the recommendations, Dr. Mackell found no evidence to suggest that pediatric use of DEET be limited in concentration or by age.

A seizure disorder is generally considered to be a contraindication to the use of mefloquine. What about mefloquine in children who have had febrile seizures? Febrile seizures occur in about 1% of children, and the great majority of these children do not subsequently have a persistent seizure disorder. Dr. Mackell, who lectures around the world on pediatric travel medicine, is not aware of any report of a mefloquine-related seizure in a child who had previously had a simple febrile seizure. Thus, mefloquine could likely be used safely in a child who only had a simple febrile seizure. If, however, the seizure was recurrent, long lasting, or associated with other neurologic deficits, the child could actually have an underlying seizure disorder; in these cases, an alternative to mefloquine would be considered.

Methylphenidate (Ritalin), like mefloquine, is postulated to lower a child's seizure threshold. There is, however, no evidence of danger when using mefloquine and methylphenidate at the same time.

Adult travelers sometimes carry a "stand-by" curative dose of an antimalarial to use in the event of a febrile illness. For children, Dr. Mackell advised, a febrile illness should be cause to immediately seek medical attention. Stand-by therapy would only be advised in very rare situations when medical care is totally unavailable.

Getting High

Karl Neumann, a pediatrician in New York who has been editing and writing travel medicine publications for years, then discussed issues relevant to children traveling in airplanes and at high altitude. He first considered the unborn child traveling by air. There is no evidence that fetal vital signs or fetal oxygenation are altered by travel in commercial aircraft. There might, however, be some concern about exposure to cosmic radiation. The exposure to cosmic rays is approximately 100 times higher at cruising altitudes than on the planet's surface. Thus, 10 hours of flight would provide a similar amount of radiation exposure to one chest radiograph. This seems not to pose any clinically significant risk for routine travelers who are pregnant, but there is still some question about what this might mean for pregnant aircraft crew members who have more extensive exposure to atmospheric radiation.

Should recently born children fly in commercial airplanes? Despite some age limits that some people might arbitrarily impose, available evidence suggests that newborns may fly safely. Their lungs are adequately developed, and their oxygen dissociation curve and relative polycythemia (compared to adults) actually would help them in oxygen-restricted environments.

Is there a risk of sudden infant death syndrome (SIDS; also called "crib death" or "cot death") related to air travel? Dr. Neumann referred to a recent *British Medical Journal* article and subsequent discussion.[2] Indeed, infants have lower oxygen saturation levels and more irregular breathing in atmospheres simulating an aircraft environment; there is not, however, any evidence that they are at increased risk of sudden death.

Dr. Neumann then went on to "debunk" some commonly held myths. He said that infants are not at particular risk of dehydration in airplanes. In fact, they do not even seem to be more irritable in planes than on the ground. The increase in intestinal air pressure (compared to the decreased aircraft ambient pressure) coupled with extra intragastric volumes of recent feedings might make children a bit more fussy. Thus, Dr. Neumann advises routine but not extra feedings for children in airplanes.

Can children with ear infections fly? Dr. Neumann surveyed more than 100 otorhinolaryngologists, and none had seen a case of ear problems related to air travel. In fact, most would not limit air travel because of a coincident ear infection. Similarly, there is no evidence that antihistamines and decongestants alter the incidence of earache with aircraft ascent or descent.

Should infants be restrained in airplanes? Again, this topic has stimulated much controversy, and Dr. Neumann noted that babies are the only on-board objects for whom restraint is not required during take-off and landing. There is anecdotal evidence that in-flight infant restraints might prevent one death or serious injury every two years. Car seats, however, are not designed to protect infants facing the sorts of impacts that occur during times of turbulence and crashes. There is also concern that mandated infant restraints in planes (with the resultant increases in cost) might actually prompt more children to travel by road rather than by air; this could be associated with more loss of infant life than would be prevented by such a measure. Thus, infant restraints (especially car seats) are not currently recommended for routine use in airplanes.

What about altitude sickness? A group of researchers in Denver, Colo., has studied altitude-related symptoms in preverbal children, and the incidence seems to be similar to that in older children and adults.[3] Rate of ascent relates to the risk of mountain sickness, but age and fitness do not. There is some evidence that having an upper respiratory infection while ascending might increase the risk of a child developing high altitude pulmonary edema. Asthma is not worse at altitude, and there is no convincing evidence that childhood seizure disorders are affected by altitude. Acetazolamide is probably safe in

children, but interventional studies have not been done in children going to altitude.

"Am I just another backpack?" The major issue, Dr. Neumann reminded workshop participants, is that families should keep the child's perspective in mind when planning trips. The child should not be considered as just another appendage to the parents' life. The activities and itineraries should be designed with the child in mind. If the child's voice could be heard, many "leisure" trips would be canceled or postponed. Travel medicine practitioners can try to instill a good dose of common sense into family travel planning.

Diarrhea

John Christenson, a specialist in pediatric infectious disease and pediatric travel medicine at the University of Utah, then treated workshop attendees to a discussion of diarrhea in traveling children. He reminded the gathered crowd that the epidemiology of travelers' diarrhea is similar in adults and children but that risk does vary a bit with age.

Dr. Christenson made it clear that children are not just "little adults." Medical therapy must be instituted with caution in young travelers. Diphenoxylate (Lomotil) can cause central nervous system effects and should be avoided in children. Kaolin-pectin combinations are not effective. Loperamide (Imodium) is effective at an adequate dose (0.8 mg/kg) but has been associated with some lethargy, sleepiness, and abdominal distension; it is generally not advised for young children, particularly those younger than 2 years of age. Probiotics such as lactobacillus seem harmless and might provide some protective efficacy; studies are continuing. Bismuth subsalicylate is somewhat helpful and can be used if needed, but it does carry a small theoretical risk of Reye syndrome.

Children, Dr. Christenson noted, should not be considered "second class citizens." Thus, it is not sensible that antibiotics considered ineffective against organisms currently causing diarrhea in traveling adults would be used in children. Since the organisms causing travelers' diarrhea are the same in adults and children and since antimicrobial resistance to trimethoprim-sulfamethoxazole has removed this agent from use as presumptive treatment in adults, then children, too, deserve more appropriate therapy when they have diarrhea. Since trimethoprim-sulfamethoxazole is no longer effective against many of the microbes causing diarrhea in traveling children, what other antibiotic should be used?

Azithromycin is highly effective against the organisms causing travelers' diarrhea, and it is safe in children. Though not licensed for use in pediatric patients, ciprofloxacin has been used in children and does not seem to cause joint or cartilage problems. Thus, one of these two agents should probably be the first choice for presumptive therapy of travelers' diarrhea in children.

Travelers' diarrhea, however, is a self-limited illness, and oral hydration can prevent the devastating consequences. Should antibiotics even be offered for presumptive treatment to children? In two reported studies of pediatric travel clinics, more than half of traveling children were offered antibiotics to use in the event of diarrhea. The hallways of the Westin Galleria continued to buzz with debate for more than 24 hours after Dr. Christenson's presentation. There is not full agreement about whether antibiotics should be used for travelers' diarrhea. Adding to the debate, however, Dr. Christenson provided clear reminders that effective antibiotics such as azithromycin and ciprofloxacin can indeed limit the duration and severity of diarrhea in traveling children as in traveling adults.

So, what should be done about diarrhea in traveling children? First, families might need to reconsider whether it is worth exposing their children to prevalent enteric flora; some trips might be postponed. Second, the use of oral rehydration and breastfeeding should be encouraged. Third, we should advocate for clean play areas and clean hands as well as for hygienic food and water. Prophylactic medications should not be used, and antibiotics should be limited to those that are effective such as azithromycin and, perhaps, ciprofloxacin. Antimotility agents should not be used in children younger than 2 years of age, but bismuth subsalicylate can be used if needed. And, children with bloody diarrhea should avoid antibiotics while seeking medical care.

Drs. Mackell, Neumann, and Christenson were well received. They managed to put available data before their audience and were able to suggest wise management decisions for the areas in which data are limited. Not all the controversies were resolved, but many participants were grateful to return to their practices better armed with a scientifically sound approach to the care of traveling children. ❖

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New Developments in Travelers' Diarrhea

By Lin Chen, MD

Updates on travelers' diarrhea were reviewed by Drs. H. DuPont, C. Ericsson, B. Connor, and D. Taylor at a symposium at the 49th Annual Meeting of the American Society of Tropical Medicine and Hygiene. Currently, the etiology of travelers' diarrhea (TD) is attributed to bacteria in 85%, parasites in 5-15%, and viruses in less than 5%. Enterotoxigenic *E. coli*, (ETEC) *Shigella*, *Salmonella*, and enterohemorrhagic *E. coli* occur more frequently in the summer, while *Campylobacter* and viral pathogens occur more frequently in the winter. Illness occurs more frequently during the first week of travel, and in children 0-2 years of age as well as young adults. Other risk factors include achlorhydria, hypochlorhydria, the use of H_2 blockers or proton pump inhibitors, blood group O, location of food consumption, tap water, alcohol, and swimming. Rainy season increases the risk for TD (*Dupont*).

Food and water precautions remain the primary prevention in TD. Nevertheless, *Lactobacillus* appears to provide 62% protection compared to placebo.

Current and future approaches to symptomatic and antimicrobial therapy of TD were discussed by Dr. Dupont. Bismuth has antisecretory and antimicrobial effects and leads to 50% decrease in stool volume. Antimotility agents can cause up to 80% reduction in stool by slowing down the intestinal transit. An oral antisecretory drug, Zaldaride, which works as a calmodulin inhibitor, is being investigated for use by travelers. Proveri (Normal Stool Formula), a chloride channel inhibitor, is available commercially and can be used in AIDS-associated diarrhea as well as in TD. Racecadotul, an enkephaline inhibitor, is being studied in adults and children with acute diarrhea.

Newer antibiotics being evaluated for the treatment of TD include azithromycin, pivamdinicillin, and rifaximin. Studies are being conducted in Mexico, Jamaica, Guatemala, and Kenya on rifaximin. In countries where the risk for TD is high, empiric treatment is recommended with levofloxacin 500 mg/d for three days (or ciprofloxacin 500 mg b.i.d.). In Thailand and Barcelona, Spain, where *Campylobacter* exhibit a high rate of resistance to fluoroquinolones, azithromycin is recommended as empiric treatment for TD. The adult dose is 500 mg on day #1, and 250 mg on days #2 and #3 p.r.n. The pediatric dose is 10 mg/kg on day #1, and 5 mg/kg on days #2 and #3 p.r.n. Furazolidine at 7.5 mg/kg/d may also be used in children.

Dr. Conner discussed chronic diarrhea in the returning traveler. It is estimated that 3-10% of travelers develop diarrhea lasting longer than two weeks, and that up to 3% of travelers have persistent diarrhea lasting longer than 30 days. Etiologies include infections, postinfectious gut damage, malabsorption, unmasking of preexisting gastrointestinal problem such as inflammatory bowel disease, celiac sprue, irritable bowel syndrome, and colon cancer, and the remainder are unknown. It was noted that the empiric treatment of TD with antibiotics correlated with a decrease in the cases of tropical sprue.

Evaluation of patients with chronic diarrhea includes antibiotic trials, elimination diets (of lactose, gluten, fat), antispasmodics such as 5HT3 antagonists, antidiarrheal agents, fiber, and cultured *Lactobacillus*. Gliadin antibody and tissue transglutamine antibodies are suggested for evaluation of sprue.

Finally, Dr. Taylor discussed vaccines for the prevention of TD. Various *Shigella* vaccines are being developed. These include a live attenuated vaccine (SC602), *S. flexeneri* 2a vaccine (SC 603), *S. sonnei* WRSSI vaccine, and a *S. dysenteriae*/1csa/stxA mutant. Vaccines against ETEC include the inactivated whole cell plus CT toxoid and a recombinant CS6. A *Campylobacter* inactivated whole cell with mucosal adjuvant is being developed.

Additional abstracts of interest to our readers are:

Abstract #60. Typhoid fever in travelers: Who should we vaccinate? Steinberg EB, et al.

All cases of *S. typhi infection* reported to the U.S. Center for Disease Control (CDC) and Prevention's National Typhoid Fever Surveillance System between 1994-1999 were reviewed. A total of 1166 laboratory-confirmed cases were reported, with 29% from California and 24% from New York. The median age was 22. A total of 26% were children younger than 10 years old; 73% of infections were acquired abroad. Six countries accounted for 70% of these infections: India (30%), Pakistan (13%), Mexico (10%), Bangladesh (6%), Haiti (6%), and the Philippines (5%). Of the travelers who reported their reason for travel, 77% of cases were visiting family, 14% were immigrants to the United States, 9% were tourists, and 3% were business travelers. Sixty-eight percent of travelers stayed less than six weeks abroad. Vaccination should be considered for the high-risk travelers, even for short-term travel, travelers to the Indian subcontinent, for children, and persons visiting family. (See Mileno MD. *Travel Medicine Advisor Update* 2000;10:47-48.)

Abstract #291. Duration of shedding of Cyclospora oocysts in U.S. citizens. Eberhard ML, et al.

The CDC studied symptomatic but untreated subjects in two outbreaks of *Cyclospora cayetanensis* in 1999.

Oocyst shedding persisted for 6.5-8.5 weeks from the time of exposure. All three subjects reported malaise, fatigue, nausea, and intermittent diarrhea throughout the time of shedding. Diarrhea abated rapidly after the cessation of oocyst shedding, but fatigue persisted.

Abstract #306. Three-year surveillance of acute diarrhea in U.S. military personnel in Thailand: Role of Campylobacter jejuni/coli in disease severity and clinical outcome. Tribble D, et al.

Clinical and microbiologic data collected on U.S. military personnel presenting with acute diarrhea in Thailand from 1995, 1998, 1999 showed *Campylobacter jujuni/coli* to be the most commonly isolated pathogen (33%). Nontyphoidal *Salmonella* spp. were isolated in 21%, ETEC 11%, multiple bacterial isolates in 20%, and no isolates in 32%. *Campylobacter* isolates presented more frequently with fever, headaches, myalgias, abdominal cramps, and decreased ability to work. Initial antibiotic used in 1995 and 1998 was a fluoroquinolone in more than 98% of patients, whereas in 1999 azithromycin was used in 30%. FQ resistance was more than 85% during all three years. Infections caused by *Campylobacter* spp. were characterized by delayed recoveries and higher failures.

Abstract #309. Enterotoxigenic Escherichia coli as a cause of diarrhea among Mexican and U.S. adults in Mexico. Bouckenooghe AR, et al.

Stool samples were obtained from resident Mexicans and U.S. travelers presenting with acute diarrhea in Guadalajara, Mexico. The most common pathogen was ETEC in both groups (10.9% vs 18.9%). *Shigella* was more common in the U.S. travelers (2.3% vs 0.4% of Mexicans). *Entamoeba histolytica* was more commonly identified in the Mexicans (3.7% vs 0% in U.S. travelers). Symptoms were milder and duration shorter in the Mexican residents.

Abstract #549. Emergence of resistant fecal flora in healthy persons during travel to Guadalajara, Mexico. Huang DB, et al.

Thirty-nine healthy students from the United States were studied for development of resistant fecal flora. Stool specimens were obtained upon their arrival to Guadalajara, Mexico, and then weekly for three weeks. None of the subjects took prophylactic or therapeutic medications for TD. Increased growth of aerobic bacteria and trimethoprim-resistant bacteria (predominantly *E. coli*) were noted over the course of this study. The isolated *E. coli* were also resistant to ampicillin (44%), chloramphenicol (39%), doxycycline (89%), erythromycin (100%), and furazolidone (72%). Travel to a developing country appears to be a risk in acquiring antibiotic-resistant fecal flora.

Abstract #553. Natural history of enteroaggregative Escherichia coli infection among U.S. travelers in Mexico. Adachi JA, et al.

Forty U.S. travelers to Guadalajara, Mexico, collected stool samples upon arrival and weekly for four weeks. Enteroaggregative *E. coli* (EAEC) colonization was identified in five asymptomatic subjects. By the fourth week, EAEC was identified in 16 subjects. Fewer EAEC infections were associated with diarrhea compared with ETEC infections.

Abstract #303. Surveillance of epidemic and sporadic cholera-like disease occurrence throughout Indonesia including the emergence of Vibrio cholerae 0139 serotype 1993-1999. Corwin AL, et al.

Abstract #307. Prevalence of infection with waterborne pathogens: A seroepidemiologic study in children 6-36 months old, San Juan Sacatepequez, Guatemala. Steinberg EB, et al.

Abstract #308. Surveillance for bacterial diarrheal disease in rural western Kenya, 1997-1999. Brooks JT, et al.

Abstract #541. A comparison of three transport mediums for recovery of intestinal parasites. Van CT, et al.

Abstract #551. Antibiotic treatment for traveler's diarrhea: A meta-analysis of published reports. De Bruyn G, et al.

Abstract #557. Prevalence of Shigella spp. and the re-emergence of Shigella dysenteriae in Indonesia. Subekti DS, et al.

Abstract #668. Detection of Cyclospora cayetanensis DNA by PCR in experimentally contaminated raspberries and blackberries. Da Silva AJ, et al.

Update on Malaria and Pregnancy

By Michele Barry, MD

Synopsis: *A short review of the current literature concerning pregnancy and malaria was presented at a Meet the Professor session in Houston, Texas, last fall. Three articles published during the past year were discussed in detail.*

Sources: Lindsey S, et al. Effect of pregnancy on exposure to malaria mosquitoes. *Lancet* 2000;355:1972; Diagne N, et al. Increased susceptibility to malaria during the early postpartum period. *N Engl J Med* 2000;343:598-603; Nosten F, et al. Effects of plasmodium vivax malaria in pregnancy. *Lancet* 1999;354:546-549.

The first article described an interesting study, comparing the relative attractiveness of pregnant and nonpregnant women to mosquitoes in rural

Gambia. Each night, three pregnant and nonpregnant women slept alone under a bed-net in six identical huts. They were given malaria chemoprophylaxis, and in the morning the total numbers of collected mosquitoes from each hut were enumerated. The procedure was carried out with the same group of women for three consecutive nights and was repeated with 12 different groups of women. Twice as many *Anopheles gambiae* mosquitoes—the main malaria vector in Gambia—were attracted to pregnant women (mean 6.3 per night 95% confidence interval [CI] 4.5-8.7) than to their nonpregnant counterparts (mean 3.1 per night 95% CI 2.1-4.5; P = 0.0002). Lindsey and colleagues postulate three mechanisms by which pregnant women might be more attractive to these vectors: 1) increased CO_2 release due to increased respiratory rate during pregnancy; 2) increased blood flow to peripheral skin causing release of attractive volatile substances; and 3) Pregnant women tended to leave their nets for urination at night twice as frequently as nonpregnant women, offering more movement as a mosquito attractant.

Pregnancy is associated with increased susceptibility to malaria. It is generally agreed that this increased risk ends with delivery; persistence of susceptibility during puerperium has never been investigated. Diagne and colleagues described a study of 71 pregnancies in 38 women in a malaria endemic area within Senegal, from the year before conception to the year after delivery. They note an increased incidence of malaria during the second and third trimesters. Of great interest, the susceptibility to malaria continued until 60 days after delivery, perhaps supporting the view that depression of components of immunity is a key factor involved in malaria in pregnant women (akin to "galloping consumption" seen in the postpartum woman with tuberculosis.) Diagne et al suggest malaria chemoprophylaxis for pregnant women should be continued for at least two months after delivery.

The last subject reviewed was a prospective study of pregnant Karen women living in camps for displaced people on the western border of Thailand. Effects of *P. vivax* on anemia and pregnancy outcome were compared with those of *P. falciparum*. As with *P. falciparum*, *P. vivax* malaria during pregnancy was more common among primigravidas and was associated with anemia and increased risk of low birth weight. Unlike *P. falciparum*, *P. vivax* malaria was not associated with miscarriage, stillbirth, or shortened duration of pregnancy. Although the degree of anemia and low birth weights were not as severe as those seen in *P. falciparum*-infected pregnant women, Nosten and associates still felt *P. vivax* chemoprophylaxis during pregnancy was justified. ❖

Mycobacterium ulcerans and Buruli ulcer: A Mycobacterium That Doesn't Follow the Rules

ABSTRACT & COMMENTARY

Synopsis: *The recent description of a patient with Buruli ulcer originating from China presents an opportunity to review the somewhat atypical and frankly unusual manifestations of this disease. Its epidemiology, pathology, and even the growth characteristics of the causative organism make this an easily missed infectious disease, with a clear potential for harm to travelers in certain environments. Yet, as this case will illustrate, we can expect to see more of Buruli ulcer where we least expect to find it.*

Source: Faber WR, et al. First reported case of *Mycobacterium ulcerans* infection in a patient from China. *Trans R Soc Trop Med Hyg* 2000;94:277-279.

A 40-year-old chinese woman, who had been living in Europe for nine years, traveled during July and August to Shan Dong province, People's Republic of China. She walked barelegged in grassy areas near fruit trees, and noted numerous apparent "mosquito bites." Three months later, a pale swelling, with a slightly depressed center, appeared on her left leg. Four months later it was excised while she again visited China, but it ulcerated instead of healing. When she returned to The Netherlands, a Ziehl-Neelson stain showed acid-fast bacteria that had been obtained from a painless 3 × 3.5-cm lesion with undermined borders and a necrotic bed.

Histopathological examination of tissue did not reveal granulomata; instead, there was extensive eosinophilic necrosis and some mononuclear cell infiltrate containing both scattered and clumped extracellular acid-fast bacteria. PCR analysis ultimately demonstrated sequences specific for *Mycobacterium ulcerans*. The causative organism was isolated after 40 days culture but only at 30°C. The organism was later found to be resistant to rifampicin *in vitro* and required additional curative surgery in addition to antituberculous therapy with ciprofloxacin and rifabutin. As the acid-fast organisms were gradually eliminated, tissue biopsies taken from the healing area changed and only then demonstrated a granulomatous reaction at this later stage of her disease.

COMMENT BY FRANK J. BIA, MD, MPH

Recent World Health Organization (WHO) initiatives

aimed at stopping the spread of Buruli ulcer disease, particularly in West Africa, underscore the potential importance of this disease, potentially for travelers to countries such as Ghana, Benin, the Ivory Coast, and Togo.[1-5] MacCallum et al established the association between *M. ulcerans* and the Australians noted lesions of Bairnsdale ulcer in 1948. Sir Albert Cook had first described this disease in Uganda as early as 1897.[2] The name, Buruli ulcer, now derives from the 1961 outbreak in Uganda, but the disease has been identified not only in Australia but also in Papua New Guinea, Sri Lanka, Mexico, Peru, and French Guyana. Disease distribution is not even throughout what are considered endemic areas. Rather, it tends to be both focal and intense, at times affecting more than 20% of the population, particularly those residing or working in low lying river and swamp regions, and possibly involving aquatic water insects as vectors living in slow-flowing stagnant water.[4]

Pediatric cases outnumber adults in most series and approximately 70% of cases occur in children younger than 15 years of age. The disease begins as a subcutaneous nodule that appears spontaneously, as opposed to arising from a previous site of traumatic injury. It is not known whether the source of infection is actually either traumatic or due to aerosol transmission of organisms—possibly even inoculated by insect vectors. However, there is no known person-to-person spread of this disease nor association with HIV infections.

In the experimental guinea pig model, areas of fibroblastic cell growth and necrosis within cutaneous lesions are found. The role of mycolactone toxin production in the destruction of subcutaneous tissue is critical.[2] Mycolactone is a nonimmunogenic polyketide-derived macrolide. Once an ulcerative lesion is established, antibiotics alone, without aggressive surgical intervention, will not be curative.

M. ulcerans is rather slow growing mycobacteria and may require upward of 6-9 months for primary isolation on solid media. It is analogous to *M. marinum*, being thermosensitive, growing best at 31-33ºC, but not at 37ºC, and like *M. marinum*, causing cutaneous disease. Semret et al reported a better experience isolating *M. ulcerans* with selective liquid media containing antibiotics, supplemented with 10% lysed sheep blood cells and polyoxyethylene stearate.[1] Because of its slow rate of growth on solid media, overgrowth by contaminants is frequently a problem during isolation. Unfortunately, NaOH is used in standard decontamination procedures and it inhibits the growth of *M. ulcerans*. Although a polymerase chain reaction (PCR) test is available in reference laboratories, clinical diagnosis determines therapy in endemic regions of the world.

To understand the evolution of clinical Buruli ulcer disease, it is critical to realize that the pathogenesis of this infection is quite unlike that of any other mycobacterial disease. Early lesions contain many bacteria and show extensive coagulative necrosis in the lower dermis and subcutaneous fat. Clumps of organisms are visualized, but unlike lepromatous leprosy they are rarely intracellular and there is little inflammatory response or granuloma formation. Disease progression involves both nerves and blood vessels. When epidermal undermining occurs, ulceration follows. During healing, granuloma formation and granulation tissue with epidermal ingrowth become evident. The initial necrosis within skin lesions is found beyond the site of bacterial proliferation, suggesting the macrolide toxin mediated effects are occurring without inducing any inflammatory responses. Sterile filtered supernatants of *M. ulcerans* are capable of producing these cytotoxic and ulcerative effects. Skin test positivity (burulin test) does not occur until patients are well into the healing phase of the disease.

Antibiotics administered without surgical intervention may simply not be efficacious and could lead to disfiguring lesions. These may require extensive surgical excision and skin grafting, possibly even amputation. Although the antileprosy agent, clofazimine, has *in vitro* activity against *M. ulcerans*, without surgery, it has not been beneficial. Usually resistant to isoniazid, other agents such as dapsone, streptomycin, rifampicin, and, more recently, clarithromycin have all been shown to have activity against *M. ulcerans*; however, adjunctive surgery appears to be critical for cure. Antibiotic sensitivity patterns alone do not predict clinical responses. Lesions may progress and accelerate with aggressive antimicrobial therapy alone. The role of localized heat application to skin lesions and the topical application of phenytoin to skin ulcers have unclear benefits, if any, for current therapy.[3] ❖

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CME Questions

1. **Experts at the ASTMH Houston meeting recommended that traveling children:**
   a. use DEET only in concentrations less than or equal to 10%.
   b. use mefloquine if indicated even if they have a past history of a simple febrile seizure.
   c. always use carseats on airplanes if younger than 2 years old.
   d. use trimethoprim-sulfamethoxazole as the first choice for presumptive treatment of traveler's diarrhea.

2. **In the study described, pregnant women may have been more attractive to *Anopheles gambiae* mosquitoes than their non-pregnant counterparts because:**
   a. pregnant women had increased serum progesterone levels.
   b. pregnant women used bed nets incorrectly.
   c. pregnant women expired more CO_2.
   d. pregnant women do not use their antimalarials or repellents.
   e. pregnant women offer a greater surface area than controls who are not pregnant.

3. **Buruli ulcer, associated with infection caused by *Mycobacterium ulcerans*, is characterized by each of the following except one. Which statement regarding Buruli ulcer disease is *false*?**
   a. The causative organism is thermophilic and grows best at 42ºC in the dark.
   b. Most cutaneous lesions appear to arise spontaneously rather than as the direct result of a traumatic injury.
   c. Early lesions of Buruli ulcer do not demonstrate a typical granulomatous response.
   d. Growth of *M. ulcerans* on solid media is slow and often hindered by competing growth of contaminating microflora.
   e. The mainstays of therapy are antibiotics and surgery. Without surgery, antibiotics are unlikely to cure an established skin lesion.

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