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Blastocystis hominis: Pathogen or Commensal?

ABSTRACTS & COMMENTARY

Synopsis: Blastocystis hominis*, a protozoan parasite, is frequently identified in stools of returned travelers. There is, however, no conclusive evidence that this parasite causes symptoms in humans or that it requires specific treatment.*

Sources: Chen T, et al. Clinical characteristics and endoscopic findings associated with *Blastocystis hominis* in healthy adults. *Am J Trop Med Hyg*. 2003;69:213-216; Murga-Gutierrez SN, et al. Intestinal parasites associated with acute diarrheal disease in children less than five years of age, from Alto Trujillo, Peru; Marcos L, et al. High rates of infection from intestinal parasites in different regions of Peru and the necessity of control and prevention programs: A public health problem in rural areas; Maco V, et al. Strongyloidiasis in the Amazon: A clinical and epidemiological study in soldiers. *All presented to the annual meeting of the American Society of Tropical Medicine and Hygiene. Philadelphia. December 2003.*

Chen and associates described the clinical and endoscopic findings associated with *Blastocystis hominis* infections in immunocompetent adults. They evaluated 99 individuals with stools positive for *B hominis* but negative for other parasites. These cases were compared with 193 controls who had negative stool exams for parasites. Cases and controls were matched for age, gender, and date of examination. Stool specimens were investigated by a direct wet film method for detection of leukocytes, ova, and parasites. All subjects underwent upper gastrointestinal endoscopy and sigmoidoscopic examination. Most of the subjects with positive stool exam for *B hominis* were asymptomatic (88%). There was no difference in gastrointestinal symptoms (nausea, abdominal discomfort, flatulence, and diarrhea) among cases or controls ($P = .94$). None of the subjects with positive stool smears for *B hominis* had the appearance of colitis or colonic ulceration on sigmoidoscopy. Fecal leukocytes were absent in all cases. There was no significant difference in blood cell counts, sedimentation rates, incidence of eosinophilia, or guaiac test results between cases and controls. Interestingly, an increased prevalence of *Helicobacter pylori* was found among cases in this study. Chen et al were not able to demonstrate any associated pathogenicity of *B hominis* infections.

Murga-Gutierrez and colleagues studied 72 stool samples from children with acute diarrhea and 48 samples from children without diarrhea in the same area of Peru. *B hominis* was identified in 44% of the samples from children with diarrhea and in significantly fewer children ($P < .01$) without diarrhea. Though causality was not determined, they concluded that *B hominis* is at least associated with acute diarrheal disease in children.

In a prevalence survey of 9 communities of Peru reported by Marcos and colleagues, *B hominis* was found in 30% of individuals tested (aged 1-52 years, mostly children). In Maco and colleagues' study of young adult male Peruvian military members, however, *B hominis* was identified in only 1%.

COMMENT BY MUHAMMAD R. SOHAIL, MD, AND PHILIP R. FISCHER, MD, DTM&H

B hominis is a protozoan parasite that is commonly found in the human intestinal tract. As seen in the 4 studies noted above, this parasite is frequently found in individuals both with and without gastrointestinal symptoms, but the prevalence of infection varies among various population groups studied. Since its original description 90 years ago, much controversy has surrounded its taxonomy, diagnosis, and pathogenicity in humans.

B hominis is an obligate anaerobic protozoan with worldwide distribution. In humans, it resides in the colon and cecum. The mode of transmission of *B hominis* is thought to be via the fecal-oral route. Higher prevalence rates of *Blastocystis* have been reported from developing countries (30-50%), compared with more developed parts of the world (1-10%). In such areas, travel to tropical regions is a known risk factor for acquisition of *B hominis* infection, as is the use of untreated water, abnormal gastrointestinal function, and immunosuppression.

In previously published case series where *B hominis* was presumed to be a pathogen, symptoms attributed to this organism included nausea, anorexia, acute or chronic diarrhea, abdominal pain, cramping, bloating, and fatigue. There are a few case reports of invasive disease attributed to *B hominis*, including both hemorrhagic procto-colitis and the finding of *B hominis* in the synovial fluid of a patient with rheumatoid arthritis who was on oral corticosteroids.

The actual pathogenic role of *B hominis*, however, has been a subject of much controversy. There are some published data to suggest a pathogenic role for *B hominis* in certain animals. In a murine model, Moe et al infected immunocompetent mice with fecal cysts of *B hominis*.[1] Infection was self-limited, but some mice showed weight loss and lethargy. Histological examination of the cecum and colon showed intense inflammatory-cell infiltrate, edematous lamina propria, and mucosal sloughing. However, no organisms were seen invading the colonic wall. In a study of guinea pigs infected with *B hominis*, inflammation of intestinal mucosa and invasion of superficial layers were seen. However, no similar histopathologic findings have been reported in case-control studies of humans, including Chen et al's study as summarized above.

A careful review of published literature suggests that Koch's postulates have not yet been satisfied, and several factors complicate the establishment of *B hominis* as a true pathogen in humans. First, some studies suggesting *B hominis* is a human pathogen, such as that of Murga-Gutierrez et al, are case reports or case series and uncontrolled retrospective reviews. Most studies that include control populations have failed to show a significant difference in *B hominis* prevalence or symptoms between symptomatic cases and asymptomatic controls. Second, there is a lack of standardized criteria for diagnosis of *B hominis* infection. In fact, it is conceivable that, similar to *Entamoeba* species, there may be identically appearing virulent and avirulent strains of *B hominis*. Also, a carrier or convalescent asymptomatic state might occur, as with *Giardia* and *Cryptosporidium* infections. Third, some authors have suggested that host immune status may determine both the presence and severity of symptoms. However, in a detailed study of homosexual men in which *B hominis* was the most commonly identified enteric parasite,[2] there were no differences in either prevalence or symptoms between HIV-positive and HIV-negative individuals. Fourth, any presumed response to treatment may be secondary to the eradication of other concurrently infecting, but undiagnosed, pathogens.

Chen et al's study is useful in that it found no clinical or endoscopic evidence of pathogenicity in 99 individuals with isolated *B hominis* infection. In another case-control study, Udkow et al examined fecal smears from 182 asymptomatic controls and 125 symptomatic patients.[3] No statistically significant difference in prevalence of *B hominis* was found between the groups. In addition, the clinical profile of subjects with *B hominis* and those not infected was similar, and no correlation was found between the presence of *B hominis* and that of fecal leukocytes. High stool concentrations of *B hominis* were more frequent, as were other pathogenic protozoa, in symptomatic patients than in those who were asymptomatic, suggesting that presence of *B hominis* in stools should alert clinicians for possible presence of other, coincident enteric organisms. Similarly, in Chen et al's study, *B hominis* enteric colonization was associated with hepatitis B and *H pylori* infection.

Some authors have suggested that the burden of organisms in stool correlates with symptoms in patients with *B hominis* infection, but results of several studies have refuted this argument. In a case-control study among expatriates and tourists in Nepal, investigators compared the prevalence of the organism among patients with diarrhea to that among a control group without diarrhea.[4] There was no difference in detection rate of *B hominis* among cases and controls (56 of 189 patients

with diarrhea [30%], compared with 40 of 112 asymptomatic controls [36%]). In addition, no correlation was found between higher parasite concentrations and the severity of diarrhea. Other enteric pathogens were detected in 68% of these cases. Results of this study also suggest that, despite the high prevalence of the organism among travelers and expatriates, *B hominis* does not cause diarrhea in this population, and there is no correlation between organism load and symptoms of infection.

Some studies have suggested that abnormalities of the gastrointestinal system may predispose to colonization and overgrowth of *B hominis*. Reported gastrointestinal abnormalities in such cases have included intestinal obstruction, malignancy, and irritable bowel syndrome. This suggests that *B hominis* may be a marker of other functional or organic enteric diseases, and its presence in stools should prompt clinicians to investigate for such causes in appropriate settings.

Without clear evidence for the pathogenicity of *B hominis*, the treatment of *B hominis*-positive individuals is also plagued with controversy. Treating children with *B hominis* correlated with improved resolution of diarrhea in one study and prompted the investigators to speculate that *Blastocystis* is indeed a human pathogen.[5] In HIV-positive patients with bacterial enteritis and either *Blastocystis* or *Cryptosporidium*, treatment with rifaximin facilitated clinical recovery and clearance of parasites.[6] Similarly, cotrimoxazole treatment of children and adults with *Blastocystis* and diarrhea led to clinical and parasitologic cure.[7] Metronidazole is the drug most frequently used to treat *B hominis* infection and has been associated with parasite clearance and symptomatic improvement.[8] Nonetheless, it is not known whether these agents help patients by clearing the *Blastocystis* or by eradicating another concurrent, but not identified, infection.

In summary, much remains to be learned about *B hominis* infections. In fact, a recent comprehensive review referred to *B hominis* science as "terra incognita."[9] However, based on the current state of knowledge, we believe that the pathogenic role of *B hominis* in humans is not established, and treatment directed at eradication of *B hominis* is not indicated. The presence of *B hominis* in stools of patients with gastrointestinal symptoms should prompt clinicians to look for other unrecognized enteric pathogens and noninfectious causes of gastrointestinal symptoms. In the absence of any other defined cause of symptoms, treatment with metronidazole or cotrimoxazole may be offered, keeping in mind that resolution of symptoms may be secondary to elimination of coinfections rather than to the eradication of *B hominis*. ■

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ASTMH Symposium on Neurocysticercosis

SPECIAL REPORT

By Michele Barry, MD, FACP

DR. ROBERT GILMAN CONVENED AN IMPORTANT symposium on neurocysticercosis (NCC) at the annual meeting of the American Society of Tropical Medicine and Hygiene. During that symposium, Dr. Theodore Nash from NIAID reported on the increasing evidence indicating that calcific neurocysticercosis is not necessarily clinically inactive, but may be a cause of seizures and focal symptoms associated with episodic perilesional edema. It is well known that seizures may be

common when viable or degenerating cysts are present. In contrast, few if any symptoms have been attributed previously to chronic calcific cysticercosis. Dr. Nash presented the case of a 48-year-old woman, born in the United States, who was referred to the NIH for cysticerosis contracted in India and found to be refractory to medical therapy. She was treated in 1986 when she had fever, multifocal seizures, and positive serology. By 1987, no cystic lesions remained, but 55 residual calcified cysticerci were scattered in her brain parenchyma. She then presented with episodic epilepsy and neurologic symptoms over many years, always precipitating full antiparasitic drug therapy along with corticosteroids. Each relapse was associated with perilesional edema appearing as a bright signal using MRI flair or T2 imaging.

Dr. Nash postulated several potential mechanisms. They included direct injury to brain tissue associated with single calcified granulomas. Such lesions could cause gliosis around foci and be associated with seizure activity. Also, some of the calcified lesions may have contained a scolex, as has been reported previously. These could periodically release parasitic antigens resulting in perilesional edema. Another hypothesis was calcium toxicity as a possible cause of seizures. Calcium might form an insoluble matrix that could release incorporated antigens on occasion. Corticosteroids and multiple anticysticidal courses of therapy were used in treating his patient with relapsing perilesional edema (*see Suggested Reading*).

In a separate presentation by Dr. Hector Garcia of Universidad Peruana Cayetano Heredia in Lima, Peru, more data were presented to resolve the issue as to whether antiparasitic drugs are necessary for acute NCC with 20 or fewer cystic lesions. They conducted a double-blind, randomized trial in 120 patients with seizures due to parenchymal NCC with 20 or fewer cysts. All patients were given standard anti-epileptic treatment and randomized to treatment with albendazole 400 b.i.d. for 10 days and dexamethasone 0.1 mg/kg/d for 10 days or double placebo for 10 days. Patients were evaluated by MRI scanning at 6 months and CT scans done 12 and 24 months after treatment. Clinical evaluations were performed at day 15 and 30 and every 3 months for 2 years or for 1 seizure-free year after withdrawal of anti-epileptic drugs. While the overall numbers of patients with 1 seizure were the same for both groups, the frequency of grand mal seizures was significantly lower (65%) in the treatment group. At 6 months, the placebo group had 87% viable cysts by CT scan and, surprisingly, the albendazole/dexamethasone group had 41% viable cysts by CT criteria. They concluded that antiparasitic drugs are the treatment of choice for this type of NCC.[1]

COMMENT BY MICHELE BARRY, MD, FACP

Finally, there has been some resolution of the question about treating low-burden NCC or single parenchymal cysts. Clearly, the treatment group in the data presented by Garcia showed fewer grand mal seizures after treatment.[1] In an accompanying editorial, Dr. James Maguire points out that more patients in the albendazole group had seizures during treatment, as would be expected, but by 2 months this trend reversed and the placebo group had more generalized and more frequent seizures for the rest of the 18-month follow-up.[2] What is curious about the results of therapy was the strikingly poor success rate for the eradication of viable cysts using a 10-day course of albendazole (40% viable cysts persisted). This is surprising given that an 8-day course of albendazole has been shown to be equivalent to a 15-day course in other studies. Perhaps MRI follow-up is a more sensitive way to demonstrate cyst viability? Perhaps we should be treating with longer course therapy?

Dr. Nash's presentation of the apparently relapsing symptoms of NCC, correlating with perilesional edema around appropriately treated calcified lesions over many years, implies some possible episodic immunologic reactions to parasitic antigen in old, calcified granulomas among other explanations. Regardless of the explanation, attention must be paid. Leutscher and Andriantsimahavandy reported on their evaluation of 73 Peace Corps volunteers who had been stationed in Madagascar, where cysticercosis is endemic.[3] Six (8.2%) were found to be seropositive; 1 demonstrated 2 intraparenchymal noncalcified cysts in the frontal lobe requiring therapy. Screening asymptomatic people who have immigrated from, or been long-term residents within, endemic areas for cysticercosis calls for increased consideration of screening and therapy based upon these findings. ■

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Suggested Reading

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Spotted Fever Group Rickettsiosis Among US Travelers

ABSTRACT & COMMENTARY

Synopsis: *Travelers returning from Africa are at risk for having acquired spotted fever rickettsiosis. Diagnosis requires antibody assays for IgG in paired acute and convalescent sera against* Rickettsia *antigens or immunohistochemical stains on skin biopsy specimens. The diagnosis can be missed if convalescent sera are obtained too early; therefore, convalescent specimens should be obtained at least 28 days after the onset of illness.*

Source: McQuiston JH, et al. Imported spotted fever rickettsioses in United States travelers returning from Africa: A summary of cases confirmed by laboratory testing at the Centers for Disease Control and Prevention, 1999-2002. *Am J Trop Med Hyg*. 2004;70(1):98-101.

A REVIEW WAS PERFORMED IN AN ATTEMPT TO correlate laboratory diagnosis of spotted fever group rickettsiosis (SFGR) with clinical and epidemiologic data. From 1999 to 2002, 31 cases of SFGR were confirmed in travelers returning from Africa by laboratory testing at the Centers for Disease Control and Prevention.

Diagnostic tests included immunofluorescent antibody assays for IgG against *Rickettsia conorii*, *R rickettsii*, and *R akari* antigens and immunohistochemical (IHC) stains on eschar or rash biopsy specimens. Eighteen cases of SFGR were confirmed, while 13 cases were classified as probable. Diagnoses were confirmed by a 4-fold or greater change in antibody titers (13), a 4-fold change in titer and IHC staining on biopsy specimen (3), IHC staining and a single positive antibody titer (1), and IHC staining alone (1). Twelve patients had an initial nonreactive acute-phase serum sample obtained on the third day of illness and were confirmed by testing a second convalescent-phase serum sample obtained a median of 32 days after illness onset. Nineteen patients with suspected SFGR had nonreactive sera obtained within 28 days after the onset of illness.

The most common destinations visited by these patients were South Africa (19), Zimbabwe (2), Rwanda (1), South Africa and Mozambique (1), Zambia and Tanzania (1), and 7 did not specify a country within Africa. Among patients who reported the month of illness onset, 48% reported their onset during March or April. A total of 77% of patients noted tick or other insect exposure. The most commonly reported symptoms were fever (74%) and eschar (55%). Rash was reported by only 26% of the patients. Group exposure was suggested by similarities in dates of illness, travel destinations, and surnames.

COMMENT BY LIN H. CHEN, MD

SFGR are zoonoses caused by obligate intracellular Gram-negative coccobacilli within the genus *Rickettsia*. The etiologic agent of scrub typhus, formerly *R tsutsugamushi*, has been renamed *Orientia tsutsugamushi*. Numerous human pathogens in the SFGR have been identified in recent years, as shown in the Table,[1-5] including *R parkeri* which was recognized in a human in Virginia.[5] Ticks are the usual vectors for SFGR, with the exception of *R akari* and *R felis*, which are transmitted by mites and fleas, respectively. Among the SFGR, *R aeschlimannii*, *R africae*, *R conorii*, and *R mongolotimori* have been associated with human disease in Africa.[1-4]

Additional epidemiologic information has emerged regarding SFGR. A seroepidemiologic study of acutely febrile patients in Cameroon showed that 32% contained IgM antibodies to *R africae*.[6] *R africae* has been identified in a traveler returning to France from Guadaloupe.[7] SFGR have also emerged along the Thai-Myanmar border, where sera from patients have reacted to *R helvetica*, *R conorii*, and *R felis*.[8] Another serologic survey has identified SFGR along with scrub typhus and murine typhus in Sri Lanka.[9]

R africae is the most common SFGR found in southern Africa, and it is likely the most frequently encountered SFGR in the cohort studied. Although the serologic tests used in the current study did not specifically identify *R africae*, antibodies to the SFGR cross-react with each other. An incubation period of 4-7 days usually follows a tick bite. Patients may then develop fever, rash, myalgia, abdominal pain, nausea, vomiting, and headache; additional symptoms include cough, pulmonary edema, renal failure, confusion, seizures, and arrhythmias.[10] Skin manifestations occur in about 50% of the cases and include eschars and maculopapular or vesicular rash.[11-13]

A study on Norwegian travelers to Africa found serologic evidence for SFGR in 5.3% of the travelers, including 4.0% for *R africae*.[11] Activities such as game hunting and photo safaris are associated with an increased risk. Travel during the summer (November to April) is associated with SFGR,[11] and McQuiston et al found a similar prevalence in March and April.

A previous study reviewed 52 cases of imported SFGR in US travelers returning from Africa over a 10-year period from 1977 through 1986.[14] The study by McQuiston et al collected 31 cases in a 4-year period. These figures take into account only specimens tested by the CDC and not tests performed by commercial laboratories. However, the rise in the number of cases suggests

Table

Human Diseases Associated with *Rickettsiae*[1-5]

Major Groups	Vector	Organism	Disease	Areas with Reported Disease
Spotted fever group	Tick	*R aeschlimannii*	*	Africa
		R africae	African tick bite fever	Africa, West Indies
		R australis	Queensland tick typhus	Australia
		R caspii	Astrakhan spotted fever	Russia (Astrakhan)
		R conorii	Mediterranean spotted fever	Africa, Southern Europe, Middle East
		R conorii Indian	Indian tick typhus	India
		R helvetica	*	Japan
		R heilongjiangii	*	China
		R honei	Flinders Island spotted fever	Flinders Island, Northeastern Australia
		R japonica	Japanese spotted fever	Japan
		R mongolotimonae	*	China (Mongolia), France, South Africa
		R parkeri	*	United States
		R rickettsii	Rocky Mountain spotted fever	Americas
		R sharonii	Israeli tick typhus	Israel
		R sibirica	North Asian tick typhus	Northern China, former USSR, Armenia, Pakistan
		R slovaca	*	France
	Mite	*R akari*	Rickettsialpox	US, Korea, Ukraine, Croatia
	Flea	*R felis*	Flea-borne spotted fever or California flea rickettsiosis	North America, South America, Europe, Asia
Typhus group	Flea	*R typhi*	Murine typhus or endemic typhus	Worldwide
	Louse	*R prowazekii*	Louse-borne epidemic typhus	Worldwide
Scrub typhus group	Mite (chigger)	*Orientia tsutsugamushi*	Scrub typhus	Asia

*No specific name given to disease

an increase in the incidence of SFGR, an increase in the volume of travelers, an increase in adventure travel, an increase in physician awareness of the disease, or a combination of all these factors. Travel medicine specialists should counsel travelers visiting endemic areas, especially if the itinerary includes rural exposure. In addition to wearing long sleeves, long pants, and tucking pants into socks, the use of DEET (N, N-diethyl-m-toluamide) on skin and application of permethrin on clothing are effective preventive strategies. The diagnosis of rickettsial infections should be considered in returning travelers with an acute febrile illness.

Diagnostic tests for SFGR include assaying paired acute and convalescent sera for antibodies to *Rickettsia*, IHC staining of skin biopsy specimens, and PCR (available in research laboratories). This report illustrates the use of IHC staining of skin biopsy specimens during early infection to confirm a diagnosis of SFGR in returning travelers. Given the negative serologies occurring during early infection, it is important to obtain convalescent-phase serum specimens at least 28 days after illness onset in order to establish a diagnosis. ■

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Pseudomembrane Found Upon Intubation of a Returned Traveler

ABSTRACT & COMMENTARY

Synopsis: *A case of fatal respiratory diphtheria in an unvaccinated Pennsylvania resident who had visited Haiti brings to light the need for all international travelers to be current with all recommended vaccinations, including a primary series of diphtheria toxoid.*

Source: Fatal Respiratory Diphtheria in a US Traveler to Haiti: Pennsylvania, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;52(53):1285-1286.

A 63-YEAR-OLD PENNSYLVANIA MISSIONARY WHO HAD never been vaccinated against diphtheria contracted the illness while he was in Haiti for 1 week helping to build a church. The day before leaving Haiti he noted a sore throat, and 2 days later he presented to an emergency department for evaluation of persistent pharyngitis with difficulty swallowing. Rapid tests for group A streptococci and heterophile agglutinins were negative, and he was treated with oral amoxacillin and clavulanate potassium. After 2 more days the patient returned to the ED with chills, sweating, nausea, vomiting, restlessness, and difficulty both swallowing and breathing. On examination, he was afebrile with stridor and expiratory wheezing, and his neck was swollen. Radiographs of the neck and chest showed prevertebral soft-tissue swelling, enlargement of the epiglottis, and opacity at the left lung base. He was admitted to the ICU with a diagnosis of epiglottitis and airway obstruction. During intubation for impending respiratory failure, laryngoscopy revealed a yellow exudate on the tonsils, posterior pharynx, and soft palate, with sloughing of the anterior pharyngeal folds. Despite treatment with azithromycin, ceftriaxone, nafcillin, and steroids, he became hypotensive and febrile. Culture of the throat swab specimen was negative for *Corynebacterium diphtheriae*. Sputum culture grew methicillin-susceptible *Staphylococcus aureus*. However, diphtheria was later confirmed as the diagnosis during a tracheostomy at another facility when a white exudate consistent with *C diphtheriae* infection was observed. A pseudomembrane covered all of the supraglottic structures. Gram stain of the laryngeal exudate showed Gram-positive cocci and yeast. Diphtheria antitoxin (DAT) was administered on the ninth day of illness. Two days later, cultures of the pseudomembrane were still negative, but PCR performed at the CDC for *C diphtheria* tox genes was positive. Despite treatment, the patient died on day 17 of illness due to cardiac complications. Analysis of close contacts of the patient showed no additional cases of diphtheria, but antibiotic prophylaxis and immunization with a diphtheria toxin-containing vaccine were offered to all close contacts.

COMMENT BY MARIA D. MILENO, MD

In the context of the entire travel medicine consultation, immunization with a diphtheria toxoid-containing vaccine carries little "talk show interest" for persons traveling abroad. Diphtheria has fortunately been quite uncommon in the United States since universal vaccination began in the 1940s. While young children have 95% coverage rates, testing of adults indicates that the percentage of US residents with protective diphtheria antibody levels (> 0.1 IU/mL) decreases progressively with age, from 91% at 6-11 years to approximately 30% at ages 60-69 years. As our traveling population ages, we will likely see more cases in returned travelers who choose to explore endemic regions unless broader vaccination coverage of travelers can be attained.

Disease associated with respiratory diphtheria should be suspected in all persons with membranous nasopharyngitis or obstructive laryngotracheitis who returned recently from areas where the disease is endemic. See the Table or check www.cdc.gov/travel/diseases/dtp.htm. Also, diphtheria may occur especially among persons who live with local people within endemic areas. Infected travelers returning

Table

Diphtheria-Endemic Countries

Europe—Albania and all countries of the former Soviet Union.

Americas—Brazil, Dominican Republic, Ecuador, and Haiti.

Asia—Afghanistan, Bangladesh, Cambodia, China, India, Indonesia, Iran, Iraq, Laos, Mongolia, Myanmar, Nepal, Pakistan, Philippines, Syria, Thailand, Turkey, Vietnam, and Yemen.

Africa—Algeria, Egypt, and the countries in the sub-Saharan region

to the United States with incubating or untreated disease can transmit *C diphtheria* to their close contacts. The diphtheria case fatality rate is 1 in 20. Although the tetanus-diphtheria (Td) booster vaccine is administered as an IM injection, with adjuvant containing potentially irritating antigens, the usual reaction is that of local pain, swelling, and induration at the site of injection. Occasionally, there may be painful swelling from elbow to shoulder 2-8 hours following vaccination if frequent boosters have been given. Rarely, there are reports of anaphylaxis, generalized rash and itching, fever, systemic symptoms, brachial neuritis, and Guillain-Barré syndrome. Compared to the children's formulation, there is less diptheria toxoid in the Td adult booster. Contraindications include severe illness with or without fever, history of neurological or severe hypersensitivity following Td, and allergy to thimerosal or gelatin adjuvants. While the recommended protection time for this vaccine is 10 years, our clinic staff requests that individuals document diphtheria-tetanus immunization within the past 5 years and follows with a discussion of the risks involved.

In summary, all international travelers should be up to date with all apparently routine recommended vaccinations in addition to taking destination-specific disease prevention precautions. ■

CME Questions

3. **Human infection with *Blastocystis hominis*:**
   a. is associated with colonic ulceration.
   b. is rare in travelers to tropical regions.
   c. is not clearly pathogenic.
   d. is best treated upon detection using metronidazole.
   e. is associated with *D fragilis* coinfections.

4. **Relapsing cysticercosis and subsequent epilepsy:**
   a. is usually due to reinfection of brain parenchyma.
   b. only occurs when the cyst degenerates in cerebral parenchyma.
   c. can occur around old, calcified cysts, as well as degenerating cysts.
   d. is only seen when larvae migrate to the brain parenchyma.

Answers: 3(c); 4(c)

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PHARMACOLOGY WATCH

Estrogen Found to Not Affect Heart Disease, Breast Cancer

The NIH has halted the estrogen-alone wing of the Women's Health Initiative (WHI) a year before its scheduled end. The 11,000 postmenopausal women who have had a hysterectomy and were enrolled in the estrogen-alone trial recently received a letter informing them of the preliminary results of the study and asking them to stop their study medication. After nearly 7 years of follow-up it appears that estrogen alone does not affect the rates of heart disease or breast cancer (either positively or negatively), both key findings of the estrogen/progesterone wing of the study, which was halted in July 2002. The researchers did find, however, that estrogen alone led to a slightly higher incidence of stroke (8 per 10,000), similar to the rate found in the estrogen/progesterone wing. Estrogen alone was also found, however, to decrease the risk of hip fracture. The NIH statement also says that older women (65 and older) showed a trend toward increase risk of probable dementia or mild cognitive impairment with estrogen-alone treatment. All of the women in the study were taking Wyeth & Co.'s conjugated estrogen product, Premarin. The full results of the trial will be published in a major peer-reviewed journal in the next 2 months. The NIH statement concurs with the guidance from the FDA, which states that hormone use should be limited to treatment of moderate-to-severe menopausal symptoms, vulvovaginal atrophy, and prevention of osteoporosis (as a second-line drug). The NIH statement is available on its web site at www.nih.gov/news.

Antibiotics Associated With Cancer Risk

Is antibiotics use associated with an increased risk of breast cancer in women? The question, which was first raised decades ago, has been the subject of much debate, but now a new study suggests that the answer may be yes. Researchers looked at data from more than 10,000 female members of the Group Health Cooperative in Washington state and identified 2266 women with invasive breast cancer and 7953 randomly selected controls without breast cancer. The variable evaluated was cumulative days of antibiotic use over the study period from January 1993 to June 2001. Increasing cumulative days of antibiotic use was associated with increased risk of breast cancer. The categories were 0 days, 1-50, 51-100, 101-500, 501-1000, and > 1001 days. The odds ratios (95% CI) for breast cancer were, respectively, 1.00 (reference), 1.45 (1.24-1.69), 1.53 (1.28-1.83), 1.68 (1.42-2.00), 2.14 (1.60-2.88), and 2.07 (1.48-2.89) ($P < .001$ for trend). Increased risk was seen in all antibiotic classes, including women taking tetracycline or macrolides for treatment of acne or rosacea. After adjusting for age, length of enrollment, and use of postmenopausal hormones, the death rate from breast cancer also increased with cumulative days of antibiotic use. The authors conclude that use of antibiotics was associated with an increased risk of incidence of breast cancer and death from breast cancer; however, it cannot be determined

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from the study whether antibiotic use is causally related or whether the indication for use of antibiotics was the primary factor (*JAMA*. 2004; 291:827-835). The link between antibiotics for breast cancer is plausible since antibiotics affect intestinal microflora, thus affecting phytochemical metabolism in the gut. Phytochemicals are thought to play an inhibitory role in the carcinogenesis pathway. Antibiotics also affect immune and inflammatory responses, which may lead to mammary carcinogenesis. An accompanying editorial reviews the possible mechanisms of the antibiotic/breast cancer connection and suggests that this study provides more questions and answers but that further research is needed. In the mean time, antibiotic use in women should be scrutinized, especially when other treatment options are available (*JAMA*. 2004;291:880-881).

Topiramate Effective Against Migraine

Topiramate is an effective agent for migraine prevention, according to a new double-blind study of 483 migraine patients. The drug, which is approved for prevention of seizures, was used in maximal doses of 50, 100, or 200 mg for 18 weeks in patients aged 12-65, who had at least a 6-month history of migraine and averaged 3-12 migraines per month. Mean monthly migraine frequency decreased significantly in the 100-mg ($P = .008$) and 200-mg ($P \leq .001$) doses, and the benefit was seen within the first month of therapy. Migraine days and use of rescue medication were also significantly reduced in the 100-mg and 200-mg groups. Adverse events included paresthesia, fatigue, and nausea (*JAMA*. 2004;291:965-973). Johnson & Johnson has already received conditional approval from the FDA for topiramate for the indication of migraine prevention pending additional safety information.

Statin Therapy For Heart Failure

Statin therapy has been found to be beneficial for a number of chronic illnesses; now add 2 more to the list. Statins have been found to benefit patients with advanced ischemic and non-ischemic heart failure. Researchers from UCLA reviewed the records of 551 patients with systolic heart failure with ejection fractions of 40% or less. After risk adjustment, statin use was associated with improved survival without the necessity of urgent transplantation in both non-ischemic and ischemic heart failure patients (91% vs 72% [$P < .001$] and 81% vs 63% [$P < .001$], at 1-year follow-up, respectively) (*J Am Coll Cardiol*. 2004;43:642-648). A new, large, randomized trial shows statins may also reduce the risk of stroke. As part of the Heart Protection Study in the United Kingdom, 3280 adults with cerebrovascular disease and an additional 17,256 patients with other occlusive arterial disease or diabetes were randomized to simvastatin 40 mg per day or placebo. Over the 5-year treatment period, there was a significant 25% proportional reduction in the rate of first stroke (4.3% simvastatin vs 5.7% placebo; $P < .0001$). The entire benefit was found in reduction in ischemic stroke. There was no difference found in the rate of hemorrhagic stroke, either increase or decrease. Simvastatin also reduced the number of TIAs ($P = .02$) and requirement for carotid endarterectomy or angioplasty ($P = .0003$). Among patients with pre-existing cerebrovascular disease, there is no apparent reduction in the stroke rate, but there was a highly significant 20% reduction in the rate of any vascular event ($P = .001$). Interestingly, benefit was seen in all levels of LDL, even in patients with LDL levels less than 116 mg/dL. The authors conclude that statin therapy reduces the risk of ischemic stroke by one-quarter to one-third in these at-risk patients (*Lancet*. 2004;363:757-767).

FDA Actions

The consumer watchdog group Public Citizen is calling for the FDA to ban AstraZeneca's new statin, rosuvastatin (Crestor), because of the risk of myositis and rhabdomyolysis. The drug, which was introduced to the American market in September, has been associated with 7 cases of rhabdomyolysis, 9 cases of renal failure, and 1 death. Myositis is a class affect of statins, especially the high-potency statins like Crestor. AstraZeneca states that the drug has been used in more than 1 million patients and that its benefits outweigh the risks. The FDA banned Bayer's cerivastatin (Baycol) in 2001 because of more than 100 deaths associated with the drug due to rhabdomyolysis.

Drug Approved to Target Angiogenesis

The FDA has approved the first monoclonal antibody that targets tumor angiogenesis. Genentech's bevacizumab (Avastin) is approved for the treatment of metastatic colorectal cancer. The drug works by binding vascular endothelia growth factor, thus inhibiting the formation of new blood vessels in tumors. In clinical trials the drug was found to extend survival time in patients with metastatic colorectal cancer by several months. ■