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Outbreak of Acute Schistosomiasis: Brief Exposure and Severe Morbidity

ABSTRACT & COMMENTARY

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Dr. Blackburn reports no financial relationships relevant to this field of study.

This article originally appeared in the February 2009 issue of Infectious Disease Alert.

Synopsis: *A group of travelers to Tanzania experienced a high attack rate of acute schistosomiasis after swimming in a freshwater pond. Resultant short-term morbidity was high, although no patients developed clinical evidence of chronic infection within the first year of follow-up.*

Source: Leshem E, et al. Acute schistosomiasis outbreak: clinical features and economic impact. *Clin Infect Dis*. 2008;47:1499-1506.

SCHISTOSOMIASIS IS THE MOST IMPORTANT TREMATODE INFECTION WORLDWIDE, transmitted to humans through skin contact with infested freshwater.[1] Endemic primarily to the tropics, transmission is particularly intense through much of sub-Saharan Africa. Although chronic schistosomiasis can lead to portal hypertension or serious urinary tract pathology, these complications are seen mostly in long-term residents of endemic areas and are rare in travelers.[1] In contrast, acute schistosomiasis (also known as Katayama fever) often is seen among non-immune travelers, usually within 1-2 months of infection.[2] Traditionally, this syndrome has been characterized by fever, cough, rash, eosinophilia, hepatosplenomegaly, and other clinical findings.[2]

Although several outbreaks of acute schistosomiasis have been reported, most have involved prolonged freshwater exposure and few have examined the short-term morbidity of acute schistosomiasis.[3-6] Leshem et al, therefore, undertook an investigation of a cluster of cases from a group of 34 Israeli travelers who had been on a luxury safari trip to Tanzania. After the index case of acute schistosomiasis was identified, an epidemiologic investigation revealed that 27 persons in the group had been exposed to a freshwater pond at a tented lodge in Northern Tanzania. This was the only freshwater exposure for all of the travelers during this trip, and all 27 exposed persons had a single, brief exposure to the pond (mean, 39 minutes). Twenty-two (81%) of the 27 developed acute schistosomiasis, and none of the seven unexposed individuals developed schistosomiasis. Infection status was determined using stool (and urine) ova and parasite examinations, serology, and clinical findings.

Swimming time in the pond tended to be higher for infected than for non-infected (but exposed) persons (44 vs 12 minutes, p = 0.06). Cercarial dermatitis was reported shortly after exposure in three (14%) of the 22 infected persons. Symptoms experienced by those with acute schistosomiasis included: cough (78%), fever (68%), fatigue (58%), rash (37%), diarrhea (37%), and abdominal pain (26%). Three (14%) infected patients were asymptomatic. Rash and fever appeared earliest (mean, 3-4 weeks after exposure), whereas cough and gastrointestinal symptoms appeared last (mean, 5-6 weeks after exposure). Fatigue was the symptom that persisted the longest (mean 6-7 weeks), whereas cough and diarrhea lasted 3-4 weeks, and rash and fever only 1-2 weeks. Among the 22 infected travelers, elevated ALT was found in 45% and eosinophilia in 72%; the latter persisted for more than a year in two persons. All infected patients were treated with praziquantel, and eight also received corticosteroids. None experienced any late complication of schistosomiasis at 12-month follow-up.

Among the 22 infected travelers, 258 medical encounters resulted (mean, 11.7 per person) and four persons were hospitalized. Most (86%) patients missed time from work or school (mean, 8 days each), and a mean of 15 leisure activities were also missed per person. Among infected persons, health-related quality of life (assessed using a standardized questionnaire) was significantly lower than US norms for three months after infection, after which they recovered from infection.

■ COMMENTARY

This outbreak of acute schistosomiasis was characterized by high attack rate among swimmers with a single, brief exposure to a freshwater pond in Tanzania. Although many schistosomiasis outbreaks have been reported, few have demonstrated high infection rates after such a brief exposure, and in this cohort, infected travelers were exposed only 30 minutes longer than their uninfected counterparts.

Most infected patients were symptomatic with acute schistosomiasis, and the study provides a useful description of the relative frequency of symptoms and their time course. Although underreported in other outbreaks, cough was the most commonly reported symptom. Interestingly, fever was absent in nearly one-third of symptomatic patients, despite being previously considered a hallmark of acute schistosomiasis. The severity and persistence of fatigue and the impact on quality of life also was significant.

The optimal therapy for acute schistosomiasis has yet to be determined. Although all infected patients in this outbreak received praziquantel, long-term follow-up data are not available. Praziquantel is not active against schistosomula (the immature form of the parasite), and it is known that patients treated only with praziquantel during acute schistosomiasis can develop chronic disease if they are not retreated in the following months.[7] Artemesinins may be a better choice early in disease, as they do have activity against schistosomula, but clinical data to support this are lacking. In addition, although 42% of the symptomatic patients in this cohort received corticosteroids, their role in acute schistosomiasis also

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remains poorly defined. Notably, some patients in this cohort had persistent eosinophilia up to a year after treatment. Demonstrating cure after treatment also remains a challenge, especially given the difficulty of identifying the parasite in stool or urine samples, and the persistence of antibody for years or longer after cure.

This study demonstrates the importance of patient education regarding the mechanisms of transmission of this preventable disease and the severe morbidity that is possible with acute schistosomiasis. Travelers should be advised to avoid swimming or bathing in untreated freshwater sources in endemic areas (even on luxury trips), no matter how brief the exposure, particularly in sub-Saharan Africa. ■

References

1. Gryseels B, et al. Human schistosomiasis. *Lancet*. 2006; 368:1106-1118.
2. Ross AG, et al. Katayama Syndrome. *Lancet Infect Dis*. 2007;7:218-224.
3. Cetron MS, et al. Schistosomiasis in Lake Malawi. *Lancet*. 1996;348:1274-1278.
4. Schwartz E, et al. Schistosome infection among river rafters on Omo River, Ethiopia. *J Travel Med.* 2005; 12:3-8.
5. Visser LG, et al. Outbreak of schistosomiasis among travelers returning from Mali, West Africa. C*lin Infect Dis.* 1995;20:280-285.
6. Cooke GS, et al. Acute pulmonary schistosomiasis in travelers returning from Lake Malawi, sub-Saharan Africa. *Clin Infect Dis*. 1999;29:836-839.
7. Grandiàre-Pérez L, et al. Efficacy of praziquantel during the incubation and invasive phase of Schistosoma haematobium schistosomiasis in 18 travelers. *Am J Trop Med Hyg*. 2006;74:814-818.

XDR-TB in the United States

ABSTRACT & COMMENTARY

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This article originally appeared in the December 2008 issue of Infectious Disease Alert.

Synopsis: *In contrast to some regions of the world, the incidence of XDR-TB in the United States has decreased and remained at a very low level.*

Source: Shah NS, et al. Extensively drug-resistant tuberculosis in the United States, 1993-2007. *JAMA.* 2008; 300: 2153-2160.

CDC INVESTIGATORS ANALYZED 15 YEARS OF SURVEILLance data of culture-confirmed cases of tuberculosis from the 50 states and the District of Columbia, identifying 201,399 with isoniazid- and rifampin-susceptibility results. Of these, 3,379 (1%-7%) were resistant to both drugs and, thus, categorized as MDR-TB. Among the MDR-TB isolates, sufficient susceptibility testing was available to further categorize 2,087; 83 (0.04% of the total TB cases with drug susceptibility results) were XDR-TB (ie, they were additionally resistant to a fluoroquinolone and to a second-line injectable drug).

The largest annual number of cases of XDR-TB, 18, were reported at the beginning of the surveillance period in 1993, but a median of only 3.5 cases per year were reported over the last decade of the study. During 1993-1997, 25 of 40 (62%) patients with XDR-TB were known to be HIV-infected; this proportion decreased to six of 43 (14%) during 1998-2007. Just more than half were U.S.-born, and 40% were Hispanic. Three of the patients with XDR-TB were health care workers.

The median time to culture conversion among the XDR-TB-infected patients was 183 days (range, 103-344 days), a significantly longer time than for MDR-TB patients, or those infected with susceptible strains. Only 44% of XDR-TB patients, however, completed treatment, and 35% died, a death rate more than twice that of MDR-TB patients and more than six times that of patients infected with susceptible strains. Seventy percent (21 of 30) of HIV-infected patients died, while only 9% (2 of 22) without HIV coinfection died.

■ COMMENTARY

These data demonstrate that the number of cases of XDR-TB in the United States is small and diminishing, with only a few cases identified annually. This, of course, is not the case in many places in the world. Attention was drawn to the problem of XDR-TB in 2006 with the report of an outbreak in South Africa involving 53 patients, all of whom died.[1] Of note, all whose serostatus was known were HIV infected, indicating a link between these two epidemics, one also observed in the U.S. experience. This experience was a

harbinger of what was to follow. In February 2008, WHO reported that MDR-TB, a way station on the path to XDR-TB, was present in 5.5% of all cases of TB in the 81 countries surveyed, with China and countries of the former Soviet Union having the highest rates. For example, 22.3% of TB cases in Baku, Azerbaijan, were MDR-TB. Limited data were available from Africa, where only six countries were represented. It was estimated that 490,000 MDR-TB cases emerge annually and account for more than 110,000 deaths.

At least one case of XDR-TB was identified in each of the 45 countries and, once again, the former Soviet Union was among the leaders, with the proportion of MDR-TB that were XDR-TB ranging from 4% in Armenia to 24% in Estonia. WHO estimates that approximately 40,000 cases of XDR-TB will emerge annually in the world.

Many of the patients in the report by Shah et al had acquired drug resistance (ie, initial isolates were generally drug susceptible, while one or more subsequent isolates were XDR-TB). It is generally assumed that this phenomenon is the consequence of poorly chosen regimens or poor patient compliance. A recent publication from a group in South Africa, however, found that, in all 17 patients (all HIV infected) for whom adequate data were available, the development of MDR-TB or XDR-TB was the result of exogenous reinfection.[3] This circumstance is, fortunately, not likely to apply to the United States, with its lower prevalence of MDR-TB and XDR-TB and its generally superior isolation facilities. ■

References:

1. Gandhi NR, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet.* 2006;368:1575-1580.
2. http://www.who.int/tb/features_archive/drs_factsheet.pdf
3. Andrews JR, et al. Exogenous reinfection as a cause of multidrug-resistant and extensively drug-resistant tuberculosis in rural South Africa. *J Infect Dis.* 2008;198:1582-1589.

See also:

Jassai M, Bishai WR. Extensively drug-resistant tuberculosis. Lancet Infect Dis. 2008 Nov 4 [Epub ahead of print].

Putting Sunscreen to the Test

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Source: Sang SQ, et al. In vitro assessments of UVA protection by popular sunscreens available in the United States. *J Am Acad Dermatol* 2008;59:934-942.

SPF STANDS FOR "SUN PROTECTION FACTOR," BUT if FDA recommendations change, the name will soon stand for "sunburn protection factor" because of the recognition that current SPF testing reflects erythema effects of UVA light in the 320-340 nm and UVB light in the 290-320 nm wavelengths, but does not necessarily reflect efficacy for other photodamaging wavelengths. UVA light in the 340-400 nm range is also dermotoxic, but impact of sunscreen on this light component has not previously been included in labeling. In August 2007, the FDA suggested a new rating scale that includes a ratio of UVA 340-400 nm (termed UVA1) to total UV light absorption. Agents that have low efficacy for absorbing UVA1, even though they have good efficacy for other wavelengths, would be rated lower in overall efficacy.

An analysis of 13 OTC sunscreen products using the new FDA criteria found 8 to provide medium protection and 5 to provide high protection. All but one of the selected products had an SPF of at least 30. If the proposed FDA metric becomes widely accepted, consumers will have an opportunity to better appraise the overall efficacy of sunscreen products. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Warning Regarding Topical Anesthetics

In this issue: FDA warning on topical anesthetics; antipsychotics increase sudden cardiac death; the step up vs step down debate; treating pain, fatigue, mood, and sleep in fibromyalgia; FDA Actions.

Something for your pain?

The FDA has issued a warning regarding topical anesthetics and the risk of life-threatening side effects. This is the second warning in 2 years regarding this issue, the first coming in February 2007 following the deaths of two women who used extensive topical anesthetics in preparation for cosmetic procedures. The latest warning was prompted by a study published in *Radiology*, which compared oral acetaminophen or ibuprofen vs lidocaine gel applied to the skin of the breasts to reduce discomfort during mammography. In the study, 4% lidocaine gel was applied by a nurse from the clavicles to the inferior costal margins and laterally to the mid axillary lines and then covered with plastic wrap to ensure consistency of application. Discomfort from mammograms was significantly lower in the lidocaine gel group and the authors postulate that decreased discomfort may improve the likelihood of future mammographic screening (Lambertz CK, et al. *Radiology* 2008;248:765-772). The FDA's previous warning in 2007 followed on the heels of two reports of young women undergoing laser hair removal who applied either lidocaine or tetracaine topical preparations to the lower extremities and then covered the application with plastic wrap. Both women developed seizures, fell into a coma, and eventually died due to excessive blood levels of the topical anesthetic. Many of these topical products are available over the counter. The FDA strongly advises consumers not to: make heavy application of topical anesthetics over large areas of skin, use concentrated formulas, apply to broken or irritated skin, wrap the treated skin with plastic wrap or other dressings, or apply heat to skin treated with these products.

Increase in sudden cardiac death

Antipsychotics, both typical and atypical, are associated with a dose-related increase in sudden cardiac death according to a new study. Typical antipsychotics such as thioridazine (Mellaril®) and haloperidol (Haldol®) block repolarizing potassium currents and prolong QT intervals. Multiple studies have shown a dose-related increased risk of sudden cardiac death associated with these drugs. Less is known about the atypical antipsychotic drugs although many have similar cardiovascular effects. Researchers from Nashville reviewed the records of Medicaid enrollees in Tennessee including the records of 44,218 and 46,089 baseline users of a single typical and atypical antipsychotic, respectively. These were matched with 186,600 nonusers of antipsychotic drugs. Thioridazine and haloperidol were

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the most frequently prescribed typical agents, while clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), and risperidone (Risperdal®) were the most commonly used atypical agents. Both users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers with adjusted incident rate ratios of 1.99 (95% CI, 1.68-2.34) and 2.26 (95% CI, 1.8-2.72), respectively. There was a higher rate for users of atypical antipsychotic drugs vs typical antipsychotics with an incident rate of 1.14 for the comparison (95% CI, 0.93-1.39). For both classes of drugs, the risk for current users increased significantly with increasing dose. The authors conclude that current users of typical and of atypical antipsychotic drugs had similar, dose-related increased risk of sudden cardiac death and that atypical antipsychotic drugs are no safer than the older drugs (Ray WA, et al. *N Engl J Med* 2009;360:225-235). An accompanying editorial suggests that children and the elderly are particularly vulnerable to these drugs and their use in these populations should be "sharply reduced" (Schneeweiss S, Avorn J. *N Engl J Med* 2009;360:294-296).

Step up vs step down

Which is more effective for treating dyspepsia: Starting with aggressive therapy and tapering down, or starting with antacids and progressing to more aggressive therapy depending on symptoms? The so called step-up vs step-down debate has raged for years, particularly in managed-care settings. In a new study from the Netherlands, patients with dyspepsia were randomized to treatment with an antacid, H2-receptor antagonist, and proton pump inhibitor (step up) vs the same drugs in reverse order (step down), with each step lasting 4 weeks. Primary outcome was symptom relief and cost-effectiveness of initial management at 6 months. Treatment success after 6 months was achieved in 72% of patients in the step-up group and 70% of patients with step-down group. The average medical costs were lower for patients in the step-up group (€228 vs €245; P = 0.0008) mainly because of the cost of medication. The rate of adverse effects was the same in both groups and were generally mild. The authors suggest that treatment success is similar in both groups but the step-up strategy was more cost-effective for patients with new onset dyspeptic symptoms (van Marrewijk CJ, et al. *Lancet* 2009;373:215-225). An accompanying editorial suggests that the degree of cost difference between the two groups was overestimated because costs were based on brand name drugs and generics are now available. It furthers suggested that the study may not change practice in primary care as the author recommends a 4-8 week course of a proton pump inhibitor for patients with symptoms of the upper gastrointestinal tract with discontinuation of treatment if patients remain asymptomatic (van Zanten SV. *Lancet* 2009;373:187-189).

Pain, fatigue, mood, sleep and fibromyalgia

Tricyclics work better than other antidepressants for the treatment of fibromyalgia according to new study from Germany. In a meta-analysis of 18 randomized controlled trials of antidepressants for the treatment of fibromyalgia, researchers reviewed studies utilizing tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAO). All antidepressants were associated with a reduction in pain, fatigue, depressed mood, and sleep disturbances. Pain reduction was particularly good for tricyclic antidepressants, while MAO inhibitors showed modest effect and SSRIs and SNRIs showed a small effect. TCAs were effective in low doses of 12.5-50 mg, far below the doses commonly employed to treat depression, and were very effective for reducing pain, fatigue, and sleep disturbance (*JAMA* 2009;301:198-209). Currently duloxetine (Cymbalta®), pregablin (Lyrica®), and milnacipran (Savella™) are the only FDA-approved drugs for the treatment of fibromyalgia.

FDA Actions

The FDA is launching a program to improve the safety of imported drugs to the United States. The pilot program would allow manufacturers of drugs outside United States to apply for 1 of 100 certifications, which would require that companies have a secure supply chain for their product. Criteria would include holding an FDA-approved drug application, guaranteeing that active pharmaceutical ingredients would be imported only to make FDA-approved drugs, complying with Good Manufacturing Practices, and guaranteeing that their drug products use a secure supply chain. This program is in response to concerns about manufacturing processes outside the United States and the embargoing of several foreign manufactured drugs in the last year. ■