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INSIDE

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XDR-TB in the United States

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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

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.*

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 over half were US-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.

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■ **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 US 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. ■

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See also:

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Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-cell Transplantation

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University School of Medicine

Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: *Twenty single-nucleotide polymorphisms (SNP's) were analyzed in the toll-like receptor 2 gene (TLR2), the toll-like receptor 3 gene (TLR3), the toll-like receptor 4 gene (TLR4), and the toll-like receptor 9 gene*

(TLR9) in 336 recipients of hematopoietic stem cell transplants (HSCTs) and their unrelated donors. Two donor TLR4 haplotypes (S3 and S4) were shown to be associated with increased risk of invasive aspergillosis.

Source: Bochud P-Y, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. *N Engl J Med*. 2008;359:1766-1777.

SINGLE NUCLEOTIDE POLYMORPHISMS WERE EXAMined within *TLR2, TLR3, TLR4,* and *TLR9* in a population of 336 HSCT recipients and their unrelated donors. Using multivariate Cox regression analysis, two donor TLR4 haplotypes were found to be associated with increased risk of developing invasive aspergillosis in the HSCT recipients. The S3 and S4 haplotypes were associated with an adjusted hazard ratio of 2.2 and 6.16, respectively. Donor positivity for CMV also appeared to increase the risk of development of invasive aspergillosis in the recipients. In a validation study of 103 HSCT recipients with invasive aspergillosis and 263 matched controls (which included both related and unrelated donors), the TLR4 S4 haplotype was confirmed to be associated with the development of invasive aspergillosis, with an odds ratio of 2.29 for related donors and 5.00 for unrelated donors.

■ COMMENTARY

Toll-like receptors are transmembrane proteins on the surface of immune cells which detect microbe-associated molecular patterns from many organisms. They activate various transcription factors, leading to production of inflammatory cytokines and activation of adaptive immunity. Aspergillus species have been shown to activate TLR2 and TLR4. This study utilized the large population of HSCT patients treated at the Fred Hutchinson Cancer Center in Seattle to examine the frequencies of SNPs for four candidate TLR genes in both HSCT transplant recipients and their donors. The strong association demonstrated between the S3, and especially the S4, haplotype in donors and development of invasive aspergillosis in the recipients is a masterful demonstration of the significance of the innate immune system in host defense against an important pathogen. While it is a stretch to think that TLRs will become therapeutic targets anytime in the near future, the data presented in this paper are fascinating, and further illuminate our understanding of the delicate balance that defines the host/pathogen relationship. ■

Quality Improvement Interventions and Surgical Antimicrobial Prophylaxis

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *Forty-four acute care hospitals participated in a prospective study over four years to determine the effect of quality improvement (QI) interventions on appropriate prescribing of surgical antimicrobial prophylaxis. Hospitals were randomly assigned to either feedback on the results of the ongoing audit vs feedback plus an intensive collaborative intervention group. Both groups showed improvement in most quality indicators, but there appeared to be no benefit of the intensive QI collaborative intervention over performance feedback.*

Source: Kritchevsky SB, et al. The effect of a quality improvement collaborative to improve antimicrobial prophylaxis in surgical patients, a randomized trial. *Ann Int Med*. 2008;149:472-481.

IN THIS STUDY, 44 ACUTE CARE HOSPITALS EACH RANdomly sampled 100 surgical cases (cardiac, hip, or knee replacement, hysterectomy) at both baseline and during the remeasurement phase of the study. All hospitals received a comparative feedback report. Twenty-two hospitals were randomly assigned to the intervention group where each hospital held two in-person meetings led by experts, and monthly teleconferences, and supplemental, educational materials were distributed. The quality parameter used as the primary outcome measure was the receipt of one dose of antibiotics within 60 minutes of surgery (120 minutes for vancomycin), with secondary outcomes of change in proportion of patients receiving any antibiotics, administration of antibiotics for 24 hours or less, administration of an appropriate antibiotic, and receipt of a single, preoperative dose plus any of the other five measures.

In the intervention group, 76.3% of patients received appropriately timed preoperative antibiotics at baseline, and 83.2% at remeasure. In the feedback-only group, the numbers were 74.8% at baseline and 85.3% at follow-up. Of those in the intervention group, the baseline and follow-up values for receipt of prophylaxis were 97.4% and 98.9%, respectively, with nearly identical values for the feedback-only group. Appropriate duration of antibiotics

increased from 51.3% to 69.5% in the intervention group, with similar change seen in the feedback-only group. Appropriate antibiotic selection was high at baseline (93.8%) and did not change significantly in either the intervention or feedback groups. Interestingly, the proportion of patients who received a single preoperative dose decreased slightly from 85.1% to 80.2% in the intervention group but did not change in the feedback-only group.

■ **COMMENTARY**

Antimicrobial prophylaxis in the setting of surgery represents a significant proportion of the use of antibiotics in the United States and contributes to the cost of care. Inappropriate administration of antimicrobial prophylaxis has been shown to result in reduced prophylactic efficacy as well as excessive costs and potential selection of antibiotic-resistant organisms when prophylaxis is given for an excessive duration. While this study did not show any incremental benefit of intensive collaborative QI interventions, the good news is that it demonstrated that appropriately communicated feedback to prescribing providers did result in improvement of antimicrobial-prescribing practices in the surgical prophylaxis setting. It is likely that similarly conducted audits with communicated feedback could also be effective in improving antimicrobial prescribing for a variety of infections in both the inpatient and outpatient settings where guidelines exist. ■

Altitude Sickness and Adventure Travel

ABSTRACT & COMMENTARY

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

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

Sources: Leshem E, et al. Clinical features of patients with severe altitude illness in Nepal. *J Travel Med*. 2008;15:31-322; Kupper TEAH, et al. Low-dose theophylline reduces symptoms of acute mountain sickness. *J Travel Med*. 2008; 15:307-314.

Adventure travel and ecotourism has become a huge industry, and certain destinations are becoming ever more popular. Current estimates suggest that more than 80,000 people travel annually to Nepal alone to trek. People come from all over the world, are of all ages, and some, it turns out, are not in the greatest shape and have underlying medical problems. Many of these individuals frequently ascend to > 5,500 m over a period of 1-3 weeks; the highest altitude attained with the normal trekking permit is 5,600 m (18,400 feet), though a special permit may be obtained allowing climbers to attempt peaks from 5,600 m to 8,848 m. The risk of altitude sickness in these travelers is not trivial, as suggested by the increased frequency of annual evacuations off the mountains. Current estimates suggest that up to 30%-40% of persons trekking above 4,000 m develop some form of altitude sickness.

Lesham et al assessed the clinical and demographic features of patients seen and evaluated for altitude-related illness at the CIWED Clinic Travel Medicine Centre in Kathmandu, Nepal (located at 1,310 m), from 1999 to 2006. A total of 406 patients meeting criteria for some form of altitude-related illness were included in the study (some retrospectively), ranging in age from 15 to 73 years; 85% trekked with an organized group. Patients were grouped according to findings consistent with high-altitude cerebral edema (21%), high-altitude pulmonary edema (34%), both (27%), or acute mountain sickness (AMS) (18%). Demographic characteristics were compared with that of 39,402 trekkers without altitude-related illness (obtained from the permit registry), who served as a control group. In general, compared with controls, patients with altitude-related illness were older (38.6 vs 44 yrs, $p < .0001$), and were more frequently male. Prophylactic acetazolamide was used less frequently in patients with high-altitude cerebral edema (28%) and patients with high-altitude pulmonary edema (29%), compared with 43% of those with AMS ($p < .001$); (similar information on controls was not available). Nearly 6% of patients with altitude-related illness had a history of significant medical problems, including hypertension, heart disease, asthma, diabetes, or stroke.

While most trekkers chose to climb less risky areas, such as the Anapurnas, individuals with altitude-related illness were more likely to have trekked Everest, where the ascent was nearly twice as rapid and the maximal altitude greater than in other areas. Most evacuations and deaths were of Everest climbers. Twenty-one deaths due to altitude-related illness were recorded by 8 of the 18 local embassies. The estimate of altitude-related death in Nepal was 7.7 per 100,000 trekkers.

Lesham et al recommend that current recommendations for altitude gain per day be adjusted downward, especially in the Everest area, although this means a climb will take longer. Although one might imagine that group trekking

would be safer, the authors contend that it is characterized by a more rigorous schedule, with peer pressure to stay with the group despite early warning signs of fatigue and illness. It is worth noting that 33% of those with altitude-related illness received prophylactic acetazolamide.

In a second, smaller, randomized, placebo-controlled study, Kupper et al examined the efficacy of low-dose, slow-release theophylline 300 mg daily in 17 healthy male volunteers in the reduction of AMS. The mean age was 35 yrs, and all of the patients were experienced recreational climbers. The study was conducted on Monte Rosa in Italy at 4,559 m. A 12-channel sleep recorder recorded sleep and breathing parameters throughout the night.

Theophylline was well-tolerated, and no participant developed high blood pressure during the study. AMS symptoms were significantly less frequent in individuals receiving theophylline compared with placebo, and none of the individuals receiving theophylline had an elevated mean AMS score at any time at the intermediate altitude of 3440 m. During ascent and during all five days at the highest altitude of 4,559 m, the difference in symptoms between the groups was still significant. Periodic breathing events (34 vs 74 per hr, $p < .05$) and oxygen desaturations (62 vs 122 per hr, $p < .01$) were also significantly reduced in theophylline recipients compared to the placebo group. Kupper et al believe theophylline stimulates the respiratory drive, thereby reducing the risk of sleep disorder breathing, which adds to the hypoxic burden of high altitude. ■

2008 Prevention of Influenza Guidelines: Changes to Consider

ABSTRACT AND COMMENTARY

By Mary-Louise Scully, MD

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Dr. Scully reports no financial relationships relevant to this field of study. This article originally appeared in the October 2008 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, and peer reviewed by Philip Fischer, MD. Dr. Bia is Professor of Geographic and Laboratory Medicine., Co-Director, Tropical Medicine and International Travelers' Clinc, Yale University School of Medicine, and Dr. Fischer is Professor of Pediatrics, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN. Dr. Bia is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson, and Dr. Fischer reports no financial relationships relevant to this field of study.*

Synopsis: *The new influenza guidelines now recommend annual vaccination of children ages 5-18 years in addition to the previous recommendation of children ages 6 months to 5 years. To meet the anticipated vaccine demand, the FDA has released 113 lots of the 2008-2009 Northern Hemisphere influenza vaccine produced by 6 different manufacturers.*

Source: Fiore AE, et al. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR* 2008;57:1-60.

THIS REPORT UPDATES THE 2007 RECOMMENDATIONS by the CDC Advisory Committee on Immunization Practices (ACIP) with regard to the use of influenza vaccine and antiviral agents. The important changes include: 1) a new recommendation that annual vaccination be administered to all children ages 5-18 years beginning in the 2008-2009 influenza season, if feasible, but no later than the 2009-2010 season; 2) a recommendation that annual vaccination of all children ages 6-59 months continue to be a primary focus of vaccination efforts since these children are at higher risk of influenza complications 3) a new recommendation that either trivalent inactivated influenza vaccine (TIV) or live, attenuated influenza vaccine (LAIV) be used when vaccinating healthy persons ages 2-49 years (the previous recommendation was to administer LAIV to persons only between 5-49 years); and 4) a recommendation that vaccines containing the 2008-2009 trivalent vaccine virus strains A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens be used.

The recommendation remains that children ages 6 months to 8 years should receive two doses of influenza vaccine (doses separated by ≥ 4 weeks) if they have not been vaccinated previously at any time with either LAIV or TIV because two doses are needed for protection in these children. Two doses also should be given to children ages 6 months to 8 years who received only one dose in their first year of vaccination. In children < 5 years with asthma or reactive airways disease, LAIV should be avoided. Since LAIV is a live, attenuated vaccine, it is contraindicated in immunosuppressed individuals. Patients with a history of hypersensitivity to eggs and a history of Guillain-Barré after influenza vaccination should not be vaccinated with either LAIV or TIV.

Annual recommendations for adults have not changed, and essentially encourage vaccination for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting influenza to others. Persons older than 50 years; pregnant women; patients with chronic pulmonary, cardiac, or renal conditions; diabetic

patients; immunosuppressed patients; nursing home patients; health care workers; and caregivers of young children remain a focus of adult vaccination programs.

Other inactivated vaccines can be administered simultaneously with either TIV or LAIV. Among children 12-15 months of age, the concurrent use of LAIV with measles, mumps, rubella (MMR) alone, and MMR and varicella vaccine has been examined, and no interference in immune response was observed. In addition, based on available safety and immunogenicity data, it is acceptable to administer TIV with zoster vaccine for adults older than 50 years.

As resistance to both amantadine and rimantidine has increased rapidly in the past several years, oseltamivir and zanamivir remain the only antiviral medications recommended for influenza treatment or prophylaxis in the United States. Unfortunately, in 2007-2008, increased resistance to oseltamivir was reported in many countries among influenza A (H1N1) viruses. In the United States, during the 2007-2008 influenza season, about 10% of influenza A (H1N1) viruses were found resistant to oseltamivir, but none of the influenza A (H3N2) or influenza B viruses were found to be resistant (overall percentage of influenza A and B viruses resistant to oseltamivir was < 5%). However, antiviral recommendations may change during the 2008-2009 season, and clinicians can keep up to date with information available on the CDC's web site (http://www.cdc.gov/flu/professionals/antivirals/index.htm).

■ **COMMENTARY**

The influenza vaccine supply is projected to be abundant this year, with 113 lots of Northern Hemisphere vaccine released by the FDA to meet the expected demand for implementation of the new pediatric recommendations. In addition, the vaccine antigens have been changed to reflect the predominant strains of last year's season.

Success ultimately will depend upon both health care providers' endorsement of the implementation and, even more, the endorsement from parents and caregivers of children. The LAIV and the single-dose vials or syringes of TIV are considered thimerosal-free (0 or < 1.0 mcg per 0.5 mL dose) and, therefore, preferred for infants and pregnant women. All multi-dose vials still contain about 25 m mercury per 0.5 mL dose. In 2001, the US Public Health Service and other organizations recommended that efforts be made to remove or reduce the thimerosal content from vaccines as part of an overall plan to reduce mercury exposures from all sources.[1] Each year, it is expected that the number of influenza vaccines that do not contain thimerosal will continue to grow.

Respiratory infections are second after gastrointestinal infections as a cause of illness in travelers, and influenza accounts for 5%-6% of respiratory illness reported in travelers.[2] Influenza virus is spread by direct contact or aerosol (fine droplet), and the traveler's world of crowded airports, buses, museums, and churches poses a perfect setting for influenza transmission. Outbreaks have occurred on cruise ships, an increasingly favored way of traveling for many, and which are especially conducive to influenza transmission.[3] Moreover, influenza circulates at low levels year round in the tropics — a frequent destination of travelers and cruise ships. Cruise ships often have a mixture of passengers and crew from both hemispheres and, although the available vaccine in the country of departure may not be matched optimally for the circulating strains in the opposite hemisphere, it is always preferable to vaccinate than to let the individual travel without any vaccine protection at all.[4] ■

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Travelers and Eosinophilia

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD

Dr. Mileno is Director, Travel Medicine, The Miriam Hospital, Associate Professor of Medicine, Brown University, Providence, RI.

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

This article originally appeared in the October 2008 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, and peer reviewed by Philip Fischer, MD.*

Synopsis: *Travelers returning from tropical countries may have significant exposures to helminths, yet there is no established clinical approach to identify and treat those who are both infected and presenting with eosinophilia. An approach to cases of eosinophilia in which schistosomiasis in returning travelers had been excluded is outlined in this recent publication.*

Source: Meltzer E, et al. Eosinophilia among returning travelers: a practical approach. *Am J Trop Med Hyg.* 2008;78:702-709.

There is a broad differential diagnosis for eosinophilia, defined as an absolute eosinophil count of > 500 cells/µl, yet cases due to helminthic disease probably occur more often in routine travelers than in the general population. There is a high index of suspicion concerning potential eosinophilia in immigrants and refugees. Schistosomiasis is an important cause of eosinophilia, followed by filariasis, primarily in persons residing in Africa, and is not rare in travelers returning from endemic areas.

This retrospective case series from Israel, looked at travelers (excluding expatriates and immigrants) who returned from developing countries between January 1994 and June 2006. Eosinophilia was defined as total eosinophil count > 500/µl, or > 6% on differential counts. All patients had a CBC, chemistry panel, including liver function tests and one or more stool samples for ova/parasites. Travelers to schistosomiasis-endemic areas were also tested for *Schistosoma ova* in urine, and received a serologic test for schistosomiasis.

Other travelers underwent serologic tests for additional helminth infections such as strongyloidiasis and Toxocara infections performed at the Laboratory for Parasitic Diseases at the CDC in Atlanta, GA. Testing, such as imaging or biopsies, were performed according to clinical judgment. Patients diagnosed with schistosomiasis were treated with praziquantel 60 mg/kg for one day, divided into two doses. Diagnosed cases of acute schistosomiasis received repeated dosing within three months. Other cases with eosinophilia were treated with albendazole 400 mg twice each day for 3-5 days. Symptoms and eosinophil count were evaluated.

Of 995 post-travel patients evaluated, 82 (8.6%) had eosinophilia, 44 (53.7%) had schistosomiasis-associated eosinophilia (SAE), and 38 (46.3%) had post-travel non-schistosomal eosinophilia (NSE).

Age, travel duration, and male/female ratio were not significantly different between NSE and SAE cases. Geographically, SAE cases were almost exclusively acquired through travel to Africa (95%). Most NSE cases had traveled to Asia (65.7%), with Southeast Asia and India being primary areas of transmission. Acute schistosomiasis occurred in 21 of 44 SAE cases, presenting with fever, rash, and respiratory symptoms. Sixteen of 44 (36.6%) were asymptomatic fellow travelers of a diagnosed index case and were identified through screening. Only seven (16.9%) presented with chronic schistosomiasis, usually genitourinary.

At presentation, 94.7% of persons with NSE were symptomatic, with abdominal pain and protracted diarrhea as leading symptoms, followed by dermatologic findings (rash or pruritus) and respiratory symptoms, mainly dry cough. Symptoms occurred in isolation or in combination. Two patients presented with only symptoms of fatigue. Symptoms began in most cases during travel, and were already present for several weeks on presentation to the clinic. Median time to presentation was six weeks (range from one day to > 1 year).

NSE had a median initial eosinophil count of 1,700 cells/µl compared to SAE cases who had 1,400 cells/µl ($p = 0.067$). Mildly abnormal liver function tests occurred in 5.3% of NSE cases and 13.0% of SAE cases — not a statistically significantly difference. Serologic testing was positive in all 44 SAE cases. Diagnosis by observation of ova was made in 22.7% of cases. Only a smattering of NSE cases had diagnostic findings. Two cases had hookworm alone documented, and one case had hookworm and Ascaris. *Blastocystis hominis* and *Entamoeba histolytica*/*dispar* were found alone or with helminths in four cases. One patient had hookworms noted in a sputum sample. Five tests for strongyloidiasis were positive. No tests for toxocariasis, filariasis, or trichinosis were positive. In fact, definitive parasitologic diagnosis was achieved in only nine NSE cases (23.7%). Two patients had non-infectious causes of eosinophilia, one with a drug allergy, another with positive strongyloides serology had increasing lymphadenopathy and, ultimately, B-cell lymphoma was diagnosed.

In terms of treatment, all persons with SAE tolerated praziquantel with no documented treatment failure. Thirty-seven NSE patients were offered empiric therapy with albendazole. One declined and four others were lost to follow-up. Of 30 albenoazole-treated patients available for evaluation of clinical response, 90% (27/30) showed a favorable response to treatment; 76.7% had complete remission of symptoms; 13.3% had significant improvement; three cases (10%) had no response. One had lymphoma, one had eosinophilic gastroenteritis, and one remained without a specific diagnosis but responded to corticosteroid treatment, as did the patient with eosinophilic gastroenteritis.

■ COMMENTARY

This study showed that NSE is certainly not rare, and represented 4% of all referrals to this post-travel clinic. Some forms of travel pose even higher risks; the incidence of NSE reported in military personnel actively screened after deployment to a developing country has been 50%. What lessons can we learn from this study and from what we know about refugees and immigrants? Although diagnostic yields were low, responses to treatment were high. Screening for eosinophilia in travelers returning from Africa may have an important impact for the immediate and future health of these individuals. Knowing about significant levels of eosinophilia would provide an important clue to the potential diagnosis and treatment of strongyloidiasis and schistosomiasis.

Young healthy travelers to developing countries who develop eosinophilia should be evaluated, first and foremost, for helminth infections. Strongyloidiasis and schistosomiasis have the strongest associations with eosinophilia. Other infectious diseases may be associated with eosinophilia, including coccidioidomycosis, aspergillosis, isosporiasis, *Dientamoeba fragilis*, *Mycobacterium leprae,* and chronic *Mycobacterium tuberculosis* infections, although the diagnostic yields are quite low when based solely upon the finding of eosinophilia.

Schistosomiasis is an important and frequent cause of eosinophilia, and this diagnosis should be pursued using serology and attempted ova detection. Identified cases, and arguably individuals with known exposure or fellow travelers of index cases, should be treated with praziquantel.

Hookworm and strongyloides are the most prevalent helminthic infections. In some groups, strongyloides seroprevalence reached 77%. Canine hookworms have recently been shown to occasionally cause NSE and eosinophilic gastroenteritis. A case can be made that empiric therapy is most sensible, rather than an extensive diagnostic work-up in travelers returning from regions of such high endemicity. Universal treatment with albendazole, a broad-spectrum antihelminthic, is highly effective in populations with high incidence of helminthic infection, such as refugees and immigrants, and has an excellent safety record.

One algorithm for travelers returning from Africa with eosinophilia might include empiric treatment for schistosomiasis with praziquantel, followed by albendazole. Travelers with NSE might have an evaluation that includes a thorough history and physical examination, stool samples for ova and parasites, and a therapeutic trial of albendazole. If a strongyloides serology is positive, treatment with ivermectin should be administered. Further testing should be reserved for individuals who remain symptomatic.

In summary, eosinophilia that is associated with schistosomiasis is uncommon but not rare; NSE is a more common scenario. Travelers with NSE are often symptomatic, and eosinophilia is most probably associated with helminthic infection(s). A better methodology is still needed to evaluate persons with eosinophilia for potential parasitic infection. Empiric albendazole results in resolution of symptoms and eosinophilia in most cases, with further treatment reserved for the few cases that do not respond to initial empiric treatment. Lastly, consideration of the noninfectious causes of eosinophilia, including allergic disorders, medications, toxins, autoimmune diseases, and endocrine disorders such as Addison's disease may yield the diagnosis. ■

Pneumonic Tularemia in Brooklyn, New York

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP

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Synopsis: *The New York City Department of Health is investigating a laboratory-confirmed case of pneumonic tularemia and asking medical providers to consider tularemia in patients spending time camping in Gateway National Recreation Area, part of which is located in Brooklyn, NY.*

Source: Department of Health and Mental Hygiene (DOHMH) Alert #13–NYC June 11, 2008.

A BROOKLYN, NY, RESIDENT PRESENTED IN EARLY JUNE with a one-week history of fever, headaches, left-sided pleuritic chest pain, and a pleural effusion. Pleural fluid yielded a slow-growing Gram-negative bacterium that was identified as *Francisella tularensis*. The patient reported camping in Gateway National Recreation Area four days prior to onset of symptoms (*see map*). This national park spans two states and three boroughs of New York City at the entrance to its outer harbor.

■ COMMENTARY

Tularemia is very rarely recognized as a disease in New York City. Since 1965, there have been only 15 reported cases. In the United States, approximately 100-200 cases occur annually, with a recent cluster of cases having occurring in 2000 at Martha's Vineyard, MA, among landscapers presumably exposed to bacterial aerosols formed during mowing.[1] Tularemia is a zoonotic infection among a variety of animal hosts, notably rabbits, aquatic rodents (muskrats, beaver, water voles) and other rodents, squirrels, skunks, and cats. A US outbreak occurred among commercially sold prairie dogs in 2002.

F. tularensis can persist for weeks within contaminated water, soil, and vegetation and, at times, it can become airborne. It can also be found within amoebas such as Acanthamoeba species, which may represent an environmental reservoir for such. Humans can be accidentally infected by bites of infected ticks, deer flies, cats, ingestion

of contaminated food or water, or by aerosols of bacteria from animals, such as those formed during mowing grassy areas. As few as 10 organisms can cause infection and disease. The typical incubation period is 3-5 days, with a range of 1-14 days.

The clinical presentation of tularemia depends upon the route of exposure.

At least six distinct clinical syndromes or forms of tularemia have been recognized among infected patients:

- Ulceroglandular;
- Glandular;
- Typhoidal;
- Pneumonic;
- Oropharyngeal; and
- Oculoglandular.

Ulceroglandular tularemia occurs in 60%-80% of cases; these patients usually report the handling of an animal, or an animal bite, usually from a cat. Affected patients typically present with fever and a single papulo ulcerative lesion, with central eschar and tender regional lymphadenopathy. Glandular tularemia presents as enlargement of nodes, but without an obvious skin lesion. Typhoidal tularemia presents as bacterial sepsis with the occasional complication of hematogenous spread, resulting in meningitis showing a mononuclear pleocytosis within cerebrospinal fluid. Pneumonic tularemia presents with pleural effusions and nodular infiltrates, although other parenchymal lung patterns have been described. Oropharyngeal tularemia occurs rarely, and it is likely due to ingestion of poorly cooked animal meat. The diagnosis should be considered in patients with such a history and exudative pharyngitis unresponsive to penicillin. Oculoglandular disease has been attributed to inoculation of the eye by the accidental squirting of engorged fluid into eye during removal of the tick.

DOHMH in New York City has asked that any vacationer in areas such as Gateway National Park with unexplained pneumonia, sepsis, or cutaneous ulcers associated with fever or regional lymphadenopathy be cultured for *F. tularensis* (biosafety level 2). Isolation of the organism is difficult, as these bacteria are strictly aerobic and require enriched media (such as those containing cysteine and cystine or chocolate agar supplemented with IsoVitalex). Culture plates should be held for 5-7 days. Automated systems may misidentify the causative organisms as *Pasteurella multocida*. The drug of choice for treatment of tularemia is streptomycin 10 mg/kg, administered IM every 12 hours for 7-10 days. Chloramphenicol has been added to the regimen when meningitis is present. For additional information, see http://www.bt.cdc.gov/agent/tularemia. ■

Reference

1. Feldman KA, et al. An outbreak of primary pneumonic tularemia on Martha's Vineyard. *N Engl J Med* 2001;345:1601.

Map

Gateway National Recreation Area

Source: National Park Service

CME Questions

7. Which of the following is correct?

a. The incidence of XDR-TB is increasing in the United States.
b. XDR-TB is seen only in the United States and Africa.
c. XDR-TB isolates are, by definition, resistant to isoniazid, rifampin, one or more fluoroquinolones, and at least one second-line injectable antituberculous drug.
d. XDR-TB is more prevalent than MDR-TB.

8. Which of the following is correct with regard to travelers with eosinophilia seen in a travel medicine clinic in Israel?

a. Approximately one-half had schistosomiasis.
b. Stool examination is sufficient for the diagnosis of schistosomiasis.
c. The most frequently detected helminthic infections were trichinosis and ascariasis.
d. Empiric therapy with albendazole in those without schistosomiasis was never beneficial.

9. Which of the following is correct?

a. *Francisella tularensis* is a faculatative anaerobe.
b. Automated microbiology systems may misidentify *Francisella tularensis* as *Pasteurella multocida*.
c. With the exception of New York City, tularemia is not seen in states east of the Mississippi river.
d. Tularemia always presents as pneumonia.

Answers: 7. (c); 8. (a); 9. (b)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Inhaled Antibiotics in the Treatment of Hospital-acquired Pneumonia

UPDATES

By Carol A. Kemper, MD, FACP

Our Lady of 100 Victims of Norovirus

Source: Verheof L, et al. Import of norovirus infections in the Netherlands and Ireland pilgrimages to Lourdes, 2008 - following report. *Eurosurveillance*. 2008; Volume 13.

LOURDES HAS BEEN AN IMPORTANT Catholic pilgrimage site for the elderly and infirm since 1858. This year marks the 150th anniversary of the apparition known as the "Lady of Lourdes," which was observed on multiple occasions that year by a 14-year-old peasant girl out searching for firewood. Her sister and a friend did not share in the vision, but spoiled the spirit of the event by spilling the beans to the parents. Both kids got a beating, although the 14-year-old was later canonized by the church as a saint in 1933. By the 15th vision, over 9,000 people were present at the grotto, hoping to share in the vision with the young girl, some of whom began claiming the spring waters had miraculous healing powers. By the 18th and final vision, the French gendarmes had cordoned off the site and prohibited visitors from reaching the grotto. Controversial in its own time, some believe the spot would have not have attracted as much interest had the police acted less forcibly in restricting access.

Lourdes has become the busiest Marion shrine in the Catholic Church, and anticipates more than 8 million visitors this year. As the result of an active surveillance system established in 1999, called the Food-Born Viruses in Europe (FBVE) network, a series of norovirus outbreaks in October 2008 were quickly recognized and traced back to Lourdes. The FBVE network was first alerted about an outbreak of norovirus at a mental health institution for the elderly in the Netherlands in October. Four persons died, and one remains critically ill as of the date of this publication, underscoring the high morbidity of this infection in the elderly. Twenty-four health care workers and patients from the institution had traveled to Lourdes at the end of September. During their trip, two of the party became ill with acute gastroenteritis symptoms, including one who was too ill to leave her hotel room. A total of 119 of the 550 (22%) of the institutional patients developed gastroenteritis.

An initial alert from the FBVE network was forwarded to Municipal Health Services and microbiologists, prompting reports of three other clusters of norovirus cases involving pilgrims to Lourdes at about the same time. Genotyping demonstrated the cases were due to a common norovirus strain (genotype II.4 2006b variant). As a result of this prompt response, the cases were traced back to six local hotels in Lourdes that had been housing groups of pilgrims from Italy, France, Ireland, and Denmark, at least three of which had been coping with an outbreak of diarrhea in guests between September 28 and October 16.

Thus far, the investigation has identified 90 primary cases of norovirus within seven groups of pilgrims to Lourdes, resulting in more than a hundred cases of secondary infection in three different countries. Containment efforts appear to have brought the outbreak under control, although the source for the infection has not yet been determined. French authorities routinely check the spring water for bacteriologic quality, although this would not exclude viral contamination. Under these circumstances, with such a high density of travelers, environmental contamination and person-to-person transmission is likely. The FBVE network provided a rapid and effective response to a problem spread over multiple countries.

Viral Failure Predicted in Women with Blips

Source: Geretti A, et al. Doubled risk of failure after 1 year under 50 copies in women and steady blippers. Abstract H-1256; 48th ICAAC, October 2008.

GERETTI ET AL TRACKED THE RISK of virologic failure (VF) in 1386 HIV-infected persons after starting their first HAART regimen (between 1996 through 2005) at two primary HIV care clinics in London and Frankfurt. Just over half (57%) were MSM; 80% were male; and 63% were Caucasian, 25% black African, and 12% other ethnic minorities. After achieving virologic suppression (plasma viral load < 50 copies/mL), 74.5% of the patients maintained complete virologic suppression for the first year of treatment, whereas 19.4% were transient one-time only "blippers" and 6.1% experienced two or more consecutive blips (defined as low-level viremia between 50-400 copies/mL).

Geretti et al examined multivariate predictors of virologic failure over the subsequent years (defined as two or more consecutive plasma viral loads > 400 copies/mL, or a viral load > 400 copies/mL that resulted in a regimen

change); VF occurred in 86 (6.2%) patients at a median of 2.2 years. Multivariate analysis showed that the strongest predictor of failure was the occurrence of consecutive blips during the first year of therapy (OR 2.18, CI 1.15 to 4.10). Additional predictors of VF included the use of a boosted-protease-inhibitor-containing regimen vs a non-nucleoside containing one (OR 1.88), the use of a triple nucleoside regimen vs a non-nucleoside-containing one (OR 1.87), and female gender (OR 1.79).

Patients who were frequent "blippers" during the first year of HAART therapy were more likely to prematurely fail treatment. In addition, woman and patients who received boosted PI therapy were more likely to fail their regimen. Geretti et al concluded that patients who have trouble taking their medications, experience more side effects, or who have poor access and compliance with care, such as many of their poor West African female clients, are more likely to fail therapy.

A Rabies Update

Sources: ProMED-mail post, November 11, 2008; www.promed-mail.org; ProMED-mail post, October 24, 2008.

I WAS ATTENDING A LOVELY DINNER party the other evening when the 55-year-old husband of a friend merrily shared his experience rock climbing with his son three days earlier up on Lone Ridge Reserve off of Skyline in Santa Clara County. This was only his 3rd effort at rock climbing, which he described as an incredible rush. But what gave me a rush was the next part of the story: While canvassing the cliff, he put his hand in a crevice, felt something brush up against his hand, and then felt a tingle in his index finger. Seconds later, out flew a bat. Since there was no visible bite or blood, he didn't think much of it. The party was stunned when it was suggested he should receive rabies vaccine. Presumably, this bat was healthy and peacefully taking an afternoon nap, although the local health officer on-call concurred with the assessment of higher-risk contact in this case and the need for rabies prophylaxis.

My quick review found no published cases of high-risk bat exposure associated with rock climbing. In addition, a review of rock climbing websites found no reference to a risk for bat exposure nor recommendations for rabies pre-prophylaxis, although this is often suggested for spelunkers. It may be appropriate for health authorities to consider this recommendation if bat contact in rock climbers is common.

1) A remarkable survivor of rabies encephalitis is being reported by the Department of Health in Floresta Pernambuco, Brazil. A 15-year-old boy developed onset of symptoms in early October, about 29 days after having been aggressively bitten by a hematophagous bat (eg, a vampire bat). He had received four doses of rabies vaccine before the onset of symptoms. Within four days of the onset of symptoms, he was transferred to a tertiary care center, and rabies was confirmed with a hair follicle biopsy of the nape of the neck. Rabies virus consistent with that from a vampire bat was identified by RT-PCR. Within seven days of onset of symptoms, he was transferred to the ICU, intubated, and what has become known as the Milwaukee protocol was initiated. (The Milwaukee protocol was used in the 15-year-old Wisconsin girl who miraculously survived rabies in 2004, and is intended to induce coma, and control cerebral edema and cerebral artery spasm). Four weeks later, the Brazilian patient was brought out of his induced coma, and remains clinically stable. No details on his neurologic condition are yet available.

Rare survivors of rabies who received some rabies post-exposure prophylaxis and vaccination have been reported. The young Wisconsin girl remains the only survivor of rabies to date who developed symptoms prior to initiation of medical care and rabies vaccination, although her virus was never isolated for further characterization.

2) The United Kingdom has long enjoyed its human rabies-free status (the last cases of human rabies from an animal other than bats occurred in 1902), although a bat lyssavirus has been rarely found in Great Britain, known as European Bat Lyssavirus type 2 (EBLV-2). A passive surveillance system in place since 1987 screens downed bats for possible rabies virus.

Recently, the Health Protection Agency reported the 8th confirmed EBLV-infected bat, which was found dead at a heritage site in Shropshire in October.

Although there are about 17 species of bats in the United Kingdom, all eight of the EBLV-infected bats found to date have been the same species of bat, and this is the second found in Shropshire. EBLV is in the same family as rabies virus, and is found in insectivorous bats in northern Europe. While it causes symptoms in infected bats, the risk for human infection appears to be low, unless humans are directly exposed to saliva from an infected bat. A bat handler in Scotland died of EBLV infection in 2002. For this reason, it is recommended that persons in the United Kingdom who handle bats, or come in contact with a sick or dead bat, should receive rabies vaccine, although the presence of EBLV in low levels does not threaten the UK's rabies-free status. ■

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*.

Are 5-α Reductase Inhibitors Associated with Hip Fractures?

In the issue: 5-α reductase inhibitors and hip fracture in men; the effects of drug-reimbursement policy on outcomes; new guidelines for type 2 diabetes; beta-blocker-associated bradycardia is linked to CVD events; FDA Updates.

DO 5-α REDUCTASE INHIBITORS AFFECT BONE DENsity in men? These drugs, which include finasteride (Proscar®) and dutasteride (Avodart®), have been used for more than a decade to treat benign prostatic hyperplasia (BPH). The drugs block the conversion of testosterone to dihydrotestosterone, the more powerful androgenic agent, which is responsible for secondary sex characteristics, but also adverse effects such as BPH, acne, and male pattern baldness. The 5-α reductase inhibitors shrink prostatic tissue and improve BPH symptoms over time and also can be associated with erectile dysfunction and gynecomastia. Recently researchers looked at the correlation between use of finasteride and bone health, which is highly dependent on steroid pathways. Researchers from Kaiser Permanente in Southern California performed a population-based case-control study of 7076 men age 45 and older with incident hip fractures over a 10-year period. Control patients were 7076 men without hip fracture. The rate of BPH was the same in both groups. There was no suggestion of a dose-response relationship between exposure to 5-α reductase inhibitors and hip fracture (P = 0.12). Interestingly, there was slightly higher rate of α-blocker use in the hip fracture group. The authors conclude that exposure to 5-α reductase inhibitors is not associated with increased risk of hip fracture; in fact, there was a trend toward a protective effect. The increased risk associated with exposure to α-blockers (which can cause orthostasis) needs further investigation (Jacobsen SA, et al. Association between 5-alpha reductase inhibition and risk of hip fracture. *JAMA* 2008;300:1660-1664).

Effect of drug-reimbursement policy on health care outcomes

Researchers recently looked at clopidogrel use and health outcomes for cardiac patients before and after a Canadian provincial government changed its prior-authorization policy for medications to a more liberal limited-use policy. Researchers looked at all patients 65 years or older with acute myocardial infarction who underwent PCI with stenting. The primary outcome was composite rate of death, recurrent acute myocardial infarction, PCI, and coronary artery bypass grafting at one year. After the change in benefits, the rate of clopidogrel use for 30 days after hospitalization increased from 35% to 88% and the mean time to first dispensing of clopidogrel decreased from 9 days to 0 days. The one-year composite cardiovascular outcome decreased from 15% in the prior-authorization

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group to 11% in the limited-use group ($P = 0.02$). The authors conclude that removal of prior-authorization leads to improvement in timely access to clopidogrel after coronary stenting and improved cardiovascular outcomes (Jackevicius CA, et al. Cardiovascular outcomes after a change in prescription policy for clopidogrel. *N Engl J Med* 2008;359:1802-1810).

Updated guidelines for type 2 diabetes

The American Diabetes Association and the European Association for the Study of Diabetes have updated their treatment guidelines and algorithms for the treatment of type 2 diabetes. Published simultaneously in *Diabetes Care* and the European journal *Diabetologia*, the guidelines update the initial August 2006 guideline and the January 2008 update to reflect safety issues surrounding the thiazolidinediones (TZDs) and also introduces new classes of medications to the algorithm. Retained as step 1 therapy are lifestyle interventions and metformin. Step 2 therapy includes insulin and sulfonylureas, while TZDs have been dropped as initial therapy. Of the two TZDs, only pioglitazone (Actos™) is recommended by the guideline. Safety concerns regarding rosiglitazone (Avandia®) have resulted in the guideline group to state: "…given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone." The GLP-1 agonist exenatide (Byetta®) is elevated to tier 2 with the guideline pointing out the advantage of weight loss associated with the drug, but also noting it is given by two injections per day, has frequent GI side effects, is very expensive, and does not have an established long-term safety history. Other drugs newly mentioned in the guideline include the α-glucosidase inhibitors (starch blockers), acarbose (Precose™) and miglitol (Glyset®); the glinides, repaglinide (Prandin®) and nateglinide (Starlix®); the amylin agonist primlintide (Symlin®); and the DPP-4 inhibitor sitagliptin (Januvia®) (Nathan DM, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm of the initiation and adjustment of therapy. *Diabetes Care* 2009;32:1-11; Available at: http://care.diabetesjournals.org/misc/dv08-9025.pdf).

Beta-blockers and hypertension

Beta-blockers have come under increasing fire for treatment of hypertension. Now a new study links beta-blocker-associated bradycardia with increased risk of cardiovascular events. Researchers from Columbia University performed a meta-analysis of 9 randomized controlled trials evaluating beta-blockers for hypertension and from which heart rate data were reported. The compiled studies included more than 34,000 patients taking beta-blockers and more than 30,000 on other antihypertensive agents, as well as nearly 4000 patients receiving placebo. Lower heart rate associated with beta-blocker use was linked to a greater risk for all-cause mortality ($r = -0.51$; $P < 0.0001$) and cardiovascular mortality ($r = -0.61$; $P < 0.001$). There was also a statistically significant increase in myocardial infarction, stroke, and heart failure associated with lower heart rates. The authors conclude that in contrast to patients with myocardial infarction and heart failure, beta-blocker-associated reduction in heart rate increases the risk for cardiovascular events and death for hypertensive patients. The authors even suggest that beta-blockers may no longer be indicated for treatment of hypertension in the absence of compelling indications (Bangalore S, et al. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. *J Am Coll Cardiol* 2008;52:1482-1489).

FDA Updates

The FDA has approved a new selective α-blocker for the treatment of benign prostatic hyperplasia. Silodosin is an α-1 receptor blocker with high affinity for prostate, bladder, and urethra. It will be marketed in an 8 mg dose to be given once daily; however, 4 mg should be used in men with hepatic or renal impairment. Silodosin will be marketed by Watson Pharmaceuticals as Rapaflo™.

The FDA will investigate a report for the Institute of Safe Medication Practices regarding varenicline (Chantix®), Pfizer's smoking cessation drug. For the second straight quarter, varenicline accounted for more reported serious injuries than any other prescription drug with a total of 1001 new cases reported to ISMP, including 50 deaths. The FDA has previously issued a Public Health Alert about psychiatric side effects from the drug, but the new report sites numerous cases involving vehicular or other accidents, or syncope with a high potential to cause accidents. The federal government has already taken action to ban airline pilots and military missile crews from using the drug. Sales of varenicline have dropped sharply this year as a result of these reports. ■