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INSIDE

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Balamuthia and the Brain

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Amebic encephalitis due to* Balamuthia mandrillaris *is difficult to diagnose and often fatal — but must be considered by the clinician since it is potentially treatable.*

Source: CDC. Balamuthia amebic encephalitis — California, 1999-2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:768-771.

CENTRAL NERVOUS SYSTEM INFECTION DUE TO FREE-LIVING amebae generally manifests as either acute meningitis or focal encephalitis. The former, an acute neutrophilic meningeal infection that presents in a manner similar to that of acute infection due to pyogenic bacteria, is caused by *Naegleria fowleri*. The latter is caused by either Acanthamoeba species or by *Balamuthia mandrillaris*.

An increased recognition of the role of Balamuthia as a cause of encephalitis emerged from the California Encephalitis Project, which identified seven patients with evidence of encephalitis due to this organism selected from a group with a history of occupational contact with soil, or of swimming or camping, as well as elevated cerebrospinal fluid (CSF) protein level and pleocytosis, hydrocephalus, ring-enhancing lesions, or space-occupying lesions.[1,2] This experience has now been updated to include 10 patients identified in California from 1999 to 2007 from among 500 meeting similar criteria. Two additional patients had serological evidence of infection but were not included because brain tissue was not available for confirmation.

Patients ranged from 1.5-72 years of age (median, 15.5 years); nine of the 10 were male. With the exception of one patient who developed a cutaneous lesion after cleaning a backyard pond several months previously, neurological symptoms were the first indicator of disease. Presenting symptoms seen in more than one patient included seizure, headache, emesis, altered mental status, and cranial nerve palsy. The interval from the onset of symptoms to hospitalization ranged from 1-30 days (median, 8.5 days). Diagnoses under consideration included tuberculous meningitis, coccidioidomycosis,

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lymphoma, toxoplasmosis, viral infection, pyogenic brain abscess, tumor, and stroke. Only one patient, who was receiving corticosteroid therapy for nephritic syndrome, was know to have significant immunocompromise, although one had a past history of illicit substance abuse, one had a possible lymphoma, one had had a splenectomy. Five patients had known contact with soil: occupational exposure in two, home gardening-related activities in two, and motorcycling in the desert in one. CSF analysis was performed in nine patients, and the protein concentration ranged from 64-674 mg/dL (median, 188 mg/dL), the glucose from 15-74 mg/dL (median, 40 mg/dL), and the WBC from 64-674 cells/mm^3, with lymphocyte predominance. Neuroimaging generally demonstrated single or multiple focal-enhancing lesions (usually ring-enhancing) lesions. Two patients had hydrocephalus without focal lesions; nine of the 10 patients died.

■ COMMENTARY

B. mandrillaris was first identified in the brain of a mandrill baboon at the San Diego Zoo and was subsequently found to be a cause of encephalitis in humans. Since the discovery of this protozoan infection in 1986, there have been more than 100 human cases identified worldwide.[3] Most cases have been found in individuals without significant immunocompromise, but many had exposure, often occupational, to soil, and some to stagnant water — both potential sources of free-living amoebae. In all but a few cases, the diagnosis was made at post-mortem examination. There have been only four survivors reported in the United States, each with varying degrees of neurological recovery. Treatment information was available for only three of the survivors, each of whom received pentamidine, fluconazole, flucytosine, sulfadiazine, and either azithromycin or clarithromycin. The current IDSA guidelines recommend this regimen plus a phenothiazine, which is reported to have in vitro activity against the organism.[4] It should be noted, however, that three survivors from Peru have also been reported, and one received no therapy while the other two were given albendazole and itraconazole.

Since this rare disease appears to be treatable, clinicians must keep it in mind in their evaluation of patients with unexplained focal encephalitis. Tests that have been used for the diagnosis of balamuthiasis have included indirect fluorescent antibody testing of serum and PCR of cerebrospinal fluid. Currently an unequivocal diagnosis, however, requires detection of the organism in brain tissue with confirmation by indirect immunofluorescence staining of formalin-fixed tissue. Testing is performed at the CDC[5] and by the California Encephalitis Project[6] after prior approval. ■

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Immunoprophylactics and Immunotherapeutics: Focus on *S. aureus*

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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Questions & Comments

Leslie Hamlin,
Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

The inevitability of progression of bacterial resistance to antibiotics used in the clinic and other settings dictates the need for approaches that go beyond antimicrobial stewardship and the development of new antibiotics. These include the prevention of infection by means such as vaccination and use of passive immunoprophylaxis, as well as the development of immunotherapeutics that are not subject to the mechanisms of resistance that affect small molecule antimicrobials.

Prevention of infection is indisputably the optimal means of dealing with the problem of antimicrobial resistance. Vaccines currently in use have been very effective in the prevention of several bacterial infections, but these have not been aimed at multidrug-resistant pathogens. Potential vaccine target bacterial pathogens exhibiting antibiotic resistance include organisms such as *Mycobacterium tuberculosis*, *Helicobacter pylori*, *Clostridium difficile*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. I will focus here on the last mentioned.

S. aureus, as a consequence of both its increasing prevalence and worsening antibiotic resistance, is a prime potential vaccine target. Initial experience targeting this organism has, however, been disappointing. For example, despite initial evidence suggesting efficacy in the prevention of bacteremia in chronic hemodialysis patients, a capsular polysaccharide vaccine failed in a subsequent larger Phase III trial. In recognition of the need, however, at least one other vaccine, V710, which targets *S. aureus* iron surface determinant B (IsdB), is being evaluated in early phase trials in cardiac surgery and orthopedic implant patients. Some of the target populations that could potentially benefit from a vaccine against *S. aureus* are listed in the *Table 1*.

One reason for the failure of the capsular vaccine may have been the relatively immunocompromised status of chronic dialysis patients. This and other vaccine may prove to have greater efficacy in individuals without evident immune deficiency. The emergence of community-acquired, methicillin-resistant *S. aureus* (MRSA) infection as a frequent cause of recurrent infection in previously healthy individuals provides a potential target population likely to have a more robust response to vaccination.

It is also likely, given the complexity of the panoply of means by which *S. aureus* is able to avoid the innate immune response, that an effective vaccine will have to target multiple virulence factors rather than just one.

The development of this and other bacterial vaccines requires adequate funding of basic and translational work and, in circumstances in which the target population is limited (eg, *P. aeruginosa* infections), significant incentives to industry. Successful vaccine development will, however, be a critical element of any successful attack on the problem of antibiotic resistance.

A complementary method of prevention of infection with multidrug-resistant pathogens is that of passive immunoprophylaxis in defined populations, particularly those who are unlikely to have an adequate immunological response to vaccination and/or for whom there is inadequate time for a vaccine response prior to a potential danger period. Such individuals may include those undergoing urgently required cardiac or orthopedic surgery, as well as burn patients and other patients already severely immunocompromised or about to become so. Finally, agents developed for passive immunoprophylaxis may also prove to be effective as therapeutic agents. With reference once again to *S. aureus*, several agents are undergoing current investigation (*see Table 2*).

Table 1

Potential target population for a vaccine against *S. aureus*

- Chronic dialysis patients
- Diabetes mellitus patients
- Patients with planned device implantation
  - -Cardiac
  - -Orthopedic
- Contact sport participants, prisoners, military, MSM, IDUs,etc.
- Long-term care patients
- Health care workers
- Correctional facility workers
- Persistently colonized patients
- Patients recovered from *S. aureus* infection
- Family members of colonized/infected patients and pets

Table 2

***S. aureus*: Immunotherapeutica and passive immunoprophylactics**

Product	Pharma	Target
Altastaph™	Nabi	Caps. Polysacch. 5,8
Veronate™	Inhibitex	ClfA
Aurexis™	Inhibitex	ClfA
Aurograb™	Neutec	GrfA
Pagibaximab	Biosynexus	LTA
ETI-211	Elusys	Spa

In summary, the development of vaccines and immunoprophylactics capable of preventing infection with multidrug resistant pathogens will be a necessary element in the struggle against antibiotic resistance. In addition, immunotherapeutics have the capability to save lives of patients infected with such pathogens. ■

Diagnostic Testing of *Clostridium difficile*

ABSTRACT & COMMENTARY

By Ellen Jo Baron, PhD, D(ABMM)

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

Synopsis: *CDAD was associated with a significant increase in costs for inpatient care and increased costs at 180 days after the initial hospitilization when the CDAD episode occurred.*

Although enzyme-immunoassay (EIA) tests have replaced cytotoxin assays for diagnosis of *Clostridium difficile*-associated diarrhea (CDAD) in most US laboratories, the changing epidemiology of this disease suggests that an adjustment in diagnostic testing algorithms is needed. The move to EIAs was not because the tests were more sensitive, but because they were easier and faster to perform than the gold standard cell culture cytotoxicity with a control neutralization step, now performed in only 1% of US laboratories, according to the most recent College of American Pathologists proficiency testing survey results.

Data compiled by Dr. Cliff McDonald of the CDC, gleaned from US hospital discharge summaries, suggest that there were 100,000 cases of CDAD in 1992 and around 300,000 in 2006. More than half of reported cases occur in long-term care facilities. However, these numbers may underestimate the true numbers of cases.[1] Extrapolation from smaller, more accurate studies suggests that there are 500,000 cases/year and 23,000 deaths nationwide.[2] Costs are usually estimated for hospitalization only, but if patients are followed for six months after discharge, true costs of disease probably range from $3800-$7200 per patient, totaling greater than $1 billion/year. *C. difficile* infection can increase length of stay 2.8 days,[3] and the subsequent costs due to long-term care facility utilization or home care contribute to the overall figures.

Also fueling the renewed interest in CDAD is the swift spread of a relatively recently recognized and more virulent strain known variously as NAP1 (North American Pulsed-Field type 1), PCR ribotype 027, or restriction endonucleas analysis (REA) type BI ("bee eye"). *C. difficile* diarrheal cases are currently approximately 80% healthcare-associated and 20% community-associated. Half of all strains studied in the United States in the past two years are of the BI strain, which has also emerged rapidly as a major healthcare-associated pathogen in western Europe. Enhancing the spread of the BI strain is its resistance to fluoroquinolones (FQs) concurrent with expanding utilization of FQs worldwide. Outbreaks are unlikely to be controlled by switching one FQ for another (from levofloxacin to gatifloxacin, for example).[4] However, in at least one institution after FQs were removed from the formulary completely, the rates of CDAD decreased.[5] Authorities agree that both infection control measures and antibiotic restrictions are needed for optimal control.

Several factors are implicated in the rapid emergence of this hypervirulent epidemic strain. Increased spore production, allowing better survival in the environment, particularly in an institutional setting, helps to explain the rapid spread and persistence of BI. Enhanced adherence to human intestinal epithelial cells mediated by a surface protein A appears to be another major virulence factor for this strain.[6] Yet another is its increased toxin output. The toxin genes are governed by regulatory proteins, all residing on a pathogenicity locus (*PaLoc*). Increased toxin production in the hypervirulent strains may be due to a point mutation in the regulatory gene *tcdC*. Toxin production in most *C. difficile* strains begins when cells enter stationary phase after they run short of nutrients. However, BI strains produce 16x higher levels of Toxin A and 23 times the levels of Toxin B throughout all growth stages. Toxin B has now been shown to be the primary toxin.[7] NAP1 strains also produce a characteristic binary toxin, although the contribution of this toxin to severity of disease is not known.

So why should laboratories change their testing strategies? Apparently, recent studies show that currently popular EIA tests are not as sensitive as previously thought.[8] Given the severity of CDAD disease and the need for rapid diagnosis, the other well-established test, initial stool culture on cycloserine-cefoxitin fructose agar (with taurocholate to enhance the production of vegetative cells from spores), followed by toxin testing, does not yield a turnaround time rapid enough for

meaningful clinical decisions. One possible solution is the use of a rapid and very sensitive screening test, such as an immunochromatographic test, for glutamate-dehydrogenase, a protein present in all *C. difficile* strains, whether toxigenic or not. This protein is not exclusive to *C. difficile*, however, so GDH assay specificity is not sufficient for a stand-alone test. A study from Johns Hopkins showed that a GDH screen had a sensitivity of 100%, so no potential cases were missed with this system.[8] Many laboratories are thus moving to a strategy of offering the GDH test as a rapid screen and reflecting all positives to a reference test such as cytotoxin. GDH test sensitivities vary, so microbiologists need to study the literature to choose the appropriate commercial product.

The ultimate diagnostic test will likely prove to be molecular. Two pre-clinical trials of one PCR-based test have shown better sensitivity than the GDH screening methods. Once commercially produced rapid molecular assays are widely available, which no doubt will transpire within the next year, they will surely replace all three of the current diagnostic strategies: the two-test algorithm, culture followed by cytotoxin assay, and cell culture cytotoxicity. ■

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Acinetobacter Infections Associated with the War in Iraq — Unusual Cases

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

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

Synopsis: *Eight cases of skin and soft-tissue infections (SSTI) due to* A. baumannii *were identified in patients treated on a US Navy hospital ship during early 2003. A large proportion was associated with gunshot wounds or external fixators. These infections presented as cellulitis with overlying vesicles, and when untreated, progressed to necrotizing infection with bullae. All isolates were multidrug-resistant but remained susceptible to carbapenems. In a separate report, a 55-year-old health care worker (HCW) with diabetes developed a severe pneumonia. Molecular analysis revealed the source patient to have been a wounded US serviceman with a ventilator-associated pneumonia on whom the HCW had performed tracheal suction.*

Sources: Sebeny PJ, et al. *Acinetobacter baumannii* skin and soft-tissue infection associated with war trauma. *Clin Infect Dis* 2008;47:444-449; Whitman TJ, et al. Occupational transmission of *Acinetobacter baumannii* from a United States serviceman wounded in Iraq to a health care worker. *Clin Infect Dis*. 2008;47:439-443.

A RETROSPECTIVE REVIEW OF 211 INPATIENTS ADmitted to the US Navy hospital ship USNS Comfort in early 2003 revealed 57 patients with *A. baumannii* infection. Of those, eight cases of *A. baumannii* skin/skin structure infections (SSTIs) were identified; seven occurred in Iraqi nationals and one was in an American serviceman. All patients had been evacuated from field hospitals in Iraq, where they had undergone initial resuscitation and emergent stabilizing surgical procedures. All but one of the patients received perioperative antibiotics (first or second generation cephalosporins) before admission to the USNS Comfort.

All eight patients had a similar clinical presentation as cellulitis, with a well-demarcated, erythematous and

"peau d'orange" edematous rash. In seven cases, the cellulitis appeared to arise from the adjacent wound. Cellulitis progressed to a sandpaper-like appearance containing multiple tiny vesicles. Two patients subsequently became bacteremic and developed hemorrhagic bullae, suggesting necrotizing infection.

All of the *A. baumannii* isolates were multidrug-resistant but retained susceptibility to imipenem. Co-pathogens were identified in five of eight patients, and included most commonly *Enterobacter cloacae* and Proteus species.

All eight patients required 1-6 wound debridements each; seven patients survived and one patient died of sepsis after receiving just two doses of imipenem.

The second paper describes the case of a health care worker (HCW) at National Naval Medical Center (NNMC) in Washington, DC, with poorly controlled diabetes (on metformin), who developed a severe Acinetobacter pneumonia complicated by hypotension requiring vasopressors, respiratory failure, and a large empyema requiring decortication. The patient had cared for (specifically performed endotracheal suctioning while wearing gown and gloves but no mask) a US Navy sailor who had sustained polytraumatic injuries in an explosion of an improvised explosive device (IED) in Iraq. The source patient was intubated and initially resuscitated at the Air Force Theater Hospital in Balad, then transferred to Landstuhl Regional Medical Center (LRMC) in Germany before arriving at NNMC. The source patient was shown to be colonized with *A. baumannii*, which was isolated from his sputum, abdominal wound, axilla, and nares. Pulse field gel electrophoresis (PFGE) demonstrated molecular identity between the isolates of A. baumannii cultured from the HCW and the source patient. The isolates were highly antibiotic-resistant and demonstrated in vitro susceptibility to only carbapenems, amikacin, and colistin.

■ COMMENTARY

These papers highlight the importance of *A. baumannii* as a pathogen in patients wounded in the ongoing wars in Afghanistan and Iraq, the source of which appears to be the field hospital environment.[1] The clinical observation of multidrug-resistant *A. baumannii* as a cause of SSTI in trauma patients is important. This pathogen should be suspected in patients with hospital-acquired SSTI who present with edematous cellulitis with overlying vesicles. Empiric coverage with a carbapenem and surgical debridement should be promptly instituted.

While the HCW who developed a complicated pneumonia due to *A. baumannii* may have had some degree of systemic immunocompromise due to her diabetes, the development of pneumonia in this individual and SSTI in the other patients suggest that certain strains of *A. baumannii* contain virulence factors worthy of further characterization. ■

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Leprosy in the United States

ABSTRACT & COMMENTARY

By Philip R. Fischer, MD, DTM&H

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

This article originally appeared in the August issue of Travel Medicine Advisor. It was edited by Frank Bia, MD, and peer reviewed by Philip Fischer, MD, DTM&H. Dr. Bia is Professor of Medicine and Laboratory Medicine; Co-Director, Tropical Medicine and International Travelers Clinic, 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: *Hansen disease (leprosy) still occurs in non-tropical areas including the south-central region of the United States. Contact with armadillos is a risk factor for acquisition of infections. Skin lesions are not always anesthetic, and biopsy can be diagnostic.*

Source: Abide JM, et al. Three indigenous cases of leprosy in the Mississippi delta. *South Med J.* 2008;101:635-638.

ABIDE ET AL AT THE UNIVERSITY OF MISSISSIPPI REPORT three patients who presented with skin lesions and were found to have leprosy. A 78-year-old male was noted to have two asymptomatic erythematous lesions on his back during a routine exam. Biopsies revealed granulomatous dermatitis with acid-fast bacilli. Polymerase chain reaction (PCR) testing confirmed the presence of *Mycobacterium leprae*, and a diagnosis of Hansen disease, in the borderline

spectrum, was made. He was treated with dapsone and rifampin. An 81-year-old woman had a three-week history of an initially itchy plaque-like lesion on her arm. A biopsy showed granulomatous dermatitis with acid-fast bacilli. Borderline tuberculoid leprosy was diagnosed, and she was successfully treated with dapsone and rifampin. Finally, a 73-year-old man presented with a macular, generalized erythematous eruption of two months' duration, and had some sensory loss on examination. His biopsy also showed granulomatous dermatitis with acid-fast bacilli. He was diagnosed with borderline lepromatous leprosy and was treated with clofazimine, dapsone, and rifampin. It is interesting that two of these three patients had no anesthetic skin lesions, and a least two of them had not traveled to an area outside the United States where leprosy is endemic. All three patients had either killed or eaten armadillo.

■ COMMENTARY

Historically, "tropical" diseases have not been confined to patients living or traveling between the Tropics of Cancer and Capricorn. Indeed, yellow fever killed thousands in Philadelphia during the 1790s as America was experiencing its early decades of independence. Even the location of the Mayo Clinic was influenced by a "tropical" disease; bothersome summertime fevers due to malaria prompted Dr. William W. Mayo to move from Indiana's Wabash Valley to what is now Minnesota in 1854. Still, more than 100 cases of leprosy are reported each year in the United States; while most cases occur in immigrants, there are still endemic foci of leprosy in the Gulf Coast states of Texas, Louisiana, and Mississippi.[1]

Leprosy seems to have arrived in North America during European immigrations of the 1700s.[2] Since 1981, human infection with *M. leprae* has been suspected of being associated with armadillo contact.[3] Controversy about the role of armadillos and leprosy actually representing a zoonotic infection continue,[2] but a recent case-control study shows that infection is clearly associated with armadillo contact, especially eating them.[3] In addition, having lived in Mexico has been identified as a risk factor, and it is suspected that unidentified non-zoonotic factors are still relevant to the transmission of leprosy in the Americas.[3]

Leprosy has been known for millennia, but confusion about the disease arose after the King James version of the Bible used the word "leprosy" for a variety of contagious skin conditions. To avoid undue stigmatization of affected patients, some clinicians now prefer to refer to leprosy as Hansen's or Hansen disease, after the Norwegian, G.A. Hansen, who identified *M. leprae* in the 1870s.

Currently, the World Health Organization estimates the global prevalence of leprosy to be approximately 1.4 per 10,000 people. There are about 500,000 new cases of leprosy reported each year and, in about a dozen countries, leprosy is still endemic (mostly in sub-Saharan Africa but also Brazil, Indonesia, and in parts of South Asia).[4]

Traditionally, clinicians have been taught to consider a diagnosis of leprosy for someone with an anesthetic skin lesion and a history of travel to an area endemic for leprosy. The cases reported from Mississippi remind us that a wide variety of skin lesions, even those with intact, normal sensation, may be due to leprosy, and that the American Gulf Coast states still represent an endemic area. The diagnosis of leprosy is often unnecessarily delayed,[5] so a strong index of suspicion is helpful.[6] Skin biopsy can provide a definitive diagnosis, with PCR being useful for species confirmation. Treatment depends on the classification of the disease, and is effective.[6] Expert help is available in the United States when the diagnosis of leprosy is being considered by calling the National Hansen's Disease Program (1-800-642-2477 or 225-578-9841).[5]

Humans are the main reservoir for *M. leprae*, and eradication efforts are in progress.[4,7] For now, early detection and curative treatment of leprosy infection are the keys to control and, possibly, eventual eradication of this stigmatizing scourge. ■

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Mycobacterium abscessus and Lipotourism

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

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

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

Synopsis: Mycobacterium abscessus *has caused post-operative wound infections in patients from the United States who underwent cosmetic surgery in the Dominican Republic. Increasing numbers of US residents are obtaining medical and dental care overseas, practices that can be associated with infectious diseases and complications following their return.*

Source: Furuya EY, et al. Outbreak of *Mycobacterium abscessus* wound infections among "lipotourists" from the United States who underwent abdominoplasty in the Dominican Republic. *Clin Infect Dis* 2008;46:1181-1188.

In March 2004, an infectious disease specialist in New York queried the Emerging Infections Network (EIN) listserv about treatment of a patient with *M. abscessus* wound infection following abdominoplasty in the Dominican Republic. A second physician with a similar patient saw this message and communicated with the physician in New York, which led to a review of the hospital's clinical microbiology records. Four more cases of *M. abscessus* infection were identified following surgery in the Dominican Republic, and the New York City Department of Health and Mental Hygiene and the CDC were notified and undertook an investigation of the cases.

Additional cases were identified through EIN and interviewed. Laboratory tests for Mycobacteria were done, including Auramine O staining of specimens and examination by fluorescent microscopy, mycobacterial cultures, Kinyoun staining of bacteria from colonies, and identification using liquid chromatography. CDC laboratories performed molecular characterization by pulse field gel electrophoresis (PFGE) and polymerase chain reaction (PCR), as well as susceptibility testing.

Twenty patients were identified and 19 were interviewed. They were all female, with median age of 33 years; all had had abdominoplasty. Among the 19 patients, nine had surgery at one clinic in Santo Domingo. Isolates from eight of these patients were related, whereas the other 11 were not. Seven of the patients were Dominican, and one was Puerto Rican. Ten of the patients also had breast surgery, and eight also had liposuction.

Among the eight patients with related isolates from one clinic, all had abdominal wall infection, and two also had breast infection. Their symptom onset ranged from 2-18 weeks after surgery, and patients sought evaluation a median of three weeks following their surgery. All patients had skin manifestations, a single lesion (three patients) or multiple lesions (five patients) that were palpable, 2-5 cm. Some patients presented with draining and painful lesions, whereas some presented with subjective fever, weight loss, fatigue, and nausea. None showed a leukocytosis.

The correct diagnosis was made at times ranging from < 1 to 23 weeks. Four patients had AFB present on stain, and *M. abscessus* grew from 3-28 days on cultures. The seven isolates tested by CDC were more resistant than the other 12 cases: intermediate or resistant to clarithromycin, imipenem, cefoxitin, amikacin, and were resistant to sulfamethoxazole, doxycycline, tobramycin, and ciprofloxacin. Five patients were hospitalized; all except one were eventually cured. All underwent drainage, and all required prolonged antimicrobial treatment (median six months).

■ COMMENTARY

Mycobacterium abscessus was formerly classified as *M. chelonae*, subspecies abscessus.[1] It is a rapidly growing mycobacterium (RGM), classified along with seven others (*see Table 1*), two of which have been speciated based on DNA homology studies. As the name suggests, these organisms grow rapidly on culture (usually within two weeks, as compared to several weeks for *M. tuberculosis*, *M. leprae*, and other slowly growing nontuberculous mycobacteria). They are environmental organisms, and ubiquitous in water and soil. It is important to identify RGM since therapy differs from that utilized for *M. tuberculosis*, and *M. abscessus* is usually resistant to antituberculous agents. It is recommended that susceptibility testing be carefully performed using a broth microdilution technique.

The RGM can cause skin and soft-tissue infection, pulmonary disease, lymphadenitis, disseminat-

ed disease, musculoskeletal infection, prosthetic device infections, surgical site infections, and catheter-related infections. Skin and soft-tissue infections associated with RGM include nodules (frequently with purple discoloration), recurrent abscesses, or chronic discharging sinuses. *M. abscessus* and *M. chelonae* tend to present as multiple lesions, whereas *M. fortuitum* infections more commonly present as a single lesion.[3] One recent outbreak of *M. abscessus* was due to illicit soft-tissue augmentation in New York City, and traced to a contaminated hyaluronic acid derivative smuggled in from Venezuela.[4]

Among the RGM, *M. abscessus* has been the species most commonly associated with pulmonary disease. One study of 154 such patients found 82% to be caused by *M. abscessus*, and *M. fortuitum* accounted for 15%. The major findings were: female predominance; cough was the most common presenting symptom; diagnosis was established > 2 years after symptom onset; chest radiography included interstitial, mixed interstitial and alveolar, and reticulonodular patterns; cavitation was infrequent; mycobacterial lung disease with respiratory failure caused death in 14%.[5]

This report raises some important questions. For example, how many US residents seek medical care overseas? Although the volume of patients is not tracked, a quick search on the Internet found 190,000 sites, including medical facilities listing their services to US residents, tips for patients planning to go overseas for care, reports of employers looking overseas for less expensive health care, news reports on medical tourism, and companies specializing in arranging medical care overseas. This report describes affected patients who have had cosmetic surgery, which is typically not covered by US health insurance plans. However, many of the web sites cater to patients who lack health insurance in the United States, or cannot afford the out-of-pocket costs of essential health care.

What is the quality of care overseas? Two organizations assess the quality of foreign hospitals: the International Organization for Standardization (ISO) accredits certification bodies, and Joint Commission International (JCI) is an affiliate of The Joint Commission (TJC). These have certified or accredited a number of hospitals overseas, for example in Thailand and India. Nonetheless, the patient who has a complication following the procedure or medical negligence would have lesser recourse than can be expected at home.

Does the number of US residents seeking surgery overseas affect residents of developing countries?

Table 1

Mycobacteria

Species	Clinical importance
M. fortuitum	Post-traumatic wound infection and surgical wound infection, pulmonary infections.
M. chelonae	Primarily affect immunocompromised hosts (corticosteroid therapy, transplant recipients) causing hematogenous dissemination; may also cause surgical wound infections.
M. abscessus	Pulmonary disease, post-traumatic wound infection and surgical wound infection; disseminated cutaneous disease during hematologic malignancy or hemodialysis.
M. smegmatis	Rarely identified as a cause of disease, but can cause disease similar to 1st three species.
M. peregrinum	Rarely identified as a cause of disease, but can cause disease similar to 1st three species.
M. chelonae-like organism (MCLO)	Peritonitis
M. fortuitum third biovariant complex, sorbitol positive	Less well-known
M. fortuitum third biovariant complex, sorbitol negative	Less well-known
(Based on data from CDC)	

A World Bank economist concluded that the income from treating US residents in a developing country may improve health care in that country through retention of their health care professionals (or their return to their home countries following overseas training).[6] Globalization and US health insurance costs are expected to continue the trend in seeking medical care overseas. With the increasing numbers of US residents obtaining medical and dental care overseas, health care providers need to be aware of possible complications following their procedures. ■

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CME Questions

31. Which of the following is correct?

a. *Balamuthia mandrillaris* causes an acute neutrophilic meningitis without focal brain involvement.
b. *Naegleria fowleri* cause an acute focal encephalitis, but does not cause meningitis.
c. Only severely immuncompromised patients are at risk of Balamuthia infection.
d. Infections due to *Balamuthia mandrillaris* are potentially treatable.

32. Which of the following is correct with regard to *Clostridium difficile*-associated diarrhea (CDAD)?

a. Enzyme immunoassays have 100% sensitivity for the diagnosis of CDAD.
b. Approximately one-fifth of CDAD are community-acquired.
c. Tests for glutamate dehydrogenase (GDH) are highly specific, but poorly sensitive.
d. The presence of GDH is exclusive to *Clostridium difficile*.

33. Which of the following is correct?

a. *Mycobacterium chelonae* is a slow-growing mycobacterium, with recovery on agar routinely requiring more than four weeks.
b. Rapidly growing mycobacteria (RGM) are present in the environment, especially soil and water.
c. Leprosy may be acquired in the United States.

Answers: 31. (d); 32. (b); 33. (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. ■

CME Instructions

Physicians participate in this CME program by reading the issue, using the references for research, and studying the questions. Participants should select what they believe to the correct answers, then refer to the answer key to test their knowledge. ■

In Future Issues:

CMV Reactivation and Outcome in Critically-Ill Patients

UPDATES

By Carol A. Kemper, MD, FACP

Meningococcal Vaccine Reminder

A reminder: meningococcal vaccine. *Med Lett Drugs Ther*. 2008;50:57.

As kids prepare for school this fall, remember that the United States American College of Immunization Practices (ACIP) recommends administration of meningococcal vaccine to previously unvaccinated children starting high school or going off to college. As of 2007, kids ages 11-18 years may receive a single dose of the quadrivalent conjugated polysaccharide meningococcal vaccine (Menactra, Sanofi Pasteur). The conjugate vaccine is preferred over the capsular polysaccharide vaccine (Menommune, also by Sanofi Pasteur) because of its enhanced immunogenicity.

Freshmen planning on living in dorms or dormitory-like settings (eg, group homes, fraternities) and kids starting high school are priority groups.

Malaria in Children of Immigrants

Mascarello M, et al. Imported malaria in adults and children: epidemiologic and clinical characteristics of 380 consecutive cases observed in Verona, Italy. *J Trav Med*. 2008;15:229-236.

Several of us on the board of *Infectious Disease Alert* live in an area rich in immigrants. It is estimated that 40% of the Silicon Valley workforce are immigrants, about 70% of whom are from India. This provides us specialists in infectious diseases more than the usual number of cases of endemic disease such as TB, malaria, and typhoid fever. This experience is not limited to the adult working population in our area; in my experience, immigrant parents do not think twice about taking their children home to their country of origin to visit family and friends. Just this week, I was consulting on a case of a young woman with TB lymphadenitis, who had just returned from Mumbai, India, this spring with her 2- and 4-year-old children. Another woman with FUO and skin test conversion informed me she was planning to take her 3-month-old and 2-year-old to India in October for one month. All of these children were born in the United States and had never previously stepped foot in India.

It is now estimated that half of the cases of hepatitis A in the United States are occurring in the children of immigrants who return to their country of origin with kids with their non-immune children.

Mascarello et al examined 43 cases of malaria in children admitted to hospitals in northern Italy from 2000-2004. All affected children were born to immigrant families; no case of malaria occurred in an Italian child. Nearly half (47%) of the children were born in endemic areas who had come to Italy with their parents for purposes of immigration. The other half (53%) were born in Italy (hence, were non-immune) and traveled back to their parents' country to visit relatives and friends. The mean age of the children was 9-years-old; five (12%) were under the age of 5-years-old. Mascarello et al divided these two groups into those who were presumably immune to malaria and those who were non-immune. All of the children required hospitalization. Forty-one of the 43 cases (95%) were due to *P. falciparum*; the remaining two cases were due to *P. vivax*. Forty-one of 43 (95%) had traveled to Africa; the remaining two cases had traveled to Asia. There were clear differences between the two groups. Eight of the cases were considered severe or life-threatening, as defined by WHO criteria; severe cases occurred in 30% of those who were non-immune compared with 5% of those immune. The mean age of these eight children was 3.1-years-old. Higher parasite loads, longer times to clearance of parasitemia, lower platelet counts, and duration of fever were statistically more significant in the non-immune group compared with children with immunity.

Obtaining a good travel history is essential to caring for the ill children of immigrants. Pediatricians should, however, anticipate that children of immigrants may travel and are at risk for travel-related diseases, a risk their patients may underestimate or fail to consider. Clinicians should provide travel-related and vaccine advice to such parents before travel occurs.

HIV Screening in an Acute Care Setting

Walensky RP, et al. Revising expectations from rapid HIV tests in the emergency department. *Ann Intern Med*. 2008;149:153-160; Pilcher CD, Hare CB. The deadliest catch: fishing for HIV in new waters. *Ann Intern Med*. 2008;149:204-205.

Per current USPHS guidelines, we recently implemented rapid HIV screening for all parturient women presenting to Labor and Delivery lacking prior HIV test results, or at high risk for HIV during pregnancy. Our hospital sees nearly 4,000 deliveries per year, and while at least theoretically, most if not all of these women should have been screened for HIV as part of their pre-natal care, many are not, possibly because of the low prevalence of HIV in our area.

Which puts the hospital in the difficult position of having to provide rapid

HIV screening in an acute care setting — the delivery room. Based on estimates of the low prevalence of HIV in our area, and the reported sensitivity and specificity of the rapid HIV test (> 99%), we estimated 4-10 false-positives for every true positive. This means that a number of young woman and infants will receive peripartum HIV drugs unnecessarily, not to mention the psychological distress, counseling, and time and effort.

Walensky et al at Brigham experienced similar difficulties when implementing rapid HIV testing in an ER setting. Although again, worthy in theory, they found that the specificity of the screening test was lower than expected, yielding more false-positives than anticipated, creating additional complexities at work for ER physicians and staff.

A total of 849 adults presenting to Brigham and Women's Hospital ER in Boston in 2007 were screened using the OraQuick Advance Rapid HIV-1/2 antibody test (Orasure Technologies, Bethlehem, Pennsylvania). Patients with a positive test were offered counseling and confirmatory testing using a panel of ELISA, Western Blot, and plasma HIV RNA PCR. Eligible patients were 18-75 years of age, had intermediate illness (neither too ill to participate or too well to be in the ER long enough), not knowingly HIV+, and not receiving prenatal care.

Thirty-nine (4.6%) of 849 tested had a positive test result (another 544 eligible patients were not tested, either because they declined, they were not in the ER sufficiently long, or the staff were too busy). Eight of the 39 women (21%!) declined confirmatory testing. Of the remaining 31, five (16%) were true-positives. Thirteen (50%) had indeterminate Western Blots, and 25 (96%) had negative PCRs; the remaining patient had a viral load of 86 on an initial PCR test, but tested negative two weeks later.

Based on these figures, the prevalence of confirmed HIV in this acute ER population was 0.6%. The specificity of the rapid test was 96.9%, and it provided a false-positive rate of 3.1% — more than 15 times higher than anticipated. Walensky et al advised against the use of the Western Blot alone for confirmation, as it would have mistakenly suggested many more possible early infections, prompting further testing, and instead recommend the use of the confirmatory panel, including plasma viral load.

Interestingly, Walensky et al report that the first two false-positive results prompted temporary closure of the study, pending further investigation and a laboratory audit by the Department of Public Health and the manufacturer, looking for irregularities in procedures. The audit uncovered no flaws, and the study was resumed once the informed consent form was modified to restate the accuracy of the rapid test. Despite these difficulties and their results, Walensky et al believe support for the rapid screening remains high. They comment that for every 100 patients tested in the ER at their institution, 95 leave knowing they are negative, and five leave pending confirmation. One of these will prove HIV-positive, and the other four will be generally informed of their negative status "within 24 hours."

These studies leave open several questions: the cost of the added confirmatory testing and counseling in many more pts than anticipated in an acute care setting, the imposition on busy ER personnel, and what happened to the 40% of people who either were never tested or declined testing, or those eight who refused confirmatory testing. In my experience, patients with risk factors, or those who suspect they may be positive, are often the most reluctant to be tested. In addition, these figures fall apart, to some degree, if testing is shifted to an area with a lower prevalence of HIV — while Walensky et al may accept a ratio of 4:1 false-positives to true-positives in their ER setting, an HIV prevalence of 1 in 1000 would yield a false-positive to true-positive ratio of 24:1. Although not feasible in the delivery room, at what point does it make sense to use more specific tests (but not rapid) for screening purposes in the ER? ■

TB Linked to IMF Loan Funding

ProMED-mail post, July 22, 2008; www.promedmail.org

The increase in tuberculosis in Russia and the former Soviet Eastern Bloc countries has been blamed on the downfall of the Soviet Union in the early 1990s. These authors provide an alternate and intriguing explanation. Investigators from the University of Cambridge examined TB data from 21 countries in central and Eastern Europe from 1989 forward. The premise was that International Monetary Fund loans to countries are often pegged to reductions in government spending, which all too often results in reductions in health care dollars. The IMF specifically grants loans in stages based on spending performance targets, putting pressure on governments to comply.

The investigators found increased rates of TB and increased rates of death from TB in countries receiving funding from the IMF. Despite declining rates of TB in several of these countries prior to receiving loans, cases of TB increased 13% and death rates from TB rose by 16% in countries receiving IMF loans, compared with countries not participating in IMF programs. Increased rates were associated with larger loans and a longer duration of participation in the loan program; for every year the country participated, death rates rose by another 4%. Specifically, researchers observed that the timing of the IMF program was associated with lower government spending on TB programs, and fewer persons receiving therapy through directly observed treatment (DOT).

This is an example of how national — or in this case, international — policy can have serious and unintended consequences for health care. ■

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.

Defining Diagnosis and Management of Prediabetes

In This Issue: Guidelines for prediabetes from The American College of Endocrinology; statins for the prevention of dementia? Possible help for women suffering from sexual side effects while on antidepressants; government incentives for electronic prescribing; FDA Actions.

The American College of Endocrinology has issued its Consensus Statement on the diagnosis and management of prediabetes. The guideline was prompted by evidence that complications of diabetes begin early in the progression from normal glucose tolerance to frank diabetes. They define impaired fasting glucose (IFG) as a fasting glucose 100-125 mg/dL, and impaired glucose tolerance (IGT) as 2 hour post glucose load 140-199 mg/dL. (Diagnostic for diabetes are fasting levels ≥126 mg/dl and post challenge ≥ 200 mg/dL). The guideline recommends intensive lifestyle management for pre-diabetes patients, including weight reduction by 5-10%, regular moderate-intensity physical activity for 30-60 minutes daily at least 5 days a week, a diet low in total saturated fat and transfatty acids, adequate dietary fiber along with low sodium intake, and avoidance of excess alcohol. Although they acknowledge that there are no approved pharmacologic therapies for prevention of diabetes there is evidence that both metformin and acarbose may reduce the rate of development of diabetes from prediabetes. There are safety concerns with thiazolidinediones and they must be used with caution. Persons with prediabetes should have the same lipid goals of those with established diabetes, including statin therapy to achieve LDL cholesterol, non-HDL-cholesterol, or apoB treatment goals of 100 mg/dl, 130 mg/dL, and 90 mg/dL respectively. Other lipid-lowering drugs may be used as considered appropriate. Niacin should be used with caution because of its potential to raise blood sugar. Blood pressure control should also be at the same targets as recommended for diabetics including systolic blood pressure <130 and diastolic less than 80 mmHg. ACEI/ARB should be first-line agents, with CCBs as appropriate second line treatment approaches. Thiazides, beta-blockers, or their combinations should be used with caution due to adverse effects on blood sugar. Antiplatelet therapy with aspirin is recommended for all persons with prediabetes who have no contraindications for aspirin. The full guideline can be found online at www.aace.com/meetings/consensus/hyperglycemia/hyperglycemia.pdf.

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Statins and Dementia

Do statins help prevent dementia and cognitive impairment? The medical literature has been conflicting on this issue, but now a new study from the University of Michigan raises hope that there is benefit. In a population-based cohort study, 1674 older Mexican Americans who were free of dementia or cognitive impairment at baseline were studied over 5 years. Overall, 27% of the participants took statins during the study. After adjusting for education, smoking status, genetic testing, and history of stroke or diabetes at baseline, persons who had used statins were about half as likely as those who did not to develop dementia or cognitive impairment (HR = 0.52; 95% CI 0.34-0.80). The authors conclude that statin users were less likely to have incident dementia or cognitive impairment without dementia during a 5-year follow-up. They also suggest that these results add to the emerging evidence suggesting a protective effect of statin use on cognitive outcomes (*Neurology.* 2008; 71: 344-350).

Help for Women on Antidepressants Who Suffer from Sexual Side Effects

Women with antidepressant related sexual side effects improved with sildenafil (Viagra) according to a new study. In the 8-week randomized double-blind placebo-controlled trial, 98 women who were stabilized on a serotonin reuptake inhibitor were randomized to sildenafil or placebo at a flexible dose starting at 50 mg adjustable to 100 mg. before sexual activity. The primary outcome was change in baseline to study end in the Clinical Global Impression sexual function scale. Women treated with sildenafil had significantly improved sexual function scores even factoring in women who discontinued the medication prematurely. Baseline endocrine levels were the same in both groups as were depression scale scores. Headache, flushing, and dyspepsia were the most commonly reported side effects of sildenafil. The authors conclude that sildenafil treatment of sexual dysfunction in women taking serotonin reuptake inhibitors was associated with a reduction in adverse sexual side effects (*JAMA.* 2008; 300: 395-404). The study was sponsored by Pfizer, the manufacture of sildenafil.

Electronic Prescribing Worth Your While

If you are not already utilizing electronic prescribing, the government may soon make it worth your while by providing incentive payments to physicians and qualified health care professionals who utilize the technology. Beginning in 2009 Medicare will provide incentive payments for electronic prescribers which will include 2% incentive payments in 2009 and 2010; 1% incentive payment in 2011 and 2012, and a 0.5% incentive payment in 2013. On their website, Health and Human Services states that E-prescribing is more efficient, convenient for consumers, improves the quality of care, and lowers administrative costs. They also suggest that widespread E-prescribing would eliminate thousands of medication errors every year. More information can be found at www.HHS.gov/news/facts/eprescribing.html.

FDA Actions

The FDA has ordered safety-related changes to the labeling of erythropoietin products (Procrit, Ecogen, Aranesp) to reflect safety concerns based on recent data. The new labeling states that the drugs are "not indicated for those receiving myelosuppressive therapy when anticipated outcome is cure." Additionally the agency recommended therapy should not be initiated at hemoglobin levels of 10 g/dL and above, and dosage should be withheld if hemoglobin levels exceed a level needed to avoid transfusion. The FDA also encourages health-care professionals to discuss with their patients the risk of erythropoietin therapy including increased risk of vascular events, shortened time to tumor progression recurrence, and shortened survival.

The FDA has approved the first generic divalproex (Depakote delayed-release tablets) for the treatment of seizures and bipolar disorder, and the management of migraine headaches. Both the brand and generic versions of divalproex carry a Boxed Warning regarding the risk of liver damage and pancreatitis. Eight generic companies have received approval to market divalproex including Upsher-Smith laboratories and TEVA Pharmaceuticals.

The FDA has added a Boxed Warning to fluoroquinolone antibiotics regarding the risk of tendinitis and tendon rupture. The risk is higher in patients older than 60, those taking corticosteroids, and patients with kidney, heart, and lung transplants. Patients experiencing pain, swelling, or inflammation of the tendon or tendon rupture should stop taking their fluoroquinolone immediately and contact their health-care professionals. Fluoroquinolones requiring new labeling include ciprofloxacin (Cipro, Proquin), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin) and ofloxacin (Floxin). ■