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Hands Across the Water: Fluoroquinolone-Resistant *Salmonella*

ABSTRACT & COMMENTARY

Synopsis: *This report describes a nosocomial outbreak of rare fluoroquinolone-resistant Salmonella infection among current or former nursing home residents.*

Source: Olsen SJ, et al. A nosocomial outbreak of fluoroquinolone-resistant *Salmonella* infection. *N Engl J Med*. 2001;344:1572-1579.

In 1997, 3 infections due to *Salmonella enterica* serotype Schwarzengrund were reported to the Oregon state health department. These cases were notable in that all 3 isolates were resistant to fluoroquinolones (rare in the United States), and that all 3 patients were current or former residents of a single nursing home (Nursing Home A). The index patient had been previously hospitalized in the Philippines following a stroke, with subsequent transfer to Nursing Home A. Over a 5-year period, a total of 9 patients admitted to the nursing home were colonized or infected with *S enterica* serotype Schwarzengrund. An additional 2 cases occurred in a nearby nursing home (Nursing Home B). The link between the 2 facilities appeared to be transmission within a local acute care hospital. A patient residing in Nursing Home B was admitted to the hospital at the same time as a colonized patient from Nursing Home A.

All the *Salmonella* isolates were closely related based on the results of pulsed-field gel electrophoresis (PFGE). In addition, all shared the same mutations in the gyrA gene responsible for quinolone resistance. In a case-control study, exposure to fluoroquinolones in the prior 6 months was significantly associated with isolation of fluoroquinolone-resistant *S enterica* serotype Schwarzengrund.

The only prior isolation of fluoroquinolone-resistant *Salmonella* in the United States occurred in a New York hospital in 1995. It too was serotype Schwarzengrund of the same PFGE

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type and contained the same gyrA mutations. On further investigation, it was found that the New York patient had been hospitalized in the Philippines in the same hospital as the index patient in Oregon Nursing Home A.

COMMENT BY ROBERT MUDER, MD

This report is notable for a number of reasons. Although outbreaks of *Salmonella* infection have been previously described in nursing homes, *S enterica* serotype Schwarzengrund is unusual in the United States and fluoroquinolone resistance among *Salmonella* isolates is exceedingly rare in this country. In fact, prior to the Oregon outbreak, there had been only 1 previous instance of resistance. That patient was epidemiologically linked to the Oregon outbreak by a prior hospitalization in the Philippines. In that country, fluoroquinolone-resistant *Salmonella* are not rare, accounting for 2.5% of isolates in 1993 and 4.7% of isolates in 1998. In the Philippines, fluoroquinolones, as well as many other antimicrobials, are freely available over-the-counter, a situation that undoubtedly contributes to high rates of resistance.

This report also points out that nursing homes are reservoirs of antibiotic-resistant organisms. These organisms can be unusually persistent due to the debilitated state of many residents, a high incidence of antibiotic usage, and the frequent presence of indwelling catheters and pressure sores, locations known to harbor resistant bacteria. The nursing home patients were more likely to carry the resistant *Salmonella* in the urine than in the stool, a situation that may be fairly unique to nursing homes. Patients transferred to acute care facilities from nursing homes can be the source of resistant organisms in hospitals. In this case, the resistant *Salmonella* was most likely transmitted to a resident of another nursing home during an overlapping stay in the same hospital.

Finally, this report emphasizes the fact that borders, even oceans, are not an effective barrier to the spread of infectious diseases—and of antibiotic-resistant bacteria in particular. Much of the world is only a few hours by plane from the United States. The consequences of indiscriminate use of antimicrobials and inadequate infection prevention strategies can be visited upon a geographically remote area in a very short time. ❖

Infectious Disease Alert, ISSN 0739-7348, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Infectious Disease Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $19.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

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In order to reveal any potential bias in this publication, we disclose that Dr. Deresinski is involved in research with Merck, Sharp & Dohme, Novartis (Systemix), DuPont-Merck, Gilead, Agouron, and Abbott. He also serves as a consultant to Bristol-Myers Squibb, Immunex, and Protein Design Labs and serves on the speaker's bureau of Merck, Sharp & Dohme, Bristol-Myers Squibb, GlaxoSmithKline, Ortho, Bayer, and Lederle. Dr. Kemper serves on the speaker's bureau of Virologic, GlaxoSmithKline, Pfizer, and Agouron and is involved in research with Chiron, Merck, Agouron, and Virologic. Dr. Schleis is on the speaker's bureau for Roche, Aventis, and Bayer and is a consultant for FFF Enterprises, Aventis, and Bayer. Dr. Muder does research for Ortho-McNeil, Aventis, and Pharmacia & Upjohn. Dr. Tice is a consultant for Roche, Merck, Pharmacia & Upjohn, 3M, Agouron, and Ortho and is on the speaker's bureau of Roche, Ortho, Agouron, Schering, and Pharmacia & Upjohn, and does research for Roche, Merck, and Pharmacia & Upjohn. Dr. Jenson is on the speaker's bureau of Merck and Pfizer and does research for Merck and GlaxoSmithKline. Dr. Donnelly, Dr. John, and Dr. Smilack report no speaker's bureau, research, stockholder, or consulting relationships having ties to this field of study.

TNF Receptor Blockade and Sepsis

ABSTRACT & COMMENTARY

Synopsis: *TNF blockade may be associated with an increased risk of infection.*

Source: Baghai M, et al. Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. *Mayo Clin Proc.* 2001;76:653-656.

Baghai and colleagues at the mayo clinic in Rochester report a case of fatal pneumococcal sepsis in a patient receiving etanercept, a TNF-receptor antagonist.

This 37-year-old woman with seropositive rheumatoid arthritis presented with necrotizing fasciitis of the left leg and septic arthritis of the left ankle and prosthetic left hip and knee due to *Streptococcus pneumoniae*. Despite antibiotic therapy with levofloxacin, metronidazole, and vancomycin, as well as

surgical intervention, the patient died.

The patient had been receiving corticosteroid therapy almost continuously since age 16, as well as aggressive treatment with disease-modifying agents. Despite this, her disease progressively worsened. At the time of her presentation with fever and swelling of her left leg, she was receiving prednisone 5 mg daily and etanercept 25 mg weekly.

COMMENT BY STAN DERESINSKI, MD, FACP

Etanercept (Enbrel®) is one of 2 tumor necrosis factor-alpha (TNFα) antagonists currently available for therapeutic use in the United States. TNF activity is initiated by binding to 2 distinct receptors (p55 and p75), and present on almost all cell types designated by their individual molecular weights.[1] The higher molecular mass receptor (p75) appears to largely interact with membrane-bound TNF, while p55 predominantly interacts with the soluble form of TNF. Most of the biologic effects of this cytokine are mediated through this receptor. In an apparent negative feedback system involved in modulating the inflammatory response, cells that are activated shed TNF receptors, which may then bind soluble TNF, preventing its interaction with target cells.

Etanercept appears to act much like the shed TNF receptors. It is a dimeric fusion protein in which the extracellular ligand-binding portion of the p75 TNF receptor is linked to human IgG1.[2] As a soluble form of the p75 TNF receptor, etanercept specifically binds to TNF and prevents the interaction of both TNFα and TNFβ with TNF receptors.

The other TNF antagonist available for clinical use in the United States, infliximab (Remicade®), is a chimeric human/murine monoclonal antibody that binds to human TNFα, neutralizing both the soluble and transmembrane form of this cytokine, and thereby blocking the interaction of TNF with its receptor.

Infliximab and etanercept are each approved for use in the United States for treatment of both rheumatoid arthritis and Crohn's disease. Infliximab is also approved for the treatment of polyarticular juvenile rheumatoid arthritis. These highly effective therapies were developed as a consequence of the recognition of the role played by TNF in the pathophysiology of these and other inflammatory diseases. TNF is, however, also a critical component of the innate immune response to infection. More specifically relevant to the case report by Baghai et al, some experimental evidence suggests a protective role of TNF in pneumococcal infection. Thus, endogenous intrapulmonary production of TNFa serves a protective role in a murine model of pneumonia, preventing bacteremia after intracheal instillation of *S pneumoniae*.[3] In addition, administration of anti-TNFα antibody leads to increased bacteremia and death in this model.[4]

Serious infection may accompany diseases such as rheumatoid arthritis in the absence of therapy with TNF antagonists, especially in patients receiving potentially immunosuppressive disease-modifying agents, although the incidence of such infections appears to be a matter of dispute. Kroot and colleagues reported that the death rate of 622 patients with rheumatoid arthritis during the first 10 years of their disease did not differ from that of the general population, and only 1 patient died with sepsis.[5] On the other hand, a smaller case-control study with 17-year follow-up of patients found that infection was one of the 2 major causes of death.[6]

Therapeutic TNF blockade in patients with sepsis and septic shock has also been associated with an increased risk of death, possibly as the consequence of uncontrolled infection. In a large multicenter, randomized, clinical trial, a single infusion of etanercept provided no benefit in the treatment of septic shock and the highest dose administered, 1.5 mg/kg, was associated with increased mortality.[7] Increased mortality was seen more frequently in patients with Gram-positive infection; no such trend was noted in patients with Gram-negative or polymicrobial infection. Another trial demonstrated a nonsignificant trend toward increased mortality in patients receiving the highest dose of an anti-TNFα monoclonal antibody.[8]

In randomized trials, the incidence of serious infection in etanercept recipients with rheumatoid arthritis was not significantly greater than that observed in placebo recipients (1.3% of placebo recipients and 0.9% of etanercept recipients). In examining all 745 etanercept recipients in open-label and randomized trials, 22 (3.0%) developed serious infection. In the first 5 months after its approval, 30 of approximately 25,000 drug recipients were reported to have developed serious infection.

In clinical trials of infliximab in the treatment of Crohn's disease, infection occurred in 21% of patients receiving infliximab and 11% of placebo recipients.[9] However, only 3% of infliximab recipients and 2% placebo recipients developed "serious" infections. As a consequence, the manufacturers, in cooperation with the US FDA, issued a "Dear Health Professional Letter" stating the following: "Patients who develop a new infection while undergoing treatment with ENBREL should be monitored closely. Treatment with ENBREL should be discontinued in patients with serious infections or sepsis. Treatment with ENBREL should not be initiated in patients with active infec-

tions including chronic or localized infections. Physicians should exercise caution when considering the use of ENBREL in patients with a history of recurring infections or with underlying conditions, which may predispose patients to infections such as advanced or poorly controlled diabetes."[2]

Similarly, the European Agency for the Evaluation of Medicinal Products issued a statement concerning the safety of infliximab on Dec. 20, 2000, as a result of the reporting of 28 cases of tuberculosis among an estimated 100,000 recipients of the product.[10] Infliximab had already been contraindicated in patients with serious infections. To this warning was added one that infliximab administration should be discontinued if tuberculosis is suspected and that patient should be evaluated for both active and latent tuberculosis prior to the institution of therapy. This advice is, of course, complicated by the fact that many chronically ill patients, especially those receiving immunosuppressive therapies, are anergic, rendering PPD skin testing of questionable value.

Thus, there is a strong suspicion that therapeutic TNF blockade may increase the risk of serious infection, including tuberculosis. It is interesting to consider the possibility that this risk may be increased in individuals with certain TNF polymorphisms, such as those that may be associated with increased risk of adverse outcome in sepsis.[11] Whether true or not, the use of TNF blockade will increase in the years ahead as new target diseases (eg, congestive heart failure) are identified.[12] ❖

References

1. Abbas AK, Lichtman AH, Pober JS. In: *Cellular and Molecular Immunology*. 3rd ed. Philadelphia, Pa: WB Saunders; 1997:259.
2. http://www.fda.gov/medwatch/safety/1999/enbrel. Accessed June 14, 2001.
3. Takashima K, et al. Role of tumor necrosis factor alpha in pathogenesis of pneumococcal pneumonia in mice. *Infect Immun*. 1997;65:257-260.
4. van der Poll T, et al. Passive immunization against tumor necrosis factor-alpha impairs host defense during pneumococcal pneumonia in mice. *Am J Respir Crit Care Med*. 1997;155:603-608.
5. Kroot EJ, et al. No increased mortality in patients with rheumatoid arthritis: Up to 10 years of follow-up from disease onset. *Ann Rheum Dis*. 2000;59:954-958.
6. Riise T, et al. Total mortality is increased in rheumatoid arthritis. A 17-year prospective study. *Clin Rheumatol*. 2001;20:123-127.
7. Fisher CJ Jr, et al. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med*. 1996;334:1697-1702.
8. Abraham E, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome: A randomized, controlled, double-blind, multicenter clinical trial. *JAMA*. 1995;273:934-941.
9. Remicade® manufacturing prescribing information. Centocor, Inc. August 1998.
10. http://www.eudra.org/emea.html. Accessed June 14, 2001.
11. Majetschak M, et al. Relation of a TNF gene polymorphism to severe sepsis in trauma patients. *Ann Surg*. 1999;230:207-214.
12. Bozkurt B, et al. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. *Circulation*. 2001;103:1044-1047.

Schnitzler Syndrome—A Rare Enigma

ABSTRACT & COMMENTARY

Synopsis: *Schnitzler syndrome is an idiopathic illness characterized by chronic urticaria, intermittent fever, bone pain, arthralgia or arthritis, and a monoclonal IgM gammopathy.*

Source: Lipsker D, et al. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine (Baltimore)*. 2001;80:37-44.

Let us say you were faced with a 50-year-old man or woman with a chronic urticaria rash, appearing as rose pale macules associated with a fever up to 104°, morning stiffness, arthralgia of the hands, and occasional night sweats. Sometimes the rash resolved within 12 hours. Findings were confined to the rash and axillary and inguinal lymph nodes.

Laboratory findings could include a moderate or marked leukocytosis, elevation of the sedimentation rate and C-reactive protein, monoclonal IgM gammopathy with an absent Bence Jones proteinuria, increased interleukin-6, but normal tumor necrosis factor (TNF). Complement studies and a search for auto-antibodies are negative. Skin biopsy showed a neutrophilic infiltration but no immunoglobulin infiltration.

The patient, let us say, is unresponsive to antihistamines, colchicines, aspirin, prednisone, chlorambucil,

aketoprofen, cetirizine, and hydroxyzine. The rash continued for years and the IgM increased gradually over the years.

COMMENT BY JOSEPH F. JOHN, MD

Specialists who don't recognize this syndrome should not feel bad. Schnitzler syndrome was not described until 1972 and since then, including the 4 new cases described by Lipsker and colleagues from Strasbourg, there has been a total of 52 cases described in the literature. The unrelenting continual skin rash combined with an IgM gammopathy is the hallmark of the syndrome and is usually accompanied by a constellation of symptoms or signs. The diagnostic criteria include urticarial skin rash plus monoclonal IgM spike and 2 of the following: fever; arthralgia; bone pain; palpable lymph nodes; liver or spleen enlargement; increased ESR; leukocytosis; and abnormal bone morphology.

The rash is distinctive with pale rose-colored papules. The trunk and limbs are most often involved. The fever, though intermittent, may peak higher than 104° and disable patients. The fever may respond, to a degree, to nonsteroidal medications.

It is not known if the clonal IgM elevation is primary in nature or a response to some antigentic stimulation. The current report used modern insights to discover an elevation of IL-6 and/or IL-2 receptor levels.

The musculoskeletal complaints may be centered around either joint or bone pain. Amyloidosis, as Lipsker et al point out, does not occur, but patients may develop a lymphoproliferative disorder such as a lymphoma, IgM myeloma, or even Waldenström's disease.

Treatment remains very disappointing, and after reviewing the gamut of therapeutic trials, Lipsker et al concluded that no therapy is predictably useful. The intensity of the skin rash may respond to PUVA therapy. Bone and joint pain may respond to NSAIDs.

It is not surprising that readers may not recognize this syndrome: the mean time in delay of diagnosis was 5 years! The major differential diagnoses include tuberculosis, lupus, lymphoma, adult onset Still's disease, cryoglobulinemia, acquired C1 inhibitor deficiency, hyper IgD syndrome, chronic infantile neurologic cutaneous and articular syndrome, and Muckle-Wells syndrome.

Regarding etiology, I would be surprised if the ultimate cause of this syndrome is not microbial. Indeed, in the cases described by Lipsker et al, there has been inadequate study of these patients for presence of DNA viruses or of retroviruses. The few number of cases preclude clinical trials. ❖

Everybody Out of the Pool!

ABSTRACTS & COMMENTARY

Synopsis: *Prolonged outbreaks due to cryptosporidiosis resulted from exposure while swimming in chlorinated pools.*

Sources: CDC. Protracted outbreaks of cryptosporidiosis associated with swimming pool use—Ohio and Nebraska, 2000. *MMWR Morb Mortal Wkly Rep.* 2001;50:406-410; CDC. Prevalence of parasites in fecal material from chlorinated swimming pools—United States, 1999. *MMWR Morb Mortal Wkly Rep.* 2001;50:410-412.

After reports of cases of cryptosporidiosis came to their attention, the Delaware City/County Health Department (Ohio) found 700 patients meeting their clinical case definition, all of whom had been in central Ohio from June 17 to August 18, 2000. Of 268 stool samples from these individuals, 186 (70%) were found to contain *Cryptosporidium parvum*. A case-control study found that swimming at a club pool was strongly associated with illness, particularly among those involved in activities that increased the risk of pool water entering the mouth.

In an outbreak in Douglas County, Nebraska, 65 of 229 (29%) individuals meeting the clinical or laboratory definition were laboratory confirmed as cryptosporidiosis in the summer of 2000. A case-control study found that illness was strongly associated with swimming at a particular club pool and with having been splashed in the pool.

The demographics and severity of illness were similar in the 2 episodes. In the Ohio outbreak, the median age of case patients was 6 years (range, 1-46 years) and the median duration of illness was 7 days (1-36 days). In the Nebraska outbreak, the median age was 10 years (range, < 1-77 years) and the median duration of illness was also 7 days (range, 1-44 days). Approximately two-fifths at each site reported vomiting; the diarrhea was intermittent in almost one-half.

During the Nebraska outbreak, approximately 18% of case patients swam while they were experiencing symptoms, including diarrhea. "Fecal accidents" had been observed in both Nebraska and Ohio—at least 5 at the latter site, one of which was diarrheal.

Separately, the CDC examined the prevalence of detectable *C parvum* and *Giardia intestinalis* in formed stools collected after fecal accidents at 47 swimming pools, water parks, or aquatic centers throughout the

United States. Samples were tested on unconcentrated samples using an antigen detection system with positives confirmed using immunofluorescent staining. While *Giardia* was identified in 13 (4.4%) of the samples, none of these formed stools contained detectable *Cryptosporidium*.

COMMENT BY STAN DERESINSKI, MD, FACP

Cryptosporidium oocysts, at 2-4 mm in diameter, are sufficiently dimunitive that they may escape pool filtration systems and, in additon, are remarkably resistant to chlorine. While less than 1 hour of exposure is required to inactivate *G intestinalis* and only less than 1 minute to inactivate *Escherichia coli* at a concentration of 1 mg/mL of free available chlorine, approximately 7 days are required to inactivate *C parvum*.[1]

Several factors contributed to the prolonged nature of the outbreaks discussed here. In both cases diarrhea was commonly intermittent and affected individuals continued to use the pool facilities, despite symptoms of cryptosporidiosis. In addition, oocyst excretion commonly persists for a week after resolution of symptoms and may continue intermittently for as long as 2 months.[2] Thus, in addition to the ability of *C parvum* to resist standard measures of pool hygiene, episodes of contamination undoubtedly continued until the pools were closed. These factors combined with the intensity of oocyst excretion (as high as 9.2×10^5/mL of stool in adult AIDS patients) and the low infectious dose (median infective dose of 132 oocysts in healthy adult volunteers), conspired to create these prolonged outbreaks affecting large numbers of individuals.[3,4] Additional factors may play roles. Variation in infectivity among strains has been demonstrated and has variation in host susceptibility relating to the presence or absence of preexisting IgG antibody against *C parvum*.[5,6]

These are not the only 2 intestinal infections associated with exposure to swimming pool water. Perhaps the most devastating have been outbreaks of infection due to *Escherichia coli* 0157:H7, such as one that occurred at a waterpark in Georgia in 1998.[7] (*Editor's Note: The CDC maintains a web site providing information about the prevention of recreational water illness.*[8]) ❖

References

1. Carpenter C, et al. Chlorine inactivation of *Escherichia coli* 0157:H7. *Emerg Infect Dis.* 1999; 5:461-463.
2. Jokipii L, Jokipii AM. Timing of symptoms and oocyst excretion in human cryptosporidiosis. *N Engl J Med.* 1986;315:1643-1647.
3. Goodgame RW, et al. Intensity of infection in AIDS-associated cryptosporidiosis. *J Infect Dis.* 1993;167: 704-709.
4. DuPont HL, et al. The infectivity of *Cryptosporidium parvum* in healthy volunteers. *N Engl J Med.* 1995; 332:855-859.
5. Okhuysen PC, et al. Virulence of three distinct *Cryptosporidium parvum* isolates for three healthy adults. *J Infect Dis.* 1999;180:1275-1280.
6. Chappell CL, et al. Infectivity of *Cryptosporidium parvum* in healthy adults with pre-existing anti-C parvum serum immunoglobulin G. *Am J Trop Med Hyg.* 1999;60:157-164.
7. Gilbert L, Blake P. Outbreak of *Escherichia coli* 0157:H7 infections associated with a waterpark. *Georgia Epidemiol Report.* 1998;14:1-2.
8. http://www.cdc.gov/healthyswimming.

Aspergillosis: Different Patients, Different Strains

ABSTRACT & COMMENTARY

Synopsis: *The ability to detect genetic diversity in Aspergillus isolates depends on the number of techniques used.*

Source: Bertout S, et al. Genetic polymorphism of *Aspergillus fumigatus* in clinical samples from patients with invasive aspergillosis: Investigation using multiple typing methods. *J Clin Microbiol.* 2001;39:1731-1737.

This study set out to better understand the epidemiology of *Aspergillus fumigatus* involved in invasive aspergillosis. To this end, Bertout and colleagues had collected 52 isolates of the mold from the first respiratory sample obtained from 12 cases of probable invasive aspergillosis that had yielded at least 2 colonies of *A fumigatus*. The patients involved had been treated in 3 different geographical locations (Lyons and Grenoble, France and Milan, Italy) and had no connection with one another. Each isolate was subjected to 4 different molecular typing techniques, multilocus enzyme electrophoresis (MLEE) which yielded 8 different types, and 3 DNA typing methods: random-amplified polymorphic DNA (RAPD), sequence-specific DNS primer (SSDP), and microsatellite polymorphism analysis (MSP) which yielded 8, 9, and 14 types, respectively. Combining the 4 methods yielded 25 genotypes among the 52 isolates. As expected, no 2 patients shared the same isolate but, surprisingly, the samples from 6

patients had 2 distinct genotypes and for another 2 patients, 4 and 5 genotypes, respectively.

COMMENT BY J. PETER DONNELLY, PhD

The primary purpose of this study was to demonstrate that a combination of typing methods is useful for understanding the epidemiology of *A fumigatus*, and they succeeded in this regard. The number of resultant types increased proportionately with the number of techniques from 8-14 using one or another typing method to 25 using all 4 methods. With such a tool at one's disposal it should be possible to monitor individual patients over time, identify outbreaks when they arise and locate the source, and also to establish the origin of infection in immunocompromised hosts. However, such an undertaking would prove laborious and prohibitively expensive even if only 1 strain per patient is encountered. Multiply this by the number of patients who appear to be infected anyway with 2 or more different strains of mold and the workload is at least doubled. If an outbreak is encountered, finding the source would add even more work since this mold is ubiquitous both in the hospital environment as well as in the community at large and, importantly, in the laboratory. There is little wonder then why Bertout et al are reserved about using this technique routinely. However, the real power of this type of approach would be in gaining a deeper understanding of the etiology of infection. Evidence already suggests that patients with hematological diseases tend to be infected by separate and distinct strains of the mold, ruling out a common source such as the hospital ward. Instead, it would appear that aspergilli are acquired from the community, probably in the patient's own home environment. By contrast, lung transplant recipients would seem more likely to acquire aspergilli nosocomially. These patients may benefit from being nursed in a proper protected environment while in the hospital whereas other patients at risk may, after all, only benefit from the administration of potent, systemically available antifungal agents to arrest incipient infection and to protect them against further infection for as long as they are at risk whether they are at home or in hospital. With such powerful tools as reported here it should now be possible to provide enough insight into the epidemiology of aspergillosis to identify and evaluate effective means of bringing this wayward opportunist under control. ❖

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Infectious Disease Alert*. Send your questions to: Neill Larmore—Reader Questions, *Infectious Disease Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Infectious Disease Alert* via the Internet by sending e-mail to neill.larmore@ahcpub.com. We look forward to hearing from you. ❖

CME Questions

48. Which of the following is correct?

a. TNF binds to 3 separate receptors on the cell surface.
b. The use of infliximab is supected to be associated with an increased risk of active tuberculosis.
c. TNF blockade has been shown to be associated with significantly improved survival in patients with septic shock.
d. Infliximab is a chimeric form of TNF receptor while etanercept is a monoclonal antibody directed against TNF.

49. What is the most likely diagnosis of a patient with high fevers, night sweats, recurrent urticarial rash, bone and joint pain, and a pure IgM monoclonal spike?

a. Lupus erythematosis
b. Disseminated tuberculosis
c. Schnitzler syndrome
d. Amyloidosis

50. Which of the following is correct?

a. Cryptosporidiosis may be contracted as the result of swimming in a chlorinated fresh water pool.
b. In the CDC study of "fecal accidents," *Cryptosporidium* was readily found in the formed stools submitted for study.
c. *Cryptosporidium* is exquisitely susceptible to free chlorine.
d. The large size of *Cryptosporidium oocysts* makes it readily removable by pool filtration systems.

51. Which of the following is correct?

a. *Salmonella enterica* serotype Schwarzengrund is commonly isolated from patients in the United States.
b. 4.7% of *Salmonella* isolates in the United States in 1998 were resistant to fluoroquinolone antibiotics.
c. 4.7% of *Salmonella* isolates in the Philippines in 1998 were resistant to fluoroquinolone antibiotics.

52. In Bertout et al's study of aspergillosis, a combination of typing methods proved more useful than a single method.

a. True
b. False

In Future Issues:

Bone Cultures May Still be Helpful in Treating Osteomyelitis

UPDATES

By Carol A. Kemper, MD, FACP

Histoplasmosis for Spring Break?

Source: CDC. *MMWR Morb Mortal Wkly Rep.* 2001;50:359-360.

An outbreak of suspected acute histoplasmosis in college students returning from spring break in Acapulco, Mexico has authorities searching for the source of the infection. As of May 1, 229 students from 44 colleges throughout the United States have become ill after traveling to Acapulco during the first 2 weeks of March. Students typically experienced an acute febrile illness lasting ~3 days associated with dry cough, chest pain, shortness of breath, and headache. The laboratory investigation is ongoing but histoplasmosis is strongly suspected.

An investigation of the students' activities have narrowed the focus to one hotel in Acapulco—the Calinda Beach Hotel—that was significantly associated with the development of illness in univariate analysis. Further investigations at the site have not been able to pinpoint a source within the hotel or adjacent grounds. Interestingly, the CDC was recently notified by California authorities about 2 cases of histoplasmosis in a couple who had stayed at the same hotel in early April. ■

VISAs, GISAs and VTSPs

Source: Normark BH, et al. *Clin Infect Dis.* 2001;32:552-558.

Just as clinical practice has adapted to the emergence of penicillin-tolerant *Streptococcus pneumoniae* and the necessity of administering vancomycin for cases of invasive pneumococcal infection, consider this: a Swedish study of 116 clinical isolates of pneumococci identified 3 strains (3%) with tolerance to vancomycin. Eight percent of the isolates were tolerant to penicillin. The 116 isolates were collected from various countries between 1987 and 1997, and most were from cases of invasive disease or pneumonia, although a few isolates were nasopharyngeal in origin. One of the strains of vancomycin-resistant *S pneumoniae* (VISP) was from blood and the other 2 were obtained from nasopharyngeal swab specimens. All 3 isolates had high MBC:MIC ratios of 32, compared with 15 vancomycin-sensitive strains with a ratio of 1 to 2. While all 3 strains had reduced susceptiblity to PCN, only one was tolerant. All 3 strains were serotype 9V and had almost identical fingerprints, suggesting a common origin, although 1 of the isolates had come from Spain and the other 2 were Swedish (40% of PCN-resistant *S pneumoniae* isolates in the United States are believed to have arisen from a single Spanish clone).

Eradication of this organism requires a prolonged course of antimicrobial therapy with concentrations of drug well above the MIC. Patients with invasive disease due to this organism, especially those lacking effective bactericidal function, are at high risk for treatment failure. A recent report documents treatment failure in a patient with recrudescent meningitis due to VTSP infection. ■

'Exotic' Dancers Transmit TB

Source: CDC. *MMWR Morb Mortal Wkly Rep.* 2001;50:291-293.

Public health authorities in Kansas report a cluster of 18 cases of tuberculosis (TB) including a number of women who worked at local clubs as exotic dancers. Of the 18 cases, 14 were confirmed by culture. Eight of the patients were women, including 7 dancers, all of whom had cavitary pulmonary disease. The dancers worked at 6 different clubs in the area. Of the 11 nondancers, 3 of whom were children, 6 had been exposed to the dancers. Nine isolates received for DNA analysis had matching fingerprints, including isolates from 6 of the dancers.

Contact investigation identified 344 contacts, 302 of whom had tuberculin skin testing. One-fourth of those skin tested were positive. Fourteen of 32 contacts who had follow-up skin testing done had evidence of conversion, consistent with recent TB infection. About three-fourths of those eligible for treatment of latent TB infection have initiated prophylaxis.

Unfortunately, the 18 cases were identified over a 7-year period from 1994 to 2000, and the significance of the cluster was only belatedly recognized. Twelve of the 15 adult cases reported using various illicit drugs, and 10 (67%) had been incarcerated at various times during the 7-year period. This cluster shares many similarities with that which recently occurred in several transsexual communities on the East Coast that hosted large "balls," or dance contests, resulting in the facilitated transmission of TB within an isolated "community" that is otherwise fragmented and difficult to trace (Kemper CA. *Infectious Disease Alert* 2000; 19:144). The difficulty in tracking and identifying cases in situations like these, where participants may be reluctant to be identified or name contacts, and contacts often prove elusive, makes the job of the public health department TB control staff extremely difficult, especially in times of limited resources. This outbreak emphasizes the continued need for adequate resources for TB control, even in a place like Kansas with a lower case-incidence of TB that may not have the usual resources and staffing to allocate to outbreaks such as these. ■