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INSIDE

Monkeypox Virus in the United States: Beware the Prairie Dog (and the Gambian Giant Rat)

ABSTRACT & COMMENTARY

Synopsis: The first outbreak of human monkeypox infection in North America has resulted from exposure to infected prairie dogs.

Source: http://www.cdc.gov/ncidod/monkeypox/report060903.htm.

In early may, a number of individuals in the midwestern United States became ill, beginning with a prodrome of fever, headaches, myalgias, chills, and sweats and, in some, a nonproductive cough. Between 1 and 10 days later, they developed a papular rash that typically vesiculated, became pustular, developed a central umbilication, and then crusted over as it resolved. The eruption was generalized in some but typically involved the head, trunk, and extremities. In some, the lesions occurred on the palms and soles. Lesions in different stages of evolution were often simultaneously present.

All 19 patients (17 from Wisconsin and 1 each from Illinois and northwestern Indiana) identified as of June 7, 2003, reported contact with prairie dogs. Most of these prairie dogs suffered from an illness that often began with blepharoconjunctivitis that, in some, progressed to nodular lesions. The infection was lethal in some, but not all, of the animals.

Investigation determined that the prairie dogs had been obtained by a distributor along with a Gambian giant rat that was ill at the time. The prairie dogs were then sold by the distributor to 2 Milwaukee pet shops and were also sold at a pet sale/exchange meeting in northern Wisconsin.

Investigators at the Marshfield Clinic in Wisconsin isolated virus from a patient and a prairie dog that, when examined by electron microscopy, was morphologically consistent with a poxvirus. Preliminary results of serologic testing, polymerase-chain-reaction analysis, and gene sequencing performed at the CDC indicated that the causative agent is monkeypox virus.

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■ COMMENT BY STAN DERESINSKI, MD, FACP

Monkeypox virus is an orthopoxvirus that can cause human disease resembling smallpox. Genomic analysis has recently confirmed that monkeypox virus represents a distinct species and is not a direct ancestor nor a direct descendant of the agent of smallpox, variola virus.[1]

Human monkeypox primarily occurs in the rain forest countries of Central and West Africa. Animal species susceptible to monkeypox virus have been known to include nonhuman primates, lagomorphs, and some rodents. Serological surveys of captured animals in the Democratic Republic of Congo suggested that squirrels play a major role as a reservoir of the virus, with infrequent sporadic infection of humans. Human-to-human transmission occurs with an incubation period of 12 days (range, 7-21 days), but transmissibility by this route is too low to sustain continued spread in susceptible populations.[2]

Human infection results in a vesicular and pustular rash similar to that of smallpox. Limited person-to-person spread of infection has been reported in disease-endemic areas in Africa. Smallpox vaccination provides approximately 85% protection against monkeypox. The secondary attack rate in unvaccinated household members is approximately 9%. Case-fatality rates have ranged from 1-10%.

There is no known proven effective specific treatment of monkeypox infection. The CDC is evaluating the potential role of postexposure use of smallpox vaccine, as well as therapeutic use of the antiviral drug cidofovir.

Suspect cases in animals or humans should immediately be reported to state or local health departments. Physicians should consider monkeypox in persons with fever, cough, headache, myalgias, rash, or lymph node enlargement within 3 weeks after contact with prairie dogs or Gambian giant rats. The CDC recommends a combination of standard, contact, and airborne precautions in management of the patient.[3] The following is their recommendation for dealing with a suspect case in the outpatient setting: "Segregate the patient from others in the reception area as soon as possible, preferably in a private room with negative pressure relative to the surrounding area. Place a surgical mask over the patient's nose and mouth. Care should be taken to cover exposed skin lesions (sheet and/or gown on patient) to prevent contact with infectious material." Exposed health care workers may continue to work but should have twice daily body temperature measurement and be questioned regarding symptoms prior to reporting for duty each day for 21 days following exposure. Specimens for diagnostic testing should be collected and handled in the same way as in testing for vaccinia and smallpox.[4]

Editor's note: *Excellent electron micrographs and clinical photos can be found at http://research.marshfield clinic.org/ crc/monkeypox.asp.* ■

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3. http://www.cdc.gov/ncidod/monkeypox/infectioncontrol.htm.
4. http://www.bt.cdc.gov/agent/smallpox/lab-testing.

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Fatal Interaction Between Linezolid and an SSRI

ABSTRACT & COMMENTARY

Synopsis: A patient receiving the SSRI citalopram developed fatal serotonin syndrome after beginning therapy with linezolid for MRSA infection.

Source: Bernard L, et al. Serotonin syndrome after concomitant treatment with linezolid and citalopram. *Clin Infect Dis.* 2003;36:1197.

An 81-year-old man had been receiving citalopram 20 mg twice daily for 3 weeks prior to admission. He underwent debridement of chronic MRSA osteomyelitis of the ankle. Postoperatively he received linezolid 600 mg twice daily. One week after starting linezolid therapy he developed mental status changes. At 3 weeks of therapy he developed fever, hypertension, tachycardia, confusion, and tremors. A CT scan of the head showed no abnormalities, and initial cardiac isoenzymes and troponin levels were not elevated. During an attempted lumber puncture, he experienced cardiac arrest. He subsequently developed cardiac and hepatic dysfunction, as well as severe lactic acidosis. He had multiple cardiac arrests and expired. An autopsy showed diffuse encephalopathy and an acute myocardial infarction.

■ COMMENT BY ROBERT MUDER, MD

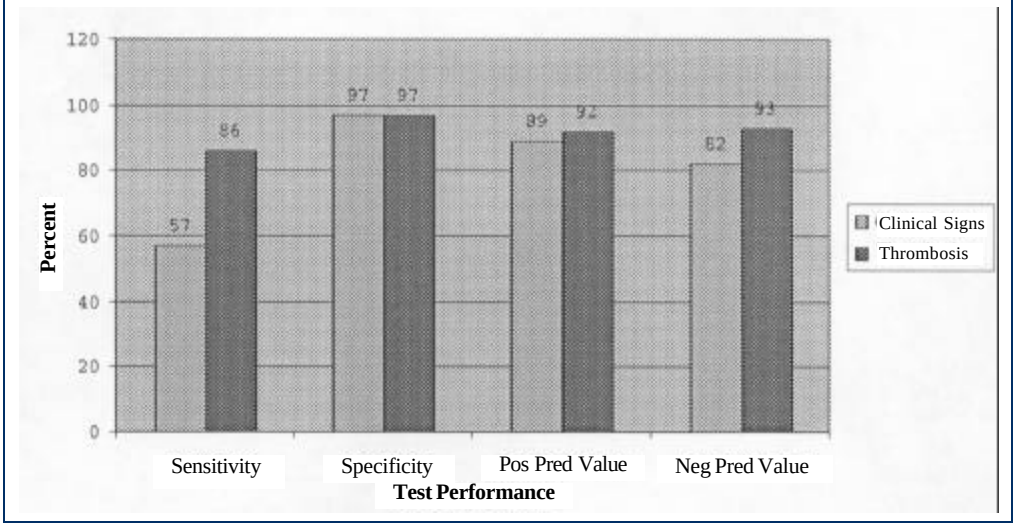
Linezolid is a weak monoamine oxidase inhibitor, and, therefore, has the potential to interact with a variety of vasoactive amines and psychotropic drugs. The serotonin syndrome is a potentially life-threatening illness that may occur with medication overdose or during the receipt of 2 or more drugs that enhance central nervous system serotonin activity.[1] The symptoms include confusion, agitation, fever, diaphoresis, and abnormal neuromuscular activity such as hyperreflexia and myoclonus. Treatment consists of withdrawal of the offending medications and supportive care. Serotonin blocking agents such as cyproheptadine may be beneficial in severe cases.

There are prior individual case reports of serotonin syndrome occurring with the SSRI paroxetine.[2] However, considering how widely SSRIs are currently being used, severe interactions between linezolid and SSRIs appear to be uncommon. Nevertheless, these case reports underscore the potential for a life-threatening occurrence. It is of note that the patient reported by Bernard and colleagues continued to receive the combination of linezolid and citalopram for 2 weeks after mental status changes were first noted. One wonders if the outcome might have been different had the linezolid been discontinued earlier. The report also underscores the fact that serotonin syndrome is easily misdiagnosed at first presentation.

Patients being switched from an SSRI to a MAO inhibitor for treatment of refractory depression typically undergo a 2-week drug-free "washout" period to reduce the likelihood of a serious drug interaction. Bernard et al suggest that patients receiving an SSRI should likewise have that drug discontinued 2 weeks before initiation of linezolid. Considering that serotonin syndrome due to coadministration of linezolid and SSRIs appears to be uncommon, it's not clear that this should be a universal practice. It would be quite reasonable to do so when treating chronic osteomyelitis, since a brief delay in antimicrobial therapy is unlikely to adversely affect outcome. If, on the other hand, linezolid treatment is necessary for a potentially life-threatening infection (for example, sepsis caused by *Enterococcus* resistant to vancomycin and quinupristin/dalfopristin) in a patient receiving an SSRI, careful monitoring of mental status and autonomic function is warranted for the duration of therapy. ■

Figure

Diagnosis of IJ Catheter-Related Infection



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Catheter-Related Infection and Ultrasound Detection of Central Venous Catheter Thrombosis

ABSTRACT & COMMENTARY

Synopsis: Detection of central venous catheter thrombosis by ultrasound may provide an early warning system for the presence of catheter-related infection.

Source: Lordick F, et al. Ultrasound screening for internal jugular vein thrombosis aids the detection of central venous catheter-related infections in patients with haemato-oncological diseases: A prospective observational study. *Br J Haematol*. 2003;120:1073-1078.

Lordick and colleagues in munich used ultrasound screening to prospectively monitor the development of thrombosis in 43 patients with malignancies who had a vascular catheter in an internal jugular (IJ) vein for at least 5 days. The catheters had been inserted using the Seldinger technique with ultrasound guidance. Of the 43 polyurethane catheters, 3 were single lumen, 27 double lumen, and 13 triple lumen. Thirty-six of the catheters were placed in the right IJ vein. Screening for the presence of IJ catheter-associated thrombosis was performed every 4 days by real-time B-mode ultrasound with a 7.5 MHz linear array transducer. Thirty of the patients received prophylactic low-dose heparin (most by continuous IV infusion), and 31 patients were prophylactically receiving either ciprofloxacin or trimethoprim/sulfamethoxazole.

Catheters were in place for 6-54 days (median, 14 days). Fourteen patients developed catheter-related infection (1996 HICPAC definitions), 2 had catheter colonization, 8 had exit-site infection, and 4 had catheter-related bloodstream infection. Of the 42 catheter tips that were cultured, 13 yielded bacteria, 12 of which were coagulase-negative staphylococci. Local evidence of inflammation at the exit site was noted in 9 patients.

A partial thrombus of at least 0.5 cm in diameter was detected in 13 (30%) of the 43 patients, 5 of whom were asymptomatic at the time. Complete thrombosis of the IJ vein was not observed. Thrombosis was first detected at a median duration of 11 days of catheterization (range, 4-20 days). Patients who became neutropenic were more likely to develop thrombosis than those who did not.

Twelve of the 13 patients who developed IJ thrombosis also developed infection, while 2 had infection without thrombosis, and 1 had thrombosis without infection ($P < .0001$). In 4 of the 14 patients with a catheter-related infection, detection of thrombus preceded the occurrence by at least 1 day or, in 1 case, the catheter was removed before clinical signs of infection developed.

COMMENT BY STAN DERESINSKI, MD, FACP

It is estimated that approximately a quarter million central venous catheter-associated infections occur annually in the United States, despite progressive improvement in methodologies aimed at prevention.[1] The infections that do occur are associated with significant morbidity and mortality, making their timely recognition critical to effective patient management. This small observational study suggests the possibility that ultrasound monitoring for catheter-associated thrombosis may prove to be an early warning system.

An association between vascular catheter-associated thrombosis and infection has previously been identified. In contrast to the current study, however, the detection of thrombosis was accomplished either after catheter removal or in postmortem studies.

This study does not answer the "chicken and egg" question (ie, which comes first, the infection or the thrombus). It does, however, demonstrate that, at least in some cases, the clot can be detected before there is clinical evidence of infection. The insensitivity of signs of inflammation at the insertion site has previously been demonstrated.[2] In the current study, both the specificity and positive predictive values of ultrasound monitoring and clinical findings were similar (*see Figure*). The negative predictive value of ultrasound monitoring was somewhat greater than that of clinical manifestations (93% vs 82%) and the sensitivity of the former was markedly better (86% vs 57%). This suggests that detection of IJ catheter-related thrombus may, in some cases, provide the first evidence of impending catheter-related infection. Furthermore, the negative predictive value of 93% indicates that this method may be of modest use in "ruling out" an infected IJ catheter as the cause of fever in some patients.

If thrombosis provides the milieu in which infection may occur or propagate, then prevention or even dissolution of catheter-related clots would be of value.

Heparin is routinely used as a catheter flush for this reason. While most patients in this study received low-dose heparin by continuous IV infusion, it is not stated if the infusion was via the central venous catheter. Although no mention is made of a heparin flush, a metaanalysis concluded that heparin given either by flush or systemically was effective in reducing the risk of catheter-related central venous thrombosis but did not significantly reduce the incidence of catheter-related bloodstream infection.[3]

A prospective randomized comparison of monthly catheter flushing with heparin alone or together with urokinase failed to demonstrate benefit of the latter.[4] In a randomized trial, minidose (1 mg) daily warfarin did not reduce the incidence of central venous catheter-related thrombosis.[5]

Another possible approach to prevention is by the identification of individuals with an increased risk of catheter-related thrombosis. In 1 study, the relative risk of thrombosis associated with tunneled catheters in allogeneic bone marrow recipients was 7.7 in individuals heterozygous for Factor V Leiden.[6] In fact, 54% of the 13 patients with this mutation developed catheter-related thrombosis, leading Fijnheer and colleagues to suggest that all bone marrow recipients be tested for this mutation.

These results require confirmation in a larger study before their applicability to the clinic can be fully assessed. Furthermore, the generalizability will also need confirmation. All the patients in this study had nontunneled catheterization of their internal jugular vein, the least preferred site for nontunneled catheters, according to current guidelines because of evidence suggesting it is associated with an excess risk of infection.[1] Nonetheless, the results are intriguing and potentially useful. ■

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Pleconaril in Infants with Enterovirus Meningitis

ABSTRACT & COMMENTARY

Synopsis: A study of pleconaril in infants with enterovirus meningitis showed good oral availability, but the limited virus shedding and benign course of enterovirus meningitis in infants precluded identifying virological or clinical benefit.

Source: Abzug MJ, et al. Double blind placebo-controlled trial of pleconaril in infants with enterovirus meningitis. *Pediatr Infect Dis J*. 2003;22:335-341.

A multicenter, double-blind, placebo-controlled study of 21 infants (children younger than 12 months of age) was conducted as part of the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Enterovirus was identified by culture or PCR. Of the 21 infants, all but 1 had proven (8 pleconaril vs 7 placebo), probable (1 placebo), or possible (4 pleconaril) enterovirus infection of the central nervous system. Subjects were randomized 2:1 in a double-blind manner to receive pleconaril 5 mg/kg/dose orally 3 times a day for 7 days or an identical placebo lacking the active agent. All but 3 of the 29 pleconaril drug concentrations obtained were > 70 ng/mL, a concentration that inhibits 90% of enterovirus isolates in vitro. Plasma trough concentrations showed that almost all of the day 2 trough and 2-hour postdose values were in the predicted range, whereas all of the day 7 trough values were at the upper limit of or greater than the expected range.

Pleconaril was well tolerated with no significant differences in adverse events between the 2 groups. Adverse events that occurred in > 2 subjects included diarrhea (4 of 12 in the pleconaril group vs 2 of 9 in the placebo group), rash (3 of 12 vs 1 of 9), fever (2 of 12 vs 0 of 9), vomiting (3 of 12 vs 1 of 9), and neutropenia (1 of 12 vs 1 of 9). Of the 20 infants with enterovirus infec-

tion (all specimens were negative by both culture and PCR in 1 patient in the placebo group), only 8 cultures from the oropharynx and 10 cultures from the rectum were positive on day 1. From the 12 subjects in whom an enterovirus was cultured from any body site, serotyping showed that 8 were Coxsackie B viruses, 2 were echoviruses, and 2 were indeterminate. Virus was rarely recovered from any site after the second day of the study. PCR of cerebrospinal fluid was positive in all subjects with proven enterovirus meningitis; none of the 6 cerebrospinal fluids negative by PCR was culture positive. Fever, irritability, anorexia, and lethargy were common among all infants but were infrequent beyond day 4. There were no significant differences in clinical manifestations or duration of hospitalization between the 2 groups.

■ COMMENT BY HAL B. JENSON, MD, FAAP

Pleconaril has in vitro activity against enteroviruses, and in some studies of enteroviral meningitis has shown reduction in intensity and duration of symptoms. The results of this study indicate significant differences of enteroviral meningitis in adults and older children compared to infants, the age group with the highest incidence of enterovirus disease. Virus shedding was considerably shorter than the more typical range of several days to 3-4 weeks from the oropharynx and up to 6-8 weeks from the rectum that usually follows enterovirus infections. As expected, PCR was more sensitive than culture for mucosal, cerebrospinal, and serum specimens. Serial cultures had low yield (< 50%) with positive cultures for < 4 days in both groups, whereas serial PCR of culture-negative specimens had high positive rates (> 50%) persisting through day 14. There was an approximately 3.5-fold accumulation of pleconaril between day 2 and day 7, although the pleconaril was generally well tolerated.

In this small study, there was no demonstrable effect of pleconaril on enterovirus shedding, either by culture or PCR. The course of enterovirus meningitis in these infants was relatively short and benign, with virus shedding generally limited to 2 days and clinical symptoms for only 3-4 days. This benign virological and clinical course is contrasted with the more protracted illness in adolescents and adults with enterovirus meningitis. Although pleconaril remains potentially valuable for enterovirus infections, especially for chronic enterovirus meningoencephalitis in immunocompromised patients, it may be difficult to prove efficacy for infants with enterovirus meningitis. The pharmaceutical sponsor (ViroPharma, Inc., Exton, Pa) has decided not to pursue an enterovirus meningitis indication for pleconaril. ■

Are PDAs the Way?

ABSTRACT & COMMENTARY

Synopsis: PDAs may soon become indispensable to ID physicians.

Source: Miller SM, et al. Personal digital assistant infectious diseases applications for health care professionals. *Clin Infect Dis*. 2003;36:1018-1029.

From the section of clinical pharmacology comes an analysis and insight into some of the computer applications in infectious diseases. This is an important growth area because of the increasing need, if not demand, for immediate information about a huge and expanding volume of information needed for optimal care of patients with infection and the queries others have about emerging infections. Miller and associates reviewed 4 computer programs related to infectious diseases that are available for hand-held devices, otherwise known as personal digital assistants (PDAs).

Their review includes ePocrates ID by ePocrates, the ABX guide by Johns Hopkins, the 2002 Guide to Antimicrobial therapy by Sanford, and the Infectious Diseases and Antimicrobial Notes (IDAN) from the University of Montreal Medical School.

All the programs have useful information and can be used to supplement one's memory or gain recent, and often timely, information about antibiotics—such as interactions with other drugs, dosing with renal failure, adverse effects, and even cost of the antimicrobial. All are available for the Palm OS operating system, and now 3 are available in a Microsoft Pocket PC format as well. Only the ABX system is free at this point, but the others are available for less than $50 per year.

All of the programs contain basic information about antimicrobial dosing, although the ABX program did not have pediatric recommendations at the time it was reviewed. The information about clinical pharmacology varied, with ePocrates ID having the most about mechanism of action, metabolism, and use in lactation. IDAN does not carry updated cost figures or adverse reaction information, but the others do. All but the IDAN program provide some literature references, with the most being available with ABX.

These PDA programs also include decision support, with the ePocrates, ABX, and IDAN versions being interactive. With the ePocrates ID program, for example, categories of infection are entered, only to find queries for more detail such as whether a foreign body is present or

whether the infection is postoperative or not. It also asks for culture results if available and gives more specific answers based on those results. The program has in excess of 300 infections that can be investigated—more than any other. ABX has the same capabilities, but Sanford simply displays tabular information from its paper edition. ABX, ePocrates ID, and IDAN all have the ability to go back to drug information with a few clicks, but Sanford does not.

Miller et al also ran some searches for recommendations for therapy of febrile neutropenia, candidemia, uncomplicated cystitis, and community-acquired pneumonia. Only the IDAN program had recommendations for febrile neutropenia. The others had information about most of the rest, but their recommendations varied.

■ COMMENT BY ALAN D. TICE, MD, FACP

The future is here in regard to computer applications in infectious diseases. You can now reach into your pocket and pull out a device, which can tell you as much, if not more than you want to know, about antimicrobials and even many infections. You can stay ahead of your colleagues in regard to the latest information and preserve your reputation as having the best memory around if you can look at it surreptitiously.

The need for mastery of data management is probably greater in infectious diseases than any other specialty, and the technology is beginning to catch up with the needs. The programs described above allow access not only to basic drug information but also useful guidelines, evidence-based medicine, and advice regarding clinical problems. If an ID specialist can learn to use the latest technology and afford the cost of a PDA program or 2, they can maintain a leadership role. If they do not adapt, it is possible for others to learn as fast and for consults to dwindle. The clinical experience with infectious diseases, however, cannot be replaced but must be supplemented with technology.

The opportunities are increasing in regard to computer applications. Not only are PDAs now practical, as evidenced by a phenomenal growth in the use of ePocrates, but they are being adapted to meet special needs. It is possible to hook up a PDA with the ability to call in prescriptions, to tell you the antibiotics on the formulary, and to force you to write more legibly. They can also be used to review recent guidelines and to record your patient visits and billing information, as well as download the day's latest medical news about SARS, which you can quietly check during Grand Rounds.

Although ePocrates seems to be the volume leader, the programs from ABX, Sanford, and IDNA all have their advantages, as well. In addition, there is Theradoc, a program hosted for free through the Merckmedicus web site. It is out of the University of Utah and provides a useful decision-support program.

The future is here in terms of practical applications with PDAs, and there is more coming. The Tablet PC developed by a number of hardware vendors and Microsoft's help will bring even more resources to the bedside with units the size and nearly the weight of a clipboard. They have all the capability of a laptop of a year or 2 ago plus the ability to allow you to scribble your notes—and possibly even translate them into text. The new ones usually have wireless connections incorporated so can be used anywhere there is Internet access—such as some Starbucks outlets and many medical libraries, although many hospitals are afraid to introduce them because of HIPAA regulations. How many new applications there will be over the next few years only time will tell, but it is worthwhile keeping up to date. ■

Sternal Puncture For Diagnosis of Mediastinitis After Median Sternotomy

ABSTRACT & COMMENTARY

Synopsis: Consistent with the notion that sternitis always accompanies poststernotomy mediastinitis, microbiologic examination of sternal puncture specimens was highly accurate in the diagnosis of deep infection in that setting.

Source: Benlolo S, et al. Sternal puncture allows an early diagnosis of poststernotomy mediastinitis. *J Thorac Cardiovasc Surg*. 2003;125:611-617.

Operating under the hypothesis that sternitis is consistently present in all cases of postoperative mediastinitis, Benlolo and colleagues in Paris performed sternal puncture on all patients with possible mediastinitis after median sternotomy over a 42-month period. The procedure was performed when local evidence of sternal wound infection (inflammation, drainage, sternal instability) was observed and/or the patient had systemic evidence of sepsis. After skin preparation with polyvidone-iodine, a 21-guauge needle was introduced between the opposing sternal edges to a depth of approximately 1 cm. This was repeated at a total of 3 levels of the sternotomy site: upper, middle, and lower. If less than 1 mL of fluid was obtained on aspiration, 1 mL of sterile saline was injected and then aspirated. Cultures yielding

Propionibacterium acnes or a coagulase-negative *Staphylococcus* other than *S epidermidis* were considered contaminated and the sternal puncture was repeated.

Sternal puncture was performed in 49 patients. Forty-three percent of these had local evidence of inflammation and/or wound drainage, and 18% had instability of the sternum. The remainder had only systemic evidence of sepsis. Sternal puncture culture, performed in 49 patients, was positive in 23 (47%); Gram stain was positive in 12 of the 23. The most frequently identified organisms were *S aureus, S epidermidis, Enterococcus faecalis,* and *Klebsiella pneumoniae*.

All 23 patients with positive microbiologic results underwent mediastinal exploration, and each had clinical and microbiologic evidence of mediastinitis. None of the 26 patients with negative sternal puncture results underwent exploration, and none had evidence of mediastinitis after 3 months of follow-up. When the microbiologic results of the 2 procedures were compared, it was found that neither sternal puncture Gram stain nor culture yielded any false-positive results; all 12 with positive Gram stain and all 23 with positive culture had the same organism(s) recovered from operative specimens. The lack of mediastinitis in the other 26 patients with negative results indicates that there were also no false-negative results in this group. Cultures of endocardial pacing wires were also performed, but the results were not predictive of deep infection.

An additional 20 patients who did not undergo sternal puncture underwent exploration and had evidence of mediastinitis. Sternal puncture was associated with earlier surgical intervention, lower SAPS II score, shorter duration of mechanical ventilation, and earlier discharge from the ICU.

■ COMMENT BY STAN DERESINSKI, MD, FACP

The stated strategy of Benlolo et al was to "consider any clinical abnormality after cardiac surgery as a potential sign of early mediastinitis and an indication to perform sternal puncture" for microbiologic diagnosis. Patients with positive Gram stain results underwent immediate exploration, while those with only positive cultures usually underwent surgery on the day after puncture. The reported results suggest that this strategy was highly effective and associated with significant clinical and, probably, economic benefit.

The results of this study are so good, however, that they invite a degree of skepticism. One question that can be raised is that of the pretest probability of mediastinitis. At least one-half of the 49 patients had local evidence of inflammation or wound drainage, making the clinical diagnosis of infection probable without reference to any microbiologic data. In fact, of the 23 patients who proved to have mediastinitis, 74% had inflammation or drainage and 30% had sternal instability (some had both), making the pretest probability very high. It can easily be argued that it would be preferable to immediately explore the mediastinum of patients with these findings, rather than bothering with sternal puncture. In fact, the cardiac surgeon with whom I am lucky enough to work would do just that, and I bless him for it. The problem occurs when the surgeon is reluctant to believe that they have had a surgical complication and prefers to watch and wait, a strategy that often ends with an unfavorable outcome. ■

One Ring to Rule Them All, One Ring to Find Them . . . *

ABSTRACT & COMMENTARY

Synopsis: Ring wearing by health care workers increases the frequency of hand contamination with nosocomial pathogens and decreases the efficacy of all types of hand hygiene studied, included alcohol-based hand rub.

Source: Trick WE, et al. Impact of ring wearing on hand contamination and comparison of hand hygiene agents in a hospital. *Clin Infect Dis.* 2003;36:1383-1390.

Trick and colleagues evaluated the risk factors for hand contamination with nosocomial pathogens, as well as the efficacy of 3 hand hygiene agents in critical care unit nurses. Using the "glove juice" technique, Trick et al cultured 1 hand before, and the other hand after, performance of hand hygiene. Hygiene was randomly allocated to 1 of 3 agents, including soap and water, 0.1% benzalkonium chloride hand wipes, and alcohol-based hand rub. Sampling was conducted during the nurses' workday.

Trick et al collected a total of 282 pairs of before and after hand hygiene samples. They performed 2 separate analyses, 1 to evaluate risk factors for hand hygiene contamination, and another to evaluate hand hygiene efficacy. Before performance of hand hygiene, hands were contaminated by Gram-negative bacilli (10%), *Staphylococcus aureus* (13%), *Candida* spp. (12%), and vancomycin-resistant enterococci (2%). Thirty-two percent of hands carried at least 1 of these pathogens. The presence of 1 or more rings was an independent risk factor

for the presence of each pathogen and for the presence of any pathogen (OR 3.0; 95% CI, 1.8-4.9). The risk of hand contamination increased with the number of rings worn. Wearing a ring at home but not at work was not a risk factor for carriage of a pathogen. Use of an alcohol hand rub significantly decreased the risk of pathogen carriage (OR 0.3; 95% CI, 0.2-0.6); use of the other hand hygiene products did not. Hands with rings were more than 2-fold more likely to be contaminated after use of alcohol-based hand rub than hands without rings.

■ COMMENT BY ROBERT MUDER, MD

This study clearly demonstrates that wearing a ring while working in an intensive care unit increases the likelihood of hand contamination by potential nosocomial pathogens. Further, the presence of a ring decreases the effectiveness of hand hygiene. The study has a number of strengths that include studying nurses during the course of work, using each nurse as his or her own control, a large number of observations, and an appropriate statistical analysis. Thus, the conclusions appear valid and are likely to be broadly applicable.

The presence of a ring may exert its deleterious effect on hand contamination and hygiene by providing a warm, moist, and relatively protected site for pathogens to persist. Local dermatitis is unlikely to be a factor since wearing a ring at home but not at work did not increase the risk of hand contamination.

As the hands of health care personnel are the means of spread of most nosocomial pathogens, it would appear prudent to discourage the wearing of rings by personnel with direct patient contact in high-risk areas such as critical care units. ■

(**from J.R.R. Tolkien's* The Lord of the Rings.)

HHV-8 (KSHV): Another Risk for Health Care Workers?

ABSTRACT & COMMENTARY

Synopsis: Health care workers who care for HIV-infected, hemodialysis, or transplant patients are at increased risk of HHV-8 infection.

Source: Gärtner BC, et al. Risk of occupational human herpesvirus 8 infection for health care workers. *J Clin Microbiol*. 2003;41:2156-2157.

Gärtner and colleagues at the university Homburg/Saar performed a serosurvey to determine the occupational risk of human herpesvirus 8 (HHV-8) infection among health care workers (HCW). The prevalences of IgG antibody against both latent and lytic antigens, determined by indirect immunofluorescence, were 0.4% and 4.7%, respectively, among 236 healthy blood donors and 0.7% and 2.0%, respectively, among 152 HCW who lacked contact with high-risk patient groups. In contrast, the prevalence of antibody directed at HHV-8 latent antigens was 6.9% and against lytic antigens was 12.5% among 72 HCW with contact with HIV-infected patients, transplant recipients, and hemodialysis patients. Thirty-one percent of the 344 at-risk patients tested had serological evidence of HHV-8 infection.

Although none themselves belonged to high-risk groups, HCW with risk-group contact had a higher prevalence of HHV-8 infection than those without such contact ($P < .01$), as well as healthy blood donors ($P = .03$). In contrast, the seroprevalence of HHV-8 antibodies among medical staff without contact with risk groups did not significantly differ from that of the blood donors. The relative risk for HHV-8 infection apparently related to occupational exposure for HCW who cared for high-risk patients was 2.5 (95% CI, 1.7-3.7).

■ COMMENT BY STAN DERESINSKI, MD, FACP

HHV-8 is highly associated with Kaposi's sarcoma (hence its alternate appellation: Kaposi's sarcoma-associated herpesvirus or KSHV), primary effusion lymphoma, and multicentric Castleman's disease. There is a high prevalence of HHV-8 infection in Africa and the Middle East and a relatively low prevalence in Northern Europe and the United States, with an intermediate prevalence in the Mediterranean region. A high prevalence is found among transplant recipients, patients undergoing chronic hemodialysis, and those infected with HIV.

HHV-8 appears to be transmitted by a variety of routes. Sexual transmission is the most common route of transmission in the United States and Northern Europe, while in regions of high prevalence, nonsexual transmission during childhood predominates. Saliva of infected individuals frequently contains the virus, suggesting that exposure to saliva may account for much of the transmission of this virus.

The study reviewed here demonstrates an apparently modestly increased risk of HHV-8 infection in HCW who care for patients at high risk of infection with this virus. The route of infection in these individuals is unclear, but could presumably be the result of sharps injuries or exposure to saliva containing HHV-8. ■

Suggested Reading
1. Martin JN. Diagnosis and epidemiology of human herpesvirus 8 infection. *Semin Hematol.* 2003;40:133-142.

Treatment of Pulmonary *M xenopi* Infection

ABSTRACT & COMMENTARY

Synopsis: Treatment of pulmonary M xenopi *infection with isoniazid and rifampin, with or without ethambutol, appeared to be only modestly effective.*

Source: Jenkins PA, Campbell IA; Research Committee of the British Thoracic Society. Pulmonary disease caused by *Mycobacterium xenopi* in HIV-negative patients: Five-year follow-up of patients receiving standardized treatment. *Respir Med*. 2003;97:439-444.

Jenkins and colleagues in the british thoracic Society randomized 42 HIV-negative adults with pulmonary infection due to *Mycobacterium xenopi* to receive either rifampin plus isoniazid or this combination plus ethambutol. The medications were given daily for 2 years. No difference in outcome between the regimens was found, although the study had limited power to detect such a difference. Jenkins et al, therefore, reported the results for the entire group of 42 patients without regard to treatment regimen.

The mean age of the patients was 65 years and two-thirds had previous or co-existing lung disease, including chronic bronchitis, emphysema or asthma (13), healed tuberculosis (5), pneumonia (4), and bronchiectasis (3). Eleven patients had possible immunocompromise and 7 had "worked in dusty occupations." One patient had previously received BCG. The pulmonary disease was extensive in 38%, and 81% had cavities, mostly large. Sixty-two percent were smear positive.

Patients were monitored for 5 years. There were 3 treatment failures and 2 relapses after apparently successful treatment. Two patients were lost to follow-up. Sixty-nine percent died within the 5-year follow-up, but only 10% died as the result of mycobacterial infection. Only 7 patients (17%) were known to be alive and free of *M xenopi* infection at 5 years.

In vitro susceptibility testing was performed on the initial isolates from 29 patients. One-third were resistant to rifampin, 86% were resistant to isoniazid, and 70% were resistant to ethambutol. There was, however, no correlation between failure of therapy and in vitro resistance.

COMMENT BY STAN DERESINSKI, MD, FACP

M xenopi is a cause of slowly progressive pulmonary infection, most often in patients with underlying lung disease, but it may also be present as a commensal. However, repeated isolation of this organism in the presence of pulmonary lesions can generally be taken as evidence that it is playing a pathogenic role.[1] The laboratory should take care, however, in distinguishing *M xenopi* from the relatively recently identified *Mycobacterium celatum*, a distinction that cannot be made on the basis of biochemical tests alone.[2]

This paper reports the results of a valiant attempt to perform a randomized trial of treatment of an uncommon infection. Unfortunately, only 42 patients could be enrolled in 5 years, making any likelihood of finding a significant difference between these 2 relatively similar regimens quite unlikely. Furthermore, the clinical isolates were largely resistant in vitro to all 3 drugs studied. In vitro resistance, however, did not predict treatment failure, a result that was quite commonly observed.

Experiments with a murine model of *M xenopi* found that the 3-drug regimen used in the study reviewed, rifampin-isoniazid-ethambutol, was significantly less effective than clarithromycin alone. Recent reports have indicated that *M xenopi* is often susceptible to clarithromycin, amikacin,[3] and linezolid (*2002 ICAAC Abstract E-535*). Seventeen isolates tested were highly susceptible to moxifloxacin (MICs < 0.47 mcg/mL) and gatifloxacin (< 0.32 mcg/mL), but 10 isolates were resistant to levofloxacin (*2002 IDSA Abstract 694*). Thus, there are a variety of drugs available from which to construct a rational regimen for treatment of *M xenopi* infection. In addition, surgical resection provides an alternative therapeutic approach in some patients with localized nodular or cavitary disease, especially if they fail chemotherapy, or in patients intolerant to antimicrobial therapy.[4] ■

References
1. Jiva TM, et al. *Mycobacterium xenopi*: Innocent bystander or emerging pathogen? *Clin Infect Dis*. 1997;24:226-232.
2. Zurawski CA, et al. Pneumonia and bacteremia due to *Mycobacterium celatum* masquerading as *Mycobacterium xenopi* in patients with AIDS: An underdiagnosed problem? *Clin Infect Dis*. 1997;24:140-143.
3. Dauendorffer JN, et al. In vitro sensitivity of *Mycobacterium xenopi* to five antibiotics. *Pathol Biol*. 2002; 50:591-594.
4. Lang-Lazdunski L, et al. Pulmonary resection for *Mycobacterium xenopi* pulmonary infection. *Ann Thorac Surg*. 2001;72:1877-1882.

CME Questions

Effective with this testing period, Infectious Disease Alert *is changing its testing procedure. You will no longer need to return a Scantron answer sheet to earn credit for the activity. Please review the text, answer the following questions, check your answers against the key on the following page, and then review the materials again regarding any questions answered incorrectly.* ***To receive credit for this activity, you must return a CE/CME evaluation at the end of the testing term.***

1. **Which of the following is correct with regard to health care workers?**
   a. The presence of 1 or more finger ring is an independent risk factor for the presence of bacterial pathogens on the hands.
   b. Wearing a ring at home but not at work remains an independent risk factor for the presence of bacterial pathogens on the hands.
   c. Use of an alcohol hand rub was not effective in reducing the risk of pathogen carriage on the hands of wearers of finger rings.
   d. Use of nonalcohol hand hygiene products significantly reduced the risk of pathogen carriage on the hands of wearers of finger rings.

2. **Which of the following is correct?**
   a. Monkeypox virus is known to affect primates, lagomorphs, and reptiles.
   b. While monkeypox virus may affect humans, human-to-human transmission does not occur.
   c. Smallpox vaccination provides approximately 85% protection against monkeypox virus infection.
   d. The case-fatality rate of monkeypox virus infection in humans is > 90%.

3. **Which of the following is correct with regard to the treatment of early Lyme disease?**
   a. Administration of doxycycline for 20 days is significantly more effective than administration for only 10 days.
   b. Patients with objective neurologic findings should be treated with ceftriaxone intravenously for 2-4 weeks.
   c. Complementing 10 days of doxycycline therapy with a single dose of ceftriaxone on day 1 significantly improves the outcome when compared to doxycycline therapy alone.
   d. Most patients who receive only orally administered therapy will develop incapacitating symptoms known as "post-Lyme syndrome."

Answers: 1(a); 2(c); 3(b)

In Future Issues:

EIT Test for *Aspergillus*

UPDATES

By Carol A. Kemper, MD, FACP

Diagnostic Testing for SARS

Source: ProMEDmail, June 4, 2003; the WHO WER and Epidemiological Bulletin, http://www.who.int/csr/don.

As of june 2, the *Weekly Epidemiological Record* is reporting a cumulative total of 8384 probable cases of SARS and 770 deaths from 29 countries. The 27 new deaths were reported from China and Hong Kong. The development of commercially available diagnostic tests for SARS have been slower than hoped. Indirect immunofluorescence assays for IgM and IgG antibodies, as well as PCR tests, directed against the SARS virus are being developed. The accuracy and diagnostic sensitivity of these tests have been hampered by several unusual and unexpected features of the SARS virus infection itself. Whereas a greater amount of viral shedding typically occurs during the initial phase of most viral illnesses, SARS appears to be different. It turns out that viral shedding is fairly low during the initial phase of SARS but then peaks in respiratory and stool specimens about 10 days after the onset of symptoms. Serologic response to infection does not appear until the fifth or sixth day of symptomatic illness, and current antibody tests can not reliably detect antibodies until about day 10.

The WHO continues to advocate that use of the SARS case definition for management and isolation of suspect cases, at least until such time as better testing is available. Based on the current situation, officials are anticipating that SARS is here to stay, although the incidence of infection may eventually prove to be more seasonal. In the United States, we may be moving toward a need for better containment policies and the designation of specific facilities for care for possible cases. ■

Itraconazole Prophylaxis in CGD

Source: Gallin JI, et al. *N Engl J Med*. 2003;348:2416-2422.

Patients with chronic granulomatous disease are especially vulnerable to bacterial and fungal infections. Although the administration of trimethoprim-sulfamethoxazole and interferon gamma reduces the incidence of bacterial infections in these patients, fungal infections, especially those due to the filamentous fungi, remain a significant problem.

Gallin and associates evaluated the efficacy and tolerance of itraconazole administered as primary prophylaxis to 39 children (at least 5 years old) and adults in a randomized, double-blind, placebo-controlled trial. Patients were randomly assigned to receive 100 mg of itraconazole daily (or 200 mg daily if 13 years or older or weight > 50 kg) or placebo, which was then alternated on an annual basis. Six females and 33 males were enrolled, with an average age of 15 years (range, 5-57 years). They received a total of 61 courses of itraconazole and 63 courses of placebo. Eight patients were withdrawn due to serious fungal infection, including 1 patient receiving itraconazole and 7 patients receiving placebo (P = .10). The specific infections included aspergillus pneumonia in 6, 1 unidentified fungal pneumonia, and 1 soft-tissue abscess due to *Paecilomyces* spp. The single patient receiving itraconazole, who developed aspergillus pneumonia, reportedly had significant problems with adherence and had likely discontinued study drug (total time on study, 3.7 years).

Patients receiving itraconazole also had fewer superficial fungal infections. Five placebo recipients developed superficial fungal infections compared with none in the treatment group (P = .06). During the study, 19 serious bacterial infections occurred, 1 of which was fatal. There was no evidence that the use of itraconazole affected the frequency of bacterial infection. Three patients receiving itraconazole were withdrawn for other reasons, including headache, rash, and liver function abnormalities in 1 each. Itraconazole levels, obtained in a subset of patients, were undetectable in 50 of 95 plasma samples; levels of the principal metabolite were also undetectable in 39 samples. This is consistent with other data, indicating that blood levels of itraconazole do not necessarily correlate with clinical benefit, and suggests that routine monitoring of itraconazole blood levels is not useful. Based on the results of this study, itraconazole should be considered for use as a long-term primary prophylactic agent in any patient with CGD. ■