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INSIDE

New Perspectives on CVC Catheter Infections

SPECIAL FEATURE

Sources: Braun BI, et al. Preventing central venous catheter-associated primary bloodstream infections: Characteristics of practices among hospitals participating in the evaluation of processes and indicators in infection control (EPIC) study. *Infect Control Hosp Epidemiol*. 2003;24:926-935; Climo M, et al. Prevalence of the use of central venous access devices within and outside of the intensive care unit: Results of a survey among hospitals in the prevention epicenter program of the Centers for Disease Control and Prevention. *Infect Control Hosp Epidemiol*. 2003;24:942-945; Kim SH, et al. Outcomes of Hickman catheter salvage in neutropenic cancer patients with Staphylococcus aureus bacteremia. *Infect Control Hosp Epidemiol*. 2003;24:897-904; Alonso-Echanove J, et al. Effect of nurse staffing and antimicrobial-impregnated central venous catheters on the risk of bloodstream infections in the intensive care unit. *Infect Control Hosp Epidemiol*. 2003;24:916-925.

MANY QUESTIONS CONTINUE TO CIRCLE AROUND THE USE OF central venous access devices (CVC). What are the demographics of their use and the practices of their insertion? How dangerous are they? What location in the hospital is central venous catheter use most prevalent? What are ways to limit infection? Are there special considerations to treat infections, including bloodstream infections, resulting from the use of CVCs?

The December issue of *Infection Control and Hospital Epidemiology* has 4 articles addressing these issues, which are discussed below.

Barbara Braun, who works for the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), assembled epidemiologists from the study group known as EPIC (Evaluation of Processes and Indicators in Infection Control). They in turn contacted those hospitals that had members in the Society for Healthcare Epidemiology of America. The goal of this study was to uncover the methodology of CVC insertion and practices to limit primary bloodstream infections related to CVCs. Novel methods were used to capture the exact characteristics of the insertion of the CVC in 54 hospitals that

VOLUME 23 • NUMBER 6 • MARCH 2004 • PAGES 61-72

completed the CVC survey; 41 were from the United States.

There were 3320 CVC insertions available for study, an average of 58 per hospital enrolled. There was a wide variation in the characteristics of insertion. Most insertions (91%) were nontunneled devices. About 20% of patients had a follow-up CVC inserted in the original site of insertion. Most CVC were placed by physicians, but their experience with insertion varied widely (ie, the number of years the clinician had inserted CVCs ranged from 0 to 39). Mask and gown barriers were used for most insertions. Up to 25% of CVCs were impregnated with an antibiotic or antiseptic. The mean time required for insertion was 10 minutes. Of note, in 8.2% of insertions, physicians had difficulties, mostly related to problems inserting the CVC at multiple sites. In almost 4% of insertions, a supply item was not available.

Hospital policies were also quite variable in dealing with prevention of BSI. Only 49% of hospital committees met 7 or more times per year. Before the study, less than a quarter of hospitals were collecting BSI data. Just more than half of the hospitals convened an immediate investigation if there was a substantial excess of bacteremias. More than 80% of hospitals had no IV team. Use of needleless systems for insertion occurred in about half of the episodes.

One interesting measure of hospital BSI surveillance was the ratio of blood cultures performed per 100 patient-days; the average in this study was 10. Hospitals in the study had an average of 2.2 individuals used for infection surveillance, and these workers spent an average of 13 hours in ICU surveillance. Almost all the hospitals had an epidemiologist.

To answer the question regarding the hospital location of patients with CVCs, Michael Climo in Richmond, Va, and a group of prominent hospital epidemiologists performed a 1-day prevalence study at 6 medical centers. The centers participated in the Prevention Epicenter Program of the CDC. During the day's study, medical personnel visually examined all the patients hospitalized in their respective academic centers. Patients in emergency rooms, outpatient areas, and psychiatry, obstetric, and ophthalmology wards were excluded from the study.

Four classes of catheter were studied: tunneled CVCs; nontunneled CVCs; peripherally inserted central catheters (PICCS); and totally implantable devices that were Portacths by name (Deltec, Inc., St. Paul, Minn). Subclavian, jugular, femoral, or PICCs were all considered for the study. Chi square tests were applied for statistical significance.

Nearly 2500 patients were enrolled, and 29% had CVCs. Rate of use averaged 55.4% in ICU patients and 24.4% in non-ICU patients, but the absolute number of patients outside the ICU was more than twice that for those patients in the ICU.

The most common access sites were subclavian (55%), jugular (22%), and femoral (6%), with the jugular and femoral sites being more frequently used inside the ICU than outside ($P < .001$ for both). The sites in more than 80% of CVCs in ward patients were either subclavian or PICCs. The most common type of catheter was nontunneled CVC (46%) and then tunneled CVC (23%). In the ICU, as expected, most catheters (74%) were nontunneled CVCs.

Separately, Alonso-Echanove, with colleagues from the CDC, performed a study called DISC (Detailed ICU Surveillance Component), a prospective, observational, multicenter cohort study of bloodstream infecions (BSI) associated with CVCs in 8 ICUs.

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A total of 4535 patients who used 8593 CVCs were studied. A total of 293 organisms were isolated: Gram-positive cocci accounted for 73% (coagulase-negative staphylococci, 44.5%), Gram-negative bacteria for 17%, and fungi for 10%.

There were 28 variables analyzed as risk factors. Those variables that were significantly associated with BSI were TPN with a nonimpregnated CVC, no antibiotics for 48 hours post-insertion, unarrousable patients, care by a float nurse, and a patient age of 45-55 years. Only 7.4% of CVCs were PICC lines, but those had a 74% lower risk of BSI. All the impregnated CVCs used chlorhexidine and silver sulfadiazine.

In a more limited study Kim and colleagues from Seoul National University sought to determine the rate of salvage of Hickman catheters associated with *Staphylococcus aureus* bacteremia in neutropenic cancer patients. The study covered 1998-2002 and involved 32 episodes in 29 patients. Vancomycin was not routinely used for empiric therapy. Empiric antibiotic therapy of the staphylococcemic episode was considered appropriate or inappropriate.

Overall mortality was 69%, and that due to *S aureus* was 38%. MRSA infections had a higher mortality rate (P = .04). Salvage was attempted in 24 of the patients (75%). Only 12 patients received appropriate empiric antistaphylococcal therapy, but the difference in salvage between appropriate (58%) and inappropriate (42%) empiric treatments was not significant.

Of 7 cases with persistent *S aureus* bacteremia in the face of specific antistaphylococcal therapy, 4 Hickman catheters were not removed. Three of the 4 died with staphylococcal bacteremia.

For patients in whom salvage was attempted, the overall success rate was 50% (12 of 24), more often in those patients with subsequent negative blood cultures (11 of 17). There was a trend toward a worse outcome in those patients with extraluminal infection and negative subsequent blood cultures.

COMMENT BY JOSEPH F. JOHN, Jr., MD

There are several cogent findings from these studies. First, use of CVCs does differ with regard to hospital location. Hospital policies for CVC use may be quite variable. Infections feature Gram-positive cocci much more than other bacteria and fungi, and coagulase-negative staphylococci are the current bane. A major risk factor for infections remains the concomitant use of total parenteral nutrition. Antibiotic impregnated CVCs reduce the risk of infection, and their use seems to be increasing. Finally, there may be some room for salvage when *S aureus* is the bloodstream pathogen, but when there is persistent staphylococcal bacteremia, the CVC should be removed.

Climo's multicenter group found that central catheters are very commonly used outside the ICU, suggesting that new guidelines for surveillance outside the ICU are needed.

The study by Braun and associates is in fact the most provocative since it highlights the lack of assumption of leadership by some hospitals with regard to policies for these important devices. There is a disconnect between the findings that almost all (96.4%) hospital committees discussed the issue of bloodstream infection, but only about half initiated an investigation if there was an increased frequency. Only 19% of the hospitals had IV teams to manage the CVCs in the study ICU, and only 38% used needleless systems for insertion. This variation in the control and monitoring of CVC, thus, is a national issue that hospitals desperately need to address. Their attention should be directed to structural factors like catheter characteristics and hospital demographics; to process-of-care factors like the skill of operators and monitoring of outcomes; and to patient factors like severity of illness and urgency of insertion.

Only catheters coated with chlorhexidine and silver sulfadiazine were examined in the Alonzo-Echanove study, but the number studied was substantial—1775 of the 8593 CVCs studied. The impregnated CVCs had a 43% lower rate of infection than nonimpregnated CVCs. The reduction in infection was most pronounced in patients on TPN, so perhaps there is at work a catheter/microbial interaction like those influencing biofilm deposition. It was encouraging that the effect of the impregnated CVC was not dependent on the duration of use. Clearly, we are going to hear more about antibiotic-impregnated catheters and the role they may be playing in high-risk patients.

The further finding that PICC lines reduced the risk of infection by 74% when compared to nonimpregnated CVC is a very important aspect of this large, multicenter study. A broader use of PICCs may require additional resources for placement, but the extra time and price may be worth it.

All of us clinicians are increasingly faced with those patients with *S aureus* bacteremia associated with an indwelling CVC. The work of Kim et al from Seoul in neutropenic cancer patients with *S aureus* bacteremia may not be totally analogous to those patients in Western hospitals, but I suspect their outcomes are similar to studies here. The rate of salvage—50%—is about what a lot of ID practitioners would have guessed, but now here are the data.

Taken together, these 4 studies emphasize the impor-

tance CVCs have assumed in modern medicine. They are relatively safe devices, but their very vascular access make them more potentially dangerous than other medical devices. We can generalize from these studies to make the following recommendations:

- CVC should be placed by experienced operators and monitored rigorously by experienced nurses;
- Hospitals should regularly collect and review data on bloodstream infections, particularly those associated with CVC;
- PICC lines are preferable to jugular and subclavian lines;
- Attempts should be made to reduce staphylococcal colonization of CVC; and
- Antibiotic-impregnated catheters should be used for patients at high risk of infection. ■

Restaurant-Associated Pontiac Fever—Will That Be Chills and Fever To Go?

ABSTRACT & COMMENTARY

Synopsis: *Shortly after patronizing a restaurant, 117 individuals developed an illness characterized by fever, myalgia, chills, and headache. Respiratory symptoms were present in fewer than half.* Legionella anisa *was found to be the cause of this outbreak of Pontiac fever.*

Source: Jones TF, et al. Epidemiologic investigation of a restaurant-associated outbreak of Pontiac fever. *Clin Infect Dis*. 2003;37:1292-1297.

Over a period of several days in April 2002, a number of people reported becoming ill shortly after eating at a restaurant in Nashville, Tenn. Predominant symptoms in the initial group of patrons were fever, headache, nausea, vomiting, and diarrhea, but later reports included chills and myalgia, with lesser gastrointestinal symptoms. County and state health departments initiated a case-control study to determine the cause and possible means of transmission of the outbreak.

After reviewing the restaurant's reservation lists and credit card receipts and receiving reports of additional cases, health department investigators identified 117 individuals who reported being ill with fever and associated symptoms within 5 days of eating at the restaurant. An unidentified number of restaurant patrons who experienced no illness after a similar interval served as a control group. Among the ill individuals, fever (present in all by case definition), myalgia (93%), chills (92%), and headache (87%) were the most common symptoms; diarrhea and vomiting occurred in 30% and 16%, respectively. The incubation period was 49 hours (range, 4-120 hours). Illness resolved after a mean of 3 days (range, 4-192 hours).

Further epidemiologic investigation could identify no link to any food consumed at the restaurant. Enterovirus, adenovirus, respiratory syncytial virus, influenza virus, parainfluenza virus, and herpesvirus cultures were negative.

Because the restaurant contained many fountains, pools, and misting machines, as well as a waterfall, large collecting pool, and several large fish tanks, environmental samples were submitted for *Legionella* cultures. *Legionella anisa* was isolated from 2 water samples and a swab specimen from a large ornamental pool. Fifty-eight percent of ill persons (vs 18% of controls) recalled sitting near the fountain and pool. Half of ill individuals who provided acute and convalescent serum specimens had a 4-fold or greater antibody titer rise to ≥ 1:256 to the suspect strain of *L anisa*; none of a healthy group of individuals from Nashville had significant levels of antibody.

Inspection of the water handling system in the restaurant revealed several areas where poor water circulation may have prevented adequate disinfection, and bromine levels and pH deviated from generally recommended standards. The air conditioning system appeared to be well maintained and functioning normally.

■ COMMENT BY JERRY D. SMILACK, MD

Jones and associates are to be congratulated for a nifty piece of epidemiologic work. Any outbreak of illness associated with a restaurant immediately raises the specter of contaminated or spoiled food or beverage. Jones et al, initially anticipating a food-borne etiology, did what all epidemiologists would have done: launch a case-control study to inquire what foods or beverages might have been the source of the illness. Surprisingly, they ran into a blind alley. However, recalling that several outbreaks of Pontiac fever have been associated with whirlpools and hot tubs and 1 with a hotel lobby decorative fountain, they pursued the possibility of *Legionella* infection by obtaining water and other environmental samples from the restaurant, where fountains, pools, and misters abounded. Their efforts were rewarded by isolating *L anisa* from several sites. They then demonstrated that many of the ill persons seroconverted to the isolated bacterial strain, clinching the case. Nice bit of detective work!

Is *Legionella*-induced Pontiac fever a common cause

of what would otherwise appear to be viral-like outbreaks? Since fewer than 2 dozen have been recognized over the past quarter-century, one can only speculate. This fascinating report by Jones et al may stimulate others to look for *Legionella* in other outbreaks. ■

Flatus—A Rapid Diagnostic Tool?

ABSTRACT & COMMENTARY

Synopsis: *Volatile organic compounds from fecal samples appear to have good sensitivity and specificity for many enteric pathogens and could lead to rapid diagnostic testing.*

Source: Probert CS, et al. A novel method for rapidly diagnosing the causes of diarrhea. *Gut*. 2004;53:58-61.

From the Bristol Royal Infirmary in the United Kingdom comes a report of an unusual application of available technology that may actually have some practical applications.

Probert and colleagues took fresh or frozen fecal samples from 35 patients with identified enteric pathogens and compared them with 6 normal controls for the presence of volatile organic compounds (VOC). They used less than a gram of stool in 10 mL sealed "headspace" vials, then assayed the vapors produced with gas chromatography and mass spectroscopy. This methodology has been used previously to detect rotting vegetables.

Analysis indicated the major VOC to be phenols in normal subjects with significant amounts of indoles, terpenes, and hydrocarbons. Organic acids were present in all samples but did not appear to be useful markers. Benzaldehyde was also present.

When VOCs were analyzed for the 6 samples from patients with *Clostridium difficile* diarrhea, furans were found to be prevalent (6 out of 6 and accounted for 25-55% of the VOC detected), but 3-methylindole was present in only 1 of the 6. Identification of 2-furancarboxaldehyde without measurable 3-methylindole was found to have a sensitivity of 83% and a specificity of 97% for *C difficile*.

The 5 rotavirus samples all contained ethyl dodecanoate, whereas only 1 of the other 36 samples, that of an adenovirus, did. The sensitivity was 100%, and specificity calculated as 97%. Ethanol was also found and may be a product of enteric organisms but could not be eliminated as originating from ingestion.

Ammonia was found in 7 of 9 Norwalk virus infections, both subjects with an astrovirus, 2 of 5 with adenoviruses, 1 of 3 with giardiasis, 1 of 5 with rotavirus but in none of those with a pure bacterial etiology.

Five *Campylobacter jejuni* samples were also studied. Phenols, indoles, and volatile organic acids were abundant but not specific. What was unusual, however, was the absence of VOC of the terpenes/hydrocarbons group. This absence was true for only 3 of the other samples.

Probert et al speculate that VOC may be a useful tool in the diagnosis of specific pathogens and possibly bowel disease, as well.

■ COMMENT BY ALAN D. TICE, MD, FACP

The problem of identification of enteric pathogens is a major one, with increasing complexity and cost and a reporting time that makes the microbiology laboratory more relevant to epidemiologic investigations than acute patient care. In fact, most decisions about antimicrobial intervention are made on clinical grounds—with the possible help of a stain of the feces for leukocytes or a direct assay for rotavirus or Giardia antigens. Not only that, but the decision about antimicrobial therapy may be an important one, especially as antibiotics may be detrimental with *C difficile* and in *E coli* O157 cases but beneficial with other invasive pathogens.

The need for better, faster, and cheaper tests for enteric pathogens is obvious, especially in developing countries, where deaths from diarrheal illness are thought to take millions of lives each year. A bedside test would be ideal.

There are obvious questions to be raised in regard to extraneous factors that may influence VOC in flatus or "vapors." Diet, alcohol, antibiotics, and likely other factors may have major effects and would need to be controlled. The ideas, however, are novel and may possibly have practical applications.

To what extent an infectious diseases specialist can use his nose in addition to the usual clinical skills and astute judgment is debatable. I have heard some speak as if their sense of smell is comparable to the microextraction techniques described. To my knowledge, their competence has never been tested in any form with an evidence-based approach. It is, however, obvious to any clinician that patients do vary in odor and that some are relatively revealing, although they usually seem more related to poor dentition or personal hygiene. To what extent the odors of the VOC that are specific for pathogens and could be refined and identified brings forth a variety of applications for cost-effective clinical

care, as well as potentially furthering the frontiers of aromatherapy, but even speculation in these areas is unwarranted at this point. In all likelihood, however, the pathogen-specific VOC of flatus in patients with diarrhea may not have a specific smell associated with them.

It is hoped this insight and the encouraging results will lead to applications in clinical care and rapid diagnostic methods. ■

ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

The following summary of selected abstracts from 3 meetings will be published in multiple parts. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene met in Philadelphia December 3-7, 2003. — ***Stan Deresinski, MD, FACP***

Mycoses

Antifungal Agents

Hemodialysis did not affect the AUC or T1/2 of either itraconazole or hydroxyitraconazole when itraconazole was administered intravenously either before or after dialysis. The major concern regarding the use of the intravenous form of itraconazole is accumulation of its cyclodextrin carrier. The clearance of cyclodextrin was significantly increased by hemodialysis (*ICAAC M-2056*).

Melanin has been demonstrated to impair the in vitro activity of caspofungin against *C neoformans* and *H capsulatum*. In contrast, the activity of voriconazole against both these organisms is not adversely affected by melaninization of the organisms (*IDSA 140*).

Lipid association reduces but does not eliminate the nephrotoxicity of amphotericin B. A retrospective review of 254 recipients of lipid formulations of amphotericin B found that approximately 15% developed nephrotoxicity, with 4.3% requiring hemodialysis. Concomitant use of cyclosporine or tacrolimus was a significant risk factor for nephrotoxicity in these patients (*A-521*).

Because the MIC may be an inaccurate measure of echinocandin activity against filamentous fungi, an alternative measure, the minimal effective concentration (MEC), has been proposed. The MEC is the lowest concentration of the echinocandin that exerts a defined morphological effect on the fungus. The use of the MEC has now been incorporated into the analysis of the pharmacodynamics of the echinocandin, caspofungin. Caspofungin demonstrated concentration-dependent pharmacodynamics in a murine model of invasive pulmonary aspergillosis with C_{max}:MEC being the parameter most closely associated with antifungal activity. Another concentration dependent ratio, AUC/MIC, is the predictive pharmacodynamic variable for caspofungin in a non-neutropenic murine model of candidiasis (*ICAAC M-476, A-1572*).

Coadministration of nelfinavir had no effect on caspofungin pharmacokinetics, while rifampin reduced caspofungin exposure without itself being affected. When given concomitantly with rifampin, the caspofungin dose should be maintained at 70 mg daily (*ICAAC A-1605*).

Aspergillus

The Platelia Aspergillus Galactomannan™ assay recently received US FDA approval for use in the diagnosis of invasive aspergillosis. Its accuracy, however, has been variously reported, and its precise value remains to be fully determined. With a cut-off value of 0.66, the Platelia Aspergillus Galactomannan™ assay had a sensitivity of 30% and specificity of 95% for the diagnosis of invasive aspergillosis in lung transplant recipients. Furthermore, a very important and potentially frequent cause of error has been identified by 2 groups who found that false-positive results for circulating *Aspergillus galactomannan* using the Platelia Aspergillus kit were observed in patients receiving either piperacillin/tazobactam or tazocillin. Another assay (Glucatell™) designed to detect circulating (1→3) ß-glucan had reasonable diagnostic sensitivity and specificity in patients with a variety of invasive fungal infections (*ICAAC M-1020, M-2062a, 2062b, M-1034a*).

An underlying pulmonary disease, most often COPD, was present in 17 of 18 patients with chronic, necrotizing pulmonary aspergillosis. The diagnosis was delayed for a median of 13 months from the onset of symptoms. *A fumigatus* was the etiologic agent in 89% of cases. Ten patients died (*IDSA 351*).

Information concerning treatment of invasive aspergillosis at specific sites other than the lungs is limited. Because of its rarity, this is especially true concerning antifungal therapy of bone and joint infections. However, voriconazole was successful in the treatment of 10 of 19 patients with *Aspergillus* infection (14 due to

A fumigatus) of bone who had failed prior therapy. Central nervous system aspergillosis has been associated with high mortality. Nonetheless, a complete or partial response was achieved in 34% of 86 patients with definite or probable CNS aspergillosis who received voriconazole (13 as primary treatment) (*ICAACM-979, M-1755*).

The toxin-producing species *A versicolor* has been identified as a cause of onychomycosis but rarely identified as the cause of invasive infection. However, 11 of 15 (73%) cancer patients with invasive pulmonary infection due to *A versicolor* died (*IDSA 389*).

A terreus causes serious invasive infections and is commonly more resistant to antifungals than is, for example, *A fumigatus*. A retrospective analysis of 87 cases of *A terreus* infection (47% proven, 53% probable) found that the attributable mortality was 66%. In a multivariate analysis, receipt of voriconazole within 1 week of diagnosis of the infection was associated with reduced mortality compared to amphotericin B (OR, 0.28; 95% CI, 0.01-0.83; *P* = .02) (*ICAAC M-1753*).

An investigative azole, posaconazole, when combined with caspofungin, was synergistic or additive against 96.5% of *Aspergillus* spp. isolates; antagonism was not detected. Because many patients with invasive aspergillosis continue to fail therapy, there is much interest in the use of antifungals in combination. Five patients with invasive aspergillosis were successfully treated with a combination of caspofungin and voriconazole. In each case, an additive effect of the combination was achieved in vitro with the combination when tested against the patient's isolate (*ICAAC M-990, M-1759*).

Mutation of a mitochondrial enzyme, an NADH-ubiquinone oxireductase subunit in *A fumigatus*, is associated with itraconazole resistance (*ICAAC M-391*).

Candida

Fluconazole is being administered with increasing frequency as prophylaxis against *Candida* infection in critical care patients in the absence of strong supporting evidence for this approach. A meta-analysis of randomized, controlled trials led to the conclusion that fluconazole prophylaxis prevents invasive fungal infections in critically ill ICU or surgical patients but does not reduce mortality (*ICAAC K-452i*).

The SCOPE study involving 42 US hospitals found that 9.1% of nosocomial bloodstream infections (BSI) were due to *Candida* spp. Candidemia occurred at a rate of 4.6 per 10,000 admissions, making it the fourth most common cause of BSI. Separately, severe sepsis was observed in 8% and septic shock in 27% of 60 patients with candidemia. The overall crude mortality was 42%, while the 7-day mortality was 27% (*ICAAC K-452e, K-770*).

Candida dubliniensis has been identified as a cause of oropharyngeal candidiasis in HIV-infected patients, but it is often misidentified as *C albicans* because it forms both chlamydospores and germ tubes. While a previous study suggested that it may be less virulent than *C albicans* (*Med Mycol*. 2002;46:2829), it was reported that *C dubliniensis* was at least as virulent in experimentally infected mice as was *C albicans* (*IDSA 730*).

Echinocandins are nonenzymatically metabolized and do not appear intact in urine in significant concentrations. Nonetheless, candiduria resolved in 11 of 12 patients given the echinocandin caspofungin. Anidulafungin is 1 of 2 echinocandins in the late stages of clinical development. In a randomized, dose-ranging trial, anidulafungin and fluconazole were equally effective in the treatment of esophageal candidiasis when assessed at the end of treatment. The proportion of sustained successes at 2 weeks post-treatment was greater with fluconazole treatment (*IDSA 135, ICAAC M-1760*).

While there appears to be a reasonable degree of correlation between in vitro susceptibility testing of yeasts vis-á-vis azole agents and clinical therapeutic outcomes, the interpretation of susceptibility testing with amphotericin B remains more problematic. In fact, an evaluation of 100 patients with bloodstream infection due to *C albicans* failed to detect a correlation of amphotericin B MICs to clinical outcome in patients treated with this polyene (*IDSA 134*).

Coccidioides immitis

The incidence of coccidioidomycosis increased from 15 to 43 per 100,000 people from 1995 to 2001 in Arizona, with the highest incidence in individuals older than 65. Peaks in activity occurred from November through February and were associated with areas of high construction activities. Rainfall, recent temperatures, and dust concentrations were predictive of seasonal outbreaks (*IDSA 354*).

Caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B were each effective in reducing fungal load and prolonging survival in mice experimentally infected with *C immitis*. The combination of caspofungin with each of the amphotericin preparations had enhanced activity; spleen and liver sterility were achieved with caspofungin plus liposomal amphotericin B (*ICAAC M-475*).

Itraconazole was superior to fluconazole in a murine model of coccidioidal meningitis (*ICAAC M-355*).

All 6 patients with coccidioidomycosis who failed or

were intolerant to other therapies who received posaconazole exhibited substantial clinical improvement (*IDSA 143*).

Cryptococcus neoformans

The polysaccharide capsule of *C neoformans* is an important virulence factor. Nonetheless, 6 of 15 patients with pulmonary cryptococcosis were infected with capsule-deficient organisms. The clinical presentation and course did not appear to differ from infection with encapsulated *C neoformans,* and only 1 patient in each group had a serum cryptococcal antigen titer > 1:8 (*IDSA 352*).

Chimeric human IgG2 directed against the major capsular polysaccharide, glucuronoxylomannan, protects mice against experimental cryptococcal infection, while IgG1 enhances infection. In addition, a monoclonal antibody derived from human immunoglobulin transgenic mice immunized with glucuronoxylomannan protected mice from challenge with *C neoformans* (*IDSA 186, M-374*).

Histoplasma capsulatum

Seven solid organ transplant recipients in Omaha developed histoplasmosis over an 8-month period. Five had a diffuse military pattern on chest x-ray. Urinary *Histoplasma* antigen was positive in all 5 patients. All were successfully treated and were alive 3 months to 1 year after diagnosis (*IDSA 393*).

Posaconazole therapy was associated with clinical improvement in 6 of 7 patients with histoplasmosis after failure or intolerance to other antifungal therapy (*ICAAC M-973*).

Zygomycetes

Four allogeneic hematopoietic stem cell recipients developed zygomycosis while receiving voriconazole as prophylaxis or empiric antifungal therapy (*ICAAC M-985*).

Posaconazole is emerging as a potentially effective agent in the treatment of the zygomycoses. Sixteen of 23 (70%) patients with zygomycosis (including 9 *Rhizopus*, 5 *Cunninghamella*, 3 *Mucor*, and 2 *Rhizomucor*) had successful outcomes after treatment with posaconazole (*ICAAC M-1757*).

Zygomycetes have been reported to be resistant to caspofungin in vitro. However, administration of caspofungin prolonged survival in mice experimentally infected with *Rhizopus oryzae*. Crude *R oryzae* cell membranes contain caspofungin-sensitive glucan synthase activity (*ICAAC M-371*).

Miscellaneous Mycoses

An outbreak of penile infections due to the dematiaceous fungus *Phialemonium curvatum* was associated with contaminated intracavernous penile injections. *P curvatum* has previously been reported to cause a variety of invasive infections (*J Clin Microbiol*. 2002;40:2207) (*ICAAC K-1431*).

Blastoschizomyces capitatus is an uncommon cause of invasive infection in severely immunocompromised patients (*Leuk Lymphoma*. 2000;39:209-212). The source of *B capitatus* infection in 4 neutropenic patients in Barcelona was identified as a contaminated thermos flask used for breakfast milk distribution (*ICAAC K-1435*).

Five of 6 patients with chromoblastomycosis due to *Fonsecaea pedrosi* were successfully treated with posaconazole (*ICAAC M-976*).

Pentamidine had in vitro antifungal activity against 10 *Fusarium* isolates at clinically relevant concentrations, being fungistatic against 5 *F solani* isolates and fungicidal against 5 isolates of species other than *F solani* (*ICAAC M-962*).

Penicillium marneffei is a common cause of opportunistic infection in Southeast Asia. Eight of 9 evaluable AIDS patients with systemic *P marneffei* infections were successfully treated with voriconazole, with the ninth patient dying of an unrelated cause (*ICAAC M-963*).

Predisposing factors in 12 patients with fungemia due to *Saccharomyces cerevisiae* included the presence of a central venous catheter, prior receipt of antibiotics, gastrointestinal disease, abdominal surgery, and immunocompromise (*IDSA 358*).

Seven patients with chronic granulomatous disease complicated by invasive filamentous fungal infections were treated with posaconazole after failure (6 patients) or intolerance to voriconazole (1). One patient had cervical lymphadenitis and 6 had pneumonia. Among the latter were 2 due to *Phaeoacremonium parasiticum* and 1 each to *A fumigatus*, *Paecilomyces variotti*, and *S apiospermum*. A complete response to posaconazole was achieved in 6 of the patients, with 1 patient with pneumonia due to *P parasiticum* failing to respond (*ICAAC M-1756*).

Viral Infection

CMV, EBV, Papillomavirus, Orthopox Viruses, HCV, HBV

Cytomegalovirus

CMV is a relatively frequent cause of a mononucleosis syndrome in previously healthy patients. A

questionnaire study reported that the mean duration of symptoms in immunocompetent patients with CMV infection was 7.8 weeks (range, 1-32 weeks), and 12% of patients reported relapsing illness (*ICAAC V-167*).

It has been believed that primary maternal CMV infection in pregnancy was a much greater risk to the fetus than reinfection. However, a prospective study concluded that CMV reinfection in pregnancy is at least as strongly associated with congenital infection and disease as is primary infection. Furthermore, CMV infection is not uncommon during pregnancy. Nine of 51 (81%) CMV-seropositive postpartum women had evidence of reinfection over a 2-year follow-up. Women with reinfection were more likely than those without to have had a sexually transmitted disease (*ICAAC V-176, IDSA 929*).

Asymptomatic CMV reactivation is common in critically ill patients. Twenty of 31 (65%) critical care patients who were not highly immunosuppressed had evidence of active CMV by PCR and/or pp65 antigen detection. Only 2 of the infections were symptomatic, each involving the lungs of patients with chronic lung disease (*ICAAC K-133*).

Epstein Barr Virus

A study of 16 university students with acute infectious mononucleosis found that disease severity peaked at day 10 after onset, and this coincided with the day of highest median concentration of EBV in whole-blood and in peripheral-blood mononuclear cells. The highest concentration of EBV from all sites sampled was found in the throat at 6-7 weeks after illness onset (*ICAAC V-1292*).

Herpes Simplex

Antiviral (acyclovir, valacyclovir, or famciclovir) prophylaxis was offered to 339 teenagers attending a 28-day wrestling camp, and 73% accepted. The incidence of primary herpes gladiatorum was 1%, comparing favorably with the 17.3% incidence of the previous year (*ICAAC V-286*).

Papillomavirus

Human papillomavirus DNA was detected in anal samples from 1414 HIV-negative men who have sex with men. The prevalence did not vary with age. HPV-16 was the most commonly identified type found (*ICAAC V-169*).

Monkeypox

Seven of the patients from Wisconsin who acquired monkeypox infection from pet prairie dogs were described. While direct contact was implicated in each case, it was warned that airborne transmission from animals to man could not be excluded. No human-to-human transmission was observed. Hospitalized patients should be placed in contact and airborne isolation; home isolation is acceptable for patients not ill enough to require hospitalization (*ICAAC V-176a*).

Clinical features of US monkeypox cases reported to the CDC included rash (97%), fever (86%), lymphadenopathy (73%), and sweats (67%). While 2 patients developed severe disease, there were no deaths. Six contacts without disease were IgM seropositive. Smallpox vaccine was administered to 30 individuals during the outbreak in an attempt to cross-immunize against smallpox (*IDSA LB-12*).

Smallpox

Twenty-five reports of myopericarditis were identified from among 34,451 civilians who received the smallpox vaccine (27% with primary vaccination), for an event-reporting rate of 72.5 per 100,000 vaccinees. In addition, 9 ischemic cardiac events, 6 with acute myocardial infarction, were reported, with 2 deaths. The average age was 56 years and two-thirds had 3 or more cardiac risk factors or a previous history compatible with ischemic heart disease. The observed number of cases of acute myocardial infarction in the 3 weeks after vaccination was higher than predicted (*IDSA 813, 814*).

Two to 16% had robust vaccine takes simulating acute cellulitis with > 3 inches of erythema, swelling, and pain. Symptoms peaked at 8-10 days postvaccination regardless of whether antibiotics were administered. Other adverse events reported included rash, fever, headache, and myalgia. Fourteen (41 out of 100,000) cases of inadvertent inoculation and 8 (23 out of 100,000) of generalized vaccinia were reported. When compared to nonocclusive dressings, semipermeable ones reduced but did not eliminate the frequency with which vaccinia virus could be cultured from the surface of the dressings. There were no cases of eczema vaccinatum, progressive vaccinia, erythema multiforme major, postvaccinial encephalitis, ocular vaccinia, or transmission to contacts (*IDSA 818, 819, 825, 816*).

Eight HIV-infected military personnel with CD4 counts of 303-751/mm^3 were inadvertently vaccinated, 2 primarily. No vaccine-related complications occurred (*IDSA 820*).

CME Questions

You 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, 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.***

8. **True or false?**
   The odor of flatus can be characteristic for a variety of enteric pathogens.

9. **True or false?**
   Volatile organic compounds from fecal samples may be distinct for some enteric pathogens and may be useful for rapid identification.

10. **What is the most common type of central venous catheter used outside the ICU?**
    a. A Swan-Ganz type
    b. A subclavian device
    c. A peripherally inserted central catheter (PICC)
    d. A internal jugular catheter

11. **What is the most common microbial cause of central venous catheter infection?**
    a. *Candida albicans*
    b. *Staphylococcus aureus*
    c. Coagulase-negative staphylococci
    d. *Pseudomonas aeruginosa*

12. **Concerning the recent report of restaurant-associated Pontiac fever, which one of the following is correct?**
    a. *L anisa* was isolated from several items of food served at the restaurant.
    b. Diarrhea and vomiting were the most frequently recognized symptoms.
    c. *L anisa* was isolated from several ill individuals.
    d. The outbreak was linked to contaminated fountains and pools at the restaurant.

Answers: 8(False); 9(True); 10(c); 11(c); 12(d)

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: Christie Messina Petrone—Reader Questions, *Infectious Disease Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. ■

In Future Issues:

Candida albicans* and *Staphylococcus aureus

UPDATES

By Carol A. Kemper, MD, FACP

I Smell a Rat—Smelling TB?

Source: NewScientist.com. News Service. December 16, 2003.

THE WORLD BANK IS FUNDING A novel project to train 30 giant pouched rats to sniff out tuberculosis (TB) in respiratory specimens in Sub-Saharan Africa. Rats have been previously successfully trained to target landmines, and a similar training/reward technique is being used with this project. Preliminary results look encouraging. In pilot trials, 5 rats were trained to detect the smell of TB in 10,000 respiratory specimens, and 5 were trained to target TB in cultures. Compared with trained technicians using light microscopy (~95% accuracy), the rats were able to accurately detect TB in 77% of positive smears and 92% of positive cultures—with less than a 2% false-positive rate. Although the rats may not be quite as accurate as trained humans, they are much faster with less prep time. While it takes a trained technician about 1 day to prep and review 20 specimens, a single rat can sniff up to 150 specimens in just 30 minutes. ■

Aerosolized *E coli* 0157 at a County Fair

Source: Varma JK, et al. *JAMA*. 2003; 290:2709-2712.

AEROSOLIZATION OF *E coli* 0157 is a novel concept, never previously considered until recently when a series of 3 outbreaks possibly caused by exposure to contaminated buildings (or air space) occurred—at the University of Wisconsin, the Lane County Fair in Oregon, and the Lorain County Fair in Ohio. In the latter outbreak, at least 23 people who attended the Lorain County Fair developed laboratory-confirmed infection with *E coli* 0157 within 7 days of attending the fair in August 2001. Six patients required hospitalization, and 2 (9%) developed hemolytic uremic syndrome. Nineteen of the 23 patients had attended a dance in an exhibition hall, usually used for exhibition of large livestock.

A case-control study was conducted matching the 23 cases (average age, 15 years), to 53 age-matched controls, all of whom attended the fair but did not develop diarrhea. Case patients were more likely than controls to have visited the exhibition hall. Specific risk factors included attending the dance in the exhibit hall, handling the sawdust from the floor, and eating or drinking in the hall. Six weeks after the fair, Shiga-toxin producing *E coli* 0157 was isolated from 22 of 54 specimens obtained from the exhibit hall, including the sawdust, rafters, and other surfaces. Ten months later, the same *E coli* could still be isolated from specimens obtained from the building.

Talk about "sick building syndrome." *E coli* is known to survive in the environment for long periods of time, but even this case, with isolation of the same organism from the building 10 months later, was surprising to those involved. It sounds as if the dust kicked up in the air (possibly by the dancing?) was either inhaled or settled and was ingested on food or drink. Once again, it sounds like activities involving eating and drinking should not occur in the same space where livestock defecate. So much for good old-fashioned barn dances, at least without changing the hay. ■

Fatal Illness Strikes Traveler

Source: *MMWR Morb Mort Wkly Rep*. 2004;52:1285-1286.

HOW QUICKLY CAN YOU GUESS this case? A 63-year-old previously healthy man traveled to Haiti for one week in October 2003, to help build a church in a more rural area. On the final day of his trip, he developed a sore throat. Two days later, back in the United States, he presented to a local emergency room in Pennsylvania with worsening sore throat and difficulty swallowing. Despite a negative rapid strep screen, he received Augmentin. Two days later, he was admitted to hospital with progressive throat pain, neck swelling, and, over the next few days, developed pulmonary infiltrates and respiratory failure. Although epiglottitis was originally suspected, laryngoscopy revealed thick yellow exudates coating the throat. However, cultures were negative for *C diphtheriae*.

Despite treatment with broad-spectrum antimicrobials (including azithromycin, ceftriaxone, and nafcillin) and steroids, he clinically deteriorated, requiring transfer

to a tertiary care facility. There, while being trached on the eighth day of illness, thick white pseudomembranes were visualized covering the supraglottic structures. Repeat cultures for *C diphtheria* were negative, but specimens forwarded to the CDC were subsequently positive for *C diphtheriae tox* genes by PCR. Despite continued treatment with antibacterials and receipt of diphtheria anti-toxin (DAT) on the ninth day of illness, he died of cardiac complications.

While diphtheria remains uncommon in the United States, travelers to areas endemic for this infection remain at risk if they have not been adequately vaccinated. Sporadic cases continue to occur (only 53 cases have been reported to the CDC between 1980 and 2001), largely in unvaccinated older adults. While > 95% of children in the United States have been adequately vaccinated, coverage amongst older adults is lower; the man described above had never been vaccinated to diphtheria. Serologic studies performed in 1988-1994 indicate that adequately protective antibodies decrease progressively with age, from 91% at ages 6-11 years to ~30% at age 60-69 years.

This unfortunate case serves as a reminder that DAT should be administered as soon as diphtheria is suspected and should not be based solely on the results of cultures (which may be negative in partially treated cases). It is crucial to neutralize the toxin before it enters cells. The duration of illness roughly correlates with the severity of symptoms and the degree of membrane formation, which roughly correlates with toxin burden. More established illness therefore requires greater amounts of antitoxin. Although not specifically addressed in this report, myocarditis is one of the complications of diphtheria and may have explained this man's cardiac demise.

Any international travelers-regardless of age or other health issues—and especially those traveling to areas where diphtheria remains endemic (www.cdc.gov/travel/diseases/dtp.htm)—should receive a primary series (> 3), including a booster of diphtheria-containing toxoid within the previous 10 years. ■

VZV Reactivation in Astronauts

Source: Mehta SM, et al. *J Med Virol.* 2004;72:174-179.

Stress is a known trigger for reactivation of herpes viruses. Just the physical and psychological trauma of swapping alpha-male mice between 2 mouse colonies and the resultant battle for new alpha-male-dom has been shown to trigger reactivation of HSV in about half the mice. Herpes zoster can also reactivate after stress, including the stress of surgery.

After a 47-year-old healthy astronaut developed herpes zoster 2 days before a space flight, Mehta and associates decided to examine whether the stress of space flight can result in the reactivation of VZV. A total of 312 saliva samples, obtained from 8 astronauts before, during, and after space flight were examined by PCR. Amazingly, 61 of 200 (30%) specimens obtained during and after space flight were positive, compared with 1 of 112 (< 1%) obtained in a 234-265 day period before flying. No VZV was detected in 88 samples from 10 control subjects who did not fly. Seven of 8 astronauts had at least 1 positive specimen during flight (2-12 days), while all 8 had anywhere from 1-8 positive specimens within 15 days of returning to earth. ■

PHARMACOLOGY WATCH

Sinus and Allergy Health Partnership Releases New Guidelines for Treatment of Bacterial Rhinosinusitis

New guidelines for the treatment of bacterial rhinosinusitis were published in the January supplement of *Otolaryngology- Head and Neck Surgery* by the Sinus and Allergy Health Partnership. The goal of the guidelines is to reduce the use of antibiotics for viral infections and to use the most appropriate antibiotic for bacterial infections. The guidelines recommend antibiotics if patients are getting worse after 5-7 days or if they are not better after 10-14 days. Patients with mild disease should be treated with cefpodoxime (Vantin), cefuroxime (Ceftin), amoxicillin, amoxicillin/clavulanate (Augmentin), or cefdinir (Omnicef). Patients with moderate disease or those with recent antibiotic exposure should receive amoxicillin/clavulanate, ceftriaxone, or one of the respiratory fluoroquinolones including gatifloxacin (Tequin), moxifloxacin (Avelox), or levofloxacin (Levaquin). The respiratory quinolones do not include ciprofloxacin. This is a follow-up to the group's first guidelines, which were published in 2000 (*Otolaryngol Head Neck Surg*. Supplement. 2004;130:1).

Steroids Not Linked to Risk of Fractures

Long-term use of inhaled steroids for the treatment of respiratory diseases or nasal steroids for the treatment of allergic rhinitis are not associated with an increased risk of fractures if they are used in normal doses, according to a study from Canada. Researchers conducted a case-control study of all elderly Québec residents who were dispensed respiratory medications and could be followed for at least 4 years from 1988 to 2001. The rate of hip or upper extremity fractures was not increased in those patients who used daily inhaled corticosteroids (RR, 0.97). The rate of upper extremity fractures increased by 12% with every 1000 µg increase in the daily inhaled corticosteroid, but the rate of hip fractures did not increase. The rate of hip fractures was only elevated with very high doses (more than 2000 µg per day) of inhaled corticosteroid. Nasal steroids did not increase the risk at any dose. The authors conclude that long-term use of inhaled and nasal corticosteroids at usual recommended doses is not associated with the risk of fracture (*Am J Resp Crit Care Med*. 2004;169:83-88).

ADT Puts Men at Risk for Osteoporosis

Men treated for prostate cancer with androgen deprivation therapy (ADT) are at risk for osteoporosis and fractures, according to a new study. One year of ADT resulted in 2-8% bone loss in the lumbar spine and 1.8-6.5% bone loss

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in the femoral neck. The study was a meta-analysis of 9 studies that included a total of 208 patients. The authors suggest that men starting ADT should be considered for bone mineral density measurement, and men at high risk should be offered a bisphosphonate (published online January 19, 2004. *Cancer*).

Study Shows Valsartan May Improve Sexual Function in Postmenopausal Women

A new study suggests that valsartan may improve sexual function in hypertensive postmenopausal women. Researchers randomized 120 postmenopausal women aged 51-55 with mild-to-moderate hypertension to valsartan 80 mg daily or atenolol 50 mg daily for 16 weeks. Doses were doubled if diastolic blood pressures remained above 90 mm Hg. The end point was a questionnaire that self-evaluated various aspects of sexual desire, orgasmic response, and coital activity. The drugs lowered blood pressure equally effectively. Women in the valsartan group noted significantly improved sexual desire (38% increase, $P < .01$), changes in behavior (45% increase, $P < .001$), and sexual fantasies (51% increase, $P < .001$). In the atenolol group, scores for sexual desire and sexual fantasies significantly worsened (18% decrease, $P < .01$, and 23% decrease, $P < .001$, respectively). The authors conclude that in the study group, hypertensive postmenopausal women in their 50s, valsartan improved some aspects of sexual function, whereas atenolol worsened it. They further speculate the drugs may have differential effects on serum hormone levels, specifically testosterone (*Am J Hyperten*. 2004;14:77-81).

New Direct-to-Consumer Pharma Advertising Rules Considered

Anyone who watched the Super Bowl can verify that direct-to-consumer advertising of prescription pharmaceuticals is big business. Now the FDA is considering tighter restrictions on the content of these ads, requiring pharmaceutical companies to highlight key risks associated with the drugs rather than listing the large number of potential side effects in small print. The guidelines encourage companies to use less cluttered formats for print ads, perhaps even using bullet points to set the import risks apart. Print ads currently contain an extensive list of side effects similar to the package insert, often in a similarly small font, frequently on a separate page from the main advertisement. The FDA is also considering changing the criteria for "reminder" ads that simply name the drug without giving the indication for its use. Currently, these ads do not require information on adverse effects and often run close to disease awareness campaigns also paid for by the drug company. These new FDA restrictions have not been finalized and are sure to be opposed by Pharma.

FDA Actions

Boehringer Ingelheim Pharmaceuticals has received FDA approval to market tiotropium bromide inhalation powder (Spiriva) for the treatment of COPD. Tiotropium, a once-daily anticholinergic agent, is indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Modafinil (Provigil) has been approved for improving wakefulness in patients with excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The drug is currently approved for improving wakefulness in patients with narcolepsy.

The FDA has approved a 3-day course of azithromycin (Zithromax) for the treatment of acute bacterial sinusitis. The drug, which is dosed at 500 mg once a day, is the only 3-day regimen approved for this indication. Azithromycin is currently approved for the treatment of community-acquired respiratory infections and skin infections, as well as otitis media.

Olanzapine (Zyprexa) has been approved for maintenance treatment of bipolar disorder. The drug appears to be effective in delaying relapse into either mania or depression in bipolar patients. Olanzapine was approved in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder.

The FDA has also approved a combination of olanzapine and fluoxetine (Prozac) for the treatment of bipolar depression. The combination drug will be marketed under the trade name Symbyax. Quetiapine fumarate (Seroquel) was also recently approved for monotherapy and adjunct therapy with lithium and divalproex, for the short-term treatment of acute manic episodes associate with bipolar I disorder. ■