

Perspective**Changing Trends in Bacterial Infections: *Staphylococcus aureus*, Bacterial Pneumonia, *Clostridium difficile***

*Changing bacterial diseases in the general population of which HIV practitioners should be aware include: new staphylococcal syndromes caused by community-acquired methicillin-resistant *Staphylococcus aureus* USA300 strains (eg, necrotizing skin infections, pneumonia, fasciitis); continued high rates of community-acquired pneumonia in the potent antiretroviral therapy era; increased rates and severity of *Clostridium difficile*-associated disease due to the fluoroquinolone-resistant NAP1 strain, and the new scare from extensively drug-resistant tuberculosis, primarily as a potential threat to health care in Africa. This article summarizes a presentation on important bacterial infections made by John G. Bartlett, MD, at the International AIDS Society–USA course in New York in March 2007. The original presentation is available as a Webcast at www.iasusa.org.*

There are a number of recent changes in bacterial infections in the general population of which HIV practitioners should be aware. Those that are most important in HIV care include the new staphylococcal syndromes caused by community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), the continued high rates of invasive pneumococcal disease, increased rates and severity of *Clostridium difficile*-associated disease due to the fluoroquinolone-resistant NAP1 variant, and the recent outbreak of extensively multidrug resistant (XDR) tuberculosis (TB) in Kwa Zulu Natal, South Africa (Ghandhi, *Lancet*, 2006).

The outbreak of XDR-TB consisted of 53 cases in which the pathogen was resistant to isoniazid/rifampin, fluoroquinolones, and at least 1 injectable agent (capreomycin, kanamycin, and amikacin). Of the 53 cases, 35 were nosocomial, 27 were previously untreated (indicating transmission of XDR-TB), each of the 44 patients tested for HIV was infected, and 52 of 53 patients died, with a median time-to-death of 16 days. It has been noted that spread of this disease threatens to undo improvements in health care for HIV that have been made in re-

source-limited settings. It is important to note that XDR-TB is not a health care problem in the United States, although many may remember the highly lethal outbreak of multidrug-resistant tuberculosis (MDR-TB) in HIV-infected patients in New York City a decade ago. The other pathogens to be discussed are more relevant to practice in the United States and Europe (Lawn et al, *BMJ*, 2006; Masjedi et al, *Clin Infect Dis*, 2006).

Community-acquired Methicillin-resistant *Staphylococcus aureus*

MRSA of the designated USA300 family has been found to be responsible for a number of new staphylococcal-related syndromes including necrotizing skin infections (“spider bite” abscesses), necrotizing pneumonia, necrotizing fasciitis, septic thrombophlebitis, and pelvic syndromes in pediatric patients (eg, septic arthritis of the hips and pelvic abscess). The USA300 family is unique compared with nosocomial MRSA and now accounts for greater than 50% of community-acquired infections due to *S aureus*. Features that distinguish the community acquired-MRSA (USA300 strains) are: 1) it involves a limited number of clones 2) it has the staphylococcal cassette chromosome *mec* (SCC*mec*) IV element as the mechanism of methicillin resistance 3) it is sensitive to a number of

antibiotics and 4) it has the gene for production of the Panton-Valentine leukocidin (PVL) toxin.

Syndromes caused by these strains are now being found throughout the general population, but there is an increased risk of acquisition from close contact as seen in some HIV risk groups such as men who have sex with men (MSM), prison inmates, and injection drug users. MRSA-USA300 has been implicated in more than 10,000 cases of skin and soft-tissue abscesses, and there have been numerous case reports and small series of necrotizing pneumonia, necrotizing fasciitis, and pyomyositis.

A study of abscesses due to MRSA-USA300 involving a professional football team (Kazakova et al, *N Engl J Med*, 2005) used pulsed-field gel electrophoresis patterns to show that the implicated strain of MRSA was also found in outbreaks among other football teams, prison inmates in 5 states, fencers in Colorado, and pediatric patients in Texas, Minnesota, and North Dakota. This now appears to be an explosive epidemic throughout the United States, Europe, and other parts of the world.

As noted, the MRSA-USA300 family carries the gene for PVL toxin that lyses polymorphonucleocytes (PMNs) by creating pores in the cell membrane, resulting in cytokine release and cell death. A recent study provides evidence that PVL is indeed a major virulence factor in community-acquired MRSA (Labandeira-Rey et al, *Science*, 2007). In this study, mice given inoculation in the nares had lethal necrotizing pneumonia when challenged with PVL-positive organisms, but only mild pneumonia with PVL-negative strains. Most convincing was the demonstration of typical necrotizing lung lesions and death when challenged by PVL alone.

The extent to which MRSA has spread in the community was indicat-

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ed by a study of purulent drainage in skin and soft-tissue infections in a consortium of 11 emergency departments across the United States in August 2004 (Moran et al, *N Engl J Med*, 2006). The study included patients aged 18 years or older who had acute skin and soft-tissue infections with purulent collections. These were cultured and isolates were sent to the Centers for Disease Control and Prevention (CDC) for analysis. Of a total of 422 cases, MRSA was isolated in 60% and was the most common pathogen in 10 of 11 centers. Analysis of 218 MRSA isolates showed that 99% were USA300 strains, 98% had PVL genes, and 98% had SCCmecIV elements for methicillin resistance. Of these 218, 74% were the USA300-0114 strain, the strain isolated from the football team and other community sources noted above. Antibiotic susceptibility testing showed 100% susceptibility to trimethoprim-sulfamethoxazole (TMP-SMX) and rifampin, 95% to clindamycin, 92% to tetracycline, 60% to fluoroquinolones, and 6% to macrolides. Treatment consisted of incision and drainage plus an antibiotic in 60% of cases, and incision and drainage alone in 19%. A beta-lactam antibiotic was used in 100 of 175 (57%) cases caused by MRSA, indicating that more than half of patients received antibiotics that would have no effect. Follow up at 15 to 21 days indicated that lesions had resolved in 96% of cases, regardless of whether the patients received an antibiotic active against MRSA, an antibiotic not active against MRSA, or no antibiotic. The implication is that incision and drainage was the essential component of treatment, and the role of antibiotics remains relatively unclear. If antibiotics are to be used, the standard recommendations of cephalexin and dicloxacillin should be avoided, in preference for agents more likely to be active against MRSA USA300 strains such as TMP-SMX, doxycycline, or clindamycin.

The other syndromes caused by MRSA-USA300 are less common but more devastating. Necrotizing pneumonia is usually found in young, previously healthy adults and children with

influenza. A recent report from the CDC reviewed 10 cases with an average age of 18 years all of whom presented with critical illness. Six patients (60%) died with an average time-to-death of 3.5 days after the onset of symptoms (CDC, *MMWR Morb Mortal Wkly Rep*, 2007). According to the 2007 guidelines for treatment of community-acquired pneumonia from the Infectious Diseases Society of America (IDSA) and The American Thoracic Society (ATS; Mandell et al, *Clin Infect Dis*, 2007), the recommended treatment is vancomycin or linezolid. Clindamycin can be used if the simple disk approximation (D) test for resistance is negative.

Bacterial Pneumonias

A prospective study of pneumonia in 1130 HIV-infected and 167 noninfected individuals from 1988 to 1990 showed bacterial pneumonia attack rates of 5.5 per 100 person-years of observation and 0.9 per 100 person-years of observation, respectively. Rates among HIV-infected patients were 10.8 per 100 person-years at CD4+ counts below 200 cells/ μ L, 6.8 per 100 person-years at 200 to 500 cells/ μ L, and 2.3 per 100 person-years at above 500 cells/ μ L (Hirschtick et al, *N Engl J Med*, 1995). Recent data indicate that HIV-infected patients still have an approximately 10-fold increased risk for bacterial pneumonia. The HIV Epidemiology Research Study (HERS), a prospective study of 885 HIV-infected and 425 noninfected women from 1993 to 2000, showed attack rates of 8.5 per 100 person-years in patients with HIV infection compared with 0.7 per 100 person-years in noninfected patients. Rates by CD4+ count in HIV-infected patients were 17.9 per 100 person-years at below 200 cells/ μ L, 8.7 per 100 person-years at 200 to 500 cells/ μ L, and 4.9 per 100 person-years at above 500 cells/ μ L (Kohli et al, *Clin Infect Dis*, 2006). The vast majority of patients in this recent study had no bacterial etiologic diagnosis; an etiologic agent was reported in 21% of patients compared with 38% of patients in the study reported by Hirschtick and colleagues. This reflects the continuing

deterioration of clinical microbiology in the evaluation of hospitalized patients with pneumonia.

Bacterial pathogens that were defined in the more recent study are shown in Table 1. Pneumococci accounted for 10% of all cases of pneumonia in HIV-infected individuals, compared with 15% in the older study. Risk for pneumonia in the HIV-infected women decreased with higher CD4+ counts (risk ratio [RR], 0.88 per 50 cell/ μ L increment) and use of TMP-SMX (in absence of potent antiretroviral therapy; RR, 0.86), and increased with higher plasma HIV RNA level (RR, 1.42) and smoking (RR, 2.12).

Several studies have shown that HIV infection predisposes patients to bacterial pneumonia, especially bacteremic pneumococcal pneumonia (Grau et al, *Arch Intern Med*, 2005; Trampuz et al, *Mayo Clin Proc*, 2004). This raises the issue of the use of pneumococcal vaccine in this population, especially in light of data showing the greatest

Table 1. Analysis of Skin and Soft-tissue Abscesses in 11 Emergency Departments

| Number of Cases | 422 |
|---|-----------|
| Bacterial Results | |
| <i>Staphylococcus aureus</i> | |
| Methicillin resistant | 249 (60%) |
| Methicillin sensitive | 71 (17%) |
| <i>Streptococcus</i> | |
| | 30 (8%) |
| Analysis of 218 Strains of MRSA | |
| USA300 strains | 216 (99%) |
| SCCmec IV positive | 214 (98%) |
| PVL genes | 213 (98%) |
| Sensitivity Test Results (% sensitive) | |
| Trimethoprim sulfa | 100 |
| Clindamycin | 95 |
| Tetracycline | 92 |
| Fluoroquinolones | 60 |
| Macrolides | 6 |

MRSA indicates methicillin-resistant *S aureus*; PVL, Panton-Valentine leukocidin. Adapted from Moran et al, *N Engl J Med*, 2006.

benefit of this vaccine is to prevent bacteremia (Whitney et al, *N Eng J Med*, 2003).

However, the most exciting pneumococcal vaccine development in recent years is the pediatric vaccine not only for children younger than 2 years who received the vaccine, but for adults who did not receive it. This vaccine was introduced in 2000 and subsequent analysis showed that risk of invasive pneumococcal pneumonia due to drug-resistant *Streptococcus pneumoniae* is dramatically reduced in young children and adults. Results showed a 98% reduction in rate of invasive disease due to serotypes covered in the vaccine among children (from 65.1 cases to 1.2 cases per 100,000 population). This might be expected, but there was also a 79% reduction in rate among individuals older than 65 years (from 12.3 to 2.6 per 100,000 population) in 2004, compared with 1999, before vaccine use. At the same time, the rate of cases due to nonvaccine serotypes increased slightly in children and older individuals, indicating the large reduction in rates of invasive pneumococcal infection was due to the vaccine. The implication of this observation is that young children are the vectors of most pneumococcal infections.

Clostridium difficile

C difficile is by far the most common identifiable cause of diarrhea in HIV-infected patients. In a study of bacterial infections in HIV-infected patients with diarrhea from 1992 to 2002, shown in Table 2, 44,778 patients were followed up for a mean of 2.6 years (Sanchez et al, *Clin Infect Dis*, 2005). During cumulative follow up of 115,979 person-years, diarrhea occurred in 11,320 patients, with a bacterial pathogen being found in 1091 cases (10%). The incidence of bacterial diarrhea was 7.2 per 1000 person-years and directly correlated with immunosuppression. The presence of AIDS was associated with an odds ratio (OR) for diarrhea of 10. *C difficile* accounted for 54% of causative organisms, followed by *Shigella* species (14%), *Campylobacter jejuni* (14%), *Salmonella* species (7%), *S*

Table 2. Bacterial Diarrhea in HIV-infected Patients

| | |
|--|------------|
| Number of patients in cohort | 44,778 |
| Duration of follow up (mean) | 2.6 years |
| Diarrheal disease | 11,320 |
| Bacterial pathogen | 1320 (10%) |
| Incidence (per 1000 person years) | 7.2 |
| Odds ratio for AIDS | 10:1 |
| Etiologic agent | |
| <i>Clostridium difficile</i> | 598 (54%) |
| <i>Shigella</i> | 156 (14%) |
| <i>Campylobacter jejuni</i> | 154 (14%) |
| <i>Salmonella</i> | 82 (7%) |
| <i>Staphylococcus aureus</i> | 43 (4%) |
| <i>Mycobacterium avium</i> complex | 22 (2%) |

Adapted from Sanchez et al, *Clin Infect Dis*, 2005.

aureus (4%), and *Mycobacterium avium* complex (2%).

With regard to *C difficile* there are several important observations to highlight, reflecting extensive studies from 1974 to 2002 (Bartlett JG, *Ann Intern Med*, 2006):

- The major risks are advanced age, antibiotic exposure, and hospitalization
- The disease is nearly always restricted to the colon
- This is a protein-losing enteropathy that often results in large protein losses so that many or most patients present with hypoalbumenia
- Like most enteric pathogens, *C difficile* causes a spectrum of enteric disease ranging from asymptomatic carriage of the *C difficile* toxin to its most fulminating and characteristic form: pseudomembranous colitis (PMC)

- *C difficile* is the only anaerobic pathogen that is transmitted from person to person
- Complications include toxic megacolon, ileus, leukemoid reactions, anasarca, and sepsis syndromes.

In terms of management, the preferred diagnostic test is the tissue culture assay because it is the most sensitive and specific, but it has the disadvantage of requiring 24 to 48 hours to complete and is technically difficult. For this reason, 95% of laboratories in the United States use the enzyme immuno-assay (EIA) test, which is fast (2-4 hours) and inexpensive, and commercial reagents are readily available. The problem is that EIA has a sensitivity of only 70% to 80% (Ticehurst et al, *J Clin Microbiol*, 2006; Borek et al, *J Clin Microbiol*, 2005) so false negative tests are common. This means clinicians need to repeat the test or treat empirically if the clinical suspicion is strong despite a negative test.

Treatment consists of: 1) discontinuing the inducing agents, 2) supportive care, and usually 3) metronidazole or oral vancomycin. Metronidazole and vancomycin are each active against essentially all strains of *C difficile*, but vancomycin has the best pharmacokinetics since it is not absorbed, so colonic levels are usually higher than 100-times the highest minimum inhibitory concentration for any strain (Bolton et al, *Gut*, 1986). By contrast, metronidazole is well absorbed and reaches the colon lumen by diffusion across the colon mucosa or by “enteric leakage” in the presence of severe diarrhea. Nevertheless, metronidazole is preferred in recommendations from the CDC, IDSA, and the Society for Healthcare Epidemiology (SHEA; Bartlett, *N Eng J Med*, 2002) because metronidazole is less expensive, avoids possible vancomycin abuse, and most importantly the drugs appear comparable in clinical trials (Teasley et al, *Lancet*, 1983). Treatment is associated with 2 distinctive complications. First, some patients do not respond owing to advanced disease, usually ileus or toxic megacolon, reflecting the inability to gel oral antibiotics to the colon

lumen. Recommendations are to deliver vancomycin (500 mg qid) using a long tube from above or by retention enema. Other tactics are intravenous immunoglobulin (IVIG), intravenous metronidazole, and colectomy, but indications and efficacy with these interventions are not well established.

The second complication with treatment is relapse. Approximately 20% of patients have recurrence of symptoms within 60 days of stopping oral vancomycin or metronidazole (Bartlett, *Gastroenterology*, 1985; Fekety et al, *Clin Infect Dis*, 1997). This reflects failure to eradicate *C difficile* spores that then revert to vegetative forms with toxin production when treatment is stopped, or it represents infections by a new *C difficile* strain (Johnson et al, *J Infect Dis*, 1989). Relapse is treated by another course of metronidazole or vancomycin, and sometimes augmented by strategies that have minimal established efficacy such as probiotics (*Saccharomyces boulardii* or *Lactobacillus rhamnosus*), IVIG, tapering courses of oral vancomycin or pulse doses of vancomycin (125 mg orally every other day for 6 weeks). All of these tactics work some of the time and none work all of the time (Bartlett, *Ann Intern Med*, 2006).

The above summarizes cumulative data for *C difficile* and its management from 1974 to 2002. But in 2002, there was a new chapter. Jacques Pepin in Quebec, Canada, found a dramatic 10-fold increase in the incidence of this complication for persons older than 65 years for 1992 to 2000 compared with 2002 to 2003 (Pepin, *CMAJ*, 2004). He later showed that the attributable mortality for *C difficile* infection was an astonishing 17% (Pepin, *CMAJ*, 2005). Common findings in these patients were that fluoroquinolones were frequently implicated as inducing agents, relapse rates were high, and many failed to respond to standard therapy. Common complications included ileus, toxic megacolon, leukemoid reactions, renal failure, sepsis syndrome, the requirement for a colectomy, and death. This more serious form of the disease and its association with fluoroquinolones use was then found in several areas of the United States. The mechanism of severe disease in this

strain is high quantities of toxin production, possibly due to deletion of the gene that down-regulates production of both toxin A and toxin B; the increased rate of disease and its association with fluoroquinolones use may reflect high levels of fluoroquinolones resistance in vitro, another property of NAP1 strains not seen in historic strains (McDonald et al, *N Engl J Med*, 2005; Warny et al, *Lancet*, 2005).

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