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MRSA Carriage Among Hospital Employees and Their Families

ABSTRACT & COMMENTARY

Synopsis: *A total of 6.2% of hospital employees were nasal carriers of MRSA, with the rate highest among workers in long-term care (36%). In 4 of 10 families surveyed, family members were colonized by the same MRSA as the employee.*

Source: Eveillard M, et al. Carriage of methicillin-resistant *Staphylococcus aureus* among hospital employees: Prevalence, duration, and transmission to households. *Infect Control Hosp Epidemiol*. 2004;25(2):114-120.

EVEILLARD AND COLLEAGUES PERFORMED NASAL SURVEILLANCE swabs on 965 employees of a French tertiary care teaching hospital; the enrollment rate was 75%. At the same time, they conducted a point prevalence survey of hospitalized patients. A total of 262 employees (27.2%) were carriers of methicillin-susceptible *Staphylococcus aureus,* and 6.2% were carriers of methicillin-resistant *S aureus* (MRSA). MRSA carriage rates varied by occupation and hospital location. The prevalence was 9.0% among workers on clinical wards compared to 2.1% for nonclinical employees ($P < .0001$). Nurses and nursing assistants had the highest prevalence of carriage (9.6%), and administrative personnel had the lowest (0.8%). MRSA carriage rates among patients and employees varied by hospital location.

Comparing patient and employee strains by pulsed-field gel electrophoresis, employee strains were identical to patient strains for 25% of isolates from medical wards and 100% of isolates from long-term care wards.

In a second study of 72 volunteer health care workers, 14 (19%) were MRSA carriers. There was a statistically significant association between length of service in the hospital and MRSA carriage. Ten volunteer families underwent screening for MRSA carriage; 6 family members (3 spouses and 3 children) were MRSA carriers in 4 families. All strains isolated from family members were identical to the heath care worker's strain by PFGE analysis.

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COMMENT BY ROBERT MUDER, MD

Most information on MRSA carriage by health care personnel derives from studies of nosocomial MRSA outbreaks. The reported rates of carriage have varied widely, and an association between staff carriage of MRSA and patient infection is not always clear. There are few data on the prevalence of endemic MRSA carriage among health care workers.

The prevalence of MRSA carriage among employees working in acute care units ranged from 0% to 12.5%, which is comparable to the range reported in prior studies. It was lowest in the maternity unit, which is not surprising, as patients there had a low rate of MRSA colonization, due, no doubt, to their low burden of underlying disease.

It was surprising that the rate of MRSA carriage among long-term care staff was 36%; this was no doubt related to the fact that 67% of long-term patients were colonized. All of the long-term care staff isolates were identical to patient isolates. This is certainly due in part to the high prevalence of MRSA carriage by patients but may also relate to the long duration of residence by the patients, allowing ample opportunity for transmission among patients and between patients and staff.

What is not clear from this study is the role played by staff MRSA carriage in the transmission of MRSA to patients. Are the staff reservoirs of MRSA that enable colonization and infection of patients, or are they innocent bystanders? This question cannot be answered by point-prevalence studies.

However, this study has some important implications for health care workers. This study confirms prior studies showing that health care workers are at risk of acquiring MRSA during the course of work.[1] These workers are at risk of developing clinical MRSA infection.[2] In addition, this study clearly demonstrates that colonized health care workers can transmit MRSA to family members.

It is premature to recommend that all health care workers be screened for MRSA. More detailed studies of MRSA acquisition and transmission between patients and staff are needed. However, acquisition of MRSA by health care workers is potentially preventable by practicing good hand hygiene and observing the principles of contact isolation. Health care workers should already be doing this out of concern for patient safety; concern for their own well-being and that of their families should provide still more incentive. ■

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Table

MRSA Carriage in Hospital Employees and Patients

Unit	Employee MRSA Prevalence	Patient MRSA Prevalence
Long-term care	36%	67%
Internal medicine	12.5%	3.0%
Surgery	6.0%	2.5%
ICU	3.0%	6.0%
Pediatrics	2.2%	1.0%
Maternity	0%	1.7%

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Spectrum of Disease Associated with Human Metapneumovirus Infection in Children

ABSTRACT & COMMENTARY

Synopsis: *Human metapneumovirus was the likely cause of 12% of all lower respiratory tract illnesses among a population of 2009 children studied from 1976 to 2001 presenting with acute respiratory symptoms. Clinical manifestations of metapneumovirus infection were bronchiolitis (59%), croup (18%), pneumonia (8%), and exacerbation of asthma (14%).*

Source: Williams JV, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med*. 2004;350:443-450.

From 1976 to 2001, 2009 children were enrolled in a prospective study of viral respiratory tract infections. Children with symptomatic lower respiratory tract infection were diagnosed with bronchiolitis, pneumonia, or laryngotracheobronchitis (croup) based on diagnostic clinical signs and radiographic findings. Nasal-wash specimens for virus cultures were obtained at 687 of 1127 visits (61%) of children diagnosed with lower respiratory tract infections. These cultures identified a viral etiology in 279 specimens, including from 103 children with respiratory syncytial virus (including 5 coinfected with another virus), 58 with parainfluenza virus, 32 with influenza virus, 28 with adenovirus, and 50 with enterovirus, rhinovirus, poliovirus, herpes simplex virus, or rotavirus. Of the remaining 408 specimens from 321 children who were previously negative by virus culture, 248 had available samples for RNA extraction for an RT-PCR assay of a highly conserved region of human metapneumovirus. Of these 248 specimens, 49 (20%) were positive for human metapneumovirus by RT-PCR. Nasal-wash specimens from 96 children diagnosed with lower respiratory tract infection who had positive cultures for another virus were tested for human metapneumovirus by RT-PCR. Of these, 4 (4%) were positive, indicating a coinfection rate of 4%. There was no apparent clinical difference in children with human metapneumovirus alone compared to those with coinfections. An additional 86 nasal-wash specimens from children without respiratory symptoms were also tested for human metapneumovirus by RT-PCR, and only 1 was positive.

For human metapneumovirus infection, the male:female ratio was 1.8:1, and the mean age of infection was 11.6 months, with a median of 6.5 months and a range of 1.5-50 months. Infection was predominantly during infancy, with 25% of infections among children younger than 6 months of age and 49% among children 6-12 months of age. The peak period of infection was March, with 78% of illnesses occurring between December and April. However, infections occurred throughout the year with less seasonal prominence than for respiratory syncytial virus. The annual proportion of lower respiratory tract infections attributable to human metapneumovirus varied from 0% to 31% during this 25-year period.

Of the 49 children with human metapneumovirus infection, the clinical diagnosis was bronchiolitis in 29 (59%), croup in 9 (18%), pneumonia in 4 (8%), and exacerbation of asthma in 7 (14%). Acute otitis medial was diagnosed in 18 (37%). Compared to respiratory syncytial virus infection, human metapneumovirus was associated with comparable rates of fever but less frequent rales (8% vs 24%; $P = .03$) and wheezing (52% vs 69%; $P = .04$), at rates similar to parainfluenza virus, influenza virus, and adenovirus infections. Fever was more common with influenza virus (87% vs 52%; $P = .001$). Chest radiographs were obtained in 14 children, with abnormalities in 7 (50%) consisting of diffuse perihilar infiltrates. Only 1 child (2%), who was 36 months of age, was hospitalized, with a diagnosis of exacerbation of asthma triggered by a viral respiratory tract infection.

COMMENT BY HAL B. JENSON, MD, FAAP

Human metapneumovirus was first reported by researchers in the Netherlands who isolated an agent from 28 respiratory specimens that induced cytopathic effects on cultured cells.[1] Sequence and phylogenetic analysis revealed that this new pathogen was likely a paramyxovirus and most closely related to an avian pneumovirus. This agent was determined to be the first human pathogen member of the genus *Metapneumovirus*, in the *Paramyxoviridae* family, and was called human metapneumovirus. The closest related human virus is respiratory syncytial virus, of the genus *Pneumovirus* and also in the *Paramyxoviridae* family. This report confirms previous reports of the frequent incidence of human metapneumovirus infection and, more importantly, defines the spectrum of clinical manifestations of human metapneumovirus disease in children.

Human metapneumovirus infection occurs primarily among infants and very young children and causes both upper and lower respiratory tract symptoms. The spectrum of disease—primarily causing bronchiolitis but also causing croup, pneumonia, and associated with exacerba-

tions of asthma—is very similar to that observed with RSV, including the predisposition to secondary otitis media. Both viruses have peak incidence in late winter months.

This study also demonstrates that human metapneumovirus has been prevalent in the United States for at least the past 25 years. In this cohort of children diagnosed with lower respiratory tract infection, human metapneumovirus accounted for 20% of all cases of lower respiratory tract infections without a prior virologic diagnosis, with an overall prevalence of 12%. The prevalence of human metapneumovirus was second only to respiratory syncytial virus (15%) and was higher than parainfluenza virus (10%), influenza virus (5%), and adenovirus (4%). One caveat is that these other viruses were confirmed by culture, and the PCR method for human metapneumovirus was likely more sensitive than was culture for the other viruses.

Human metapneumovirus is an important respiratory tract pathogen in healthy infants and young children but has escaped identification because it is difficult to detect by virus culture. It is an important cause of bronchiolitis and pneumonia in infants and very young children. It is most similar in seasonality, with late winter epidemics, and clinical manifestations to respiratory syncytial virus, but it appears less severe and with variation in severity from year to year. The frequency and severity of human metapneumovirus disease in adults and the elderly remain to be determined. ■

Reference

1. van den Hoogen BG, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med*. 2001;7:719-724.

Animal Feed and Antibiotic Resistance

ABSTRACT & COMMENTARY

Synopsis: *An antibiotic preparation meant for addition to animal feed was found to be contaminated with antibiotic resistance genes.*

Source: Lu K, et al. Antimicrobial resistance gene delivery in animal feeds. *Emerg Infect Dis*. 2004;10:679-683.

LU AND COLLEAGUES AT THE UNIVERSITY OF BRITISH Columbia and the University of California (Berkeley) detected large amounts of DNA (31 m g/g of antibiotic) in a preparation of the glycopeptide antibiotic avoparcin that was meant for use in animal feed as a growth promoter. Sequencing of the amplicon produced using primers specific for streptomycete 16S rRNA found it to be closely related to that of *Amycolatopsis coloradensis*, the producer source of avoparcin. Further analysis detected the presence of a cluster of genes encoding proteins with > 50% amino acid identity with the Van H, A, and X proteins of vancomycin-resistant enterococci (VRE).

■ COMMENT BY STAN DERESINSKI, MD, FACP

VRE were first detected in Europe, primarily as colonizing organisms in healthy individuals in the community.[1] This contrasted with the subsequent emergence of VRE in the United States, where gastrointestinal colonization in healthy individuals was uncommon as it became increasingly prevalent among hospitalized patients. This difference was believed to be the result of different locations in which the selective pressure of glycopeptide use was exerted in the 2 continents. Thus, vancomycin use in US hospitals far exceeded the rather meager use in European hospitals. On the other hand, the use of the vancomycin-related glycopeptide antibiotic, avoparcin, was widespread as an agricultural growth promoter in animal feed in Europe, but similar antibiotics were not used for this purpose in the United States. This is believed to have led to the emergence of VRE in farm animals, in whom the organisms were readily detected, both on the farm, and on, for example, chicken for sale in supermarkets. Such food thus served as the community reservoir that led to gastrointestinal colonization of healthy humans.

Vancomycin resistance in *Enterococcus*, however, requires the presence of a large gene cassette encoding a series of proteins that affect synthesis and modification of cell wall components. In the absence of these genes, the pressure exerted by avoparcin could not have resulted in the emergence of VRE. Where did these genes come from?

Lu et al provide a possible answer. Organisms that produce antibiotics must have a mechanism to protect themselves from their antimicrobial effect, as is the case with the source of vancomycin, *A coloradensis*. This study shows that feed-grade avoparcin is contaminated with bacterial DNA, including DNA encoding vancomycin resistance genes. These genes could have the potential for incorporation into enterococci in the gastrointestinal tract of the animals ingesting this contaminated feed. Ingesting the antibiotic would then select out any resistant enterococci that resulted from this sequence of events.

Avoparcin was added to animal feed in Europe from 1975 through 1996, when its use was discontinued by fiat of the European Union. Since then, there has been a significant decrease in VRE contamination of meat prod-

ucts, particularly poultry.[2] Its use continues to be banned in the United States. Other antibiotics are, however, used as agricultural growth promoters in this country, and it seems likely that a similar circumstance may apply.

One more thing: Antibiotic resistance genes are commonly being engineered into transgenic plants, including some used as animal feed.[3] Investigations and expert opinions suggest that transfer into gastrointestinal bacteria, while theoretically possible, is highly unlikely.[4] Fortunately, the genes being used generally encode for resistance mechanisms that are already highly prevalent in gastrointestinal bacteria. ■

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An Outbreak of *Clostridium difficile* Diarrhea Associated with Gatifloxacin

ABSTRACT & COMMENTARY

Synopsis: *A formulary switch from levofloxacin to gatifloxacin as the preferred quinolone in a long-term care facility was associated with a significant increase in the incidence of* Clostridium difficile*-associated diarrhea (CDAD). A case-control study showed that duration of gatifloxacin was independently associated with illness. Switching back to levofloxacin was followed by a decrease in incidence of CDAD to prior levels.*

Source: Gaynes R, et al. Outbreak of *Clostridium difficile* infection in a long-term care facility: Association with gatifloxacin use. *Clin Infect Dis*. 2004;38:640-645.

In October 2001, the pharmacy and therapeutics committee of a Veterans Affairs hospital changed the formulary quinolone from levofloxacin to gatifloxacin because of cost considerations. Shortly thereafter, there was an increase in *Clostridium difficile*-associated diarrhea (CDAD) in the facility's long-term care division. During the period of October 2001 to June 2002 (designated the epidemic period), the rate of CDAD was 1.3/1000 patient-days, compared to 0.4/1000 patient-days during the preceding 9 months ($P < .002$). During the pre-epidemic period, 58 patients received levofloxacin; 10 (17%) developed CDAD. During the epidemic period, 47 patients received gatifloxacin; 14 (30%) developed CDAD. The difference in development of CDAC between the 2 quinolones was statistically significant ($P < .02$). In a case-control study of patients acquiring CDAD during the epidemic period, only clindamycin exposure and duration of gatifloxacin therapy were independently associated with CDAD. Susceptibility testing of 45 *C difficile* isolates found that 43 were resistant to levofloxacin and 44 were resistant to gatifloxacin.

In July 2002 the formulary quinolone was changed back to levofloxacin. Subsequently, the CDAD rate in the long-term care facility decreased to 0.4/1000 patient-days during 9 months of follow-up. Of note was the fact that the rate of CDAD in the adjacent acute care facility, which shared the same formulary, also increased during the period of gatifloxacin use. The rate in acute care declined after the change back to levofloxacin.

■ COMMENT BY ROBERT MUDER, MD

CDAD is a potential complication of treatment with virtually every antimicrobial agent. Historically, clindamycin was the agent most associated with CDAD, but at present most cases are associated with penicillins and cephalosporins, reflecting the widespread use of beta-lactam agents. Following the introduction and widespread use of quinolones, it became clear, not surprisingly, that these agents could lead to CDAD as well. There has been little evidence that quinolones differ substantially in the rate of CDAD following their use. Gaynes and colleagues provide evidence that gatifloxacin use is more likely to result in CDAD than is levofloxacin use. There was a marked increase in the incidence of CDAD following a formulary change from levofloxacin and a fall in CDAD rates to pre-outbreak levels following the formulary change. The observed changes in CDAD rates may have been entirely fortuitous. However, there is additional epidemiologic evidence to indicate otherwise. The rate of CDAD following gatifloxacin treatment was nearly 2 times the rate following levofloxacin treatment. Furthermore, a case-control study identified duration of gatifloxacin treatment as a significant risk factor for CDAD.

The reason for the differential rates of CDAD associated with the 2 quinolones in question may be due to the fact that gatifloxacin is more active against anaerobes than levofloxacin and, thus, more likely to have an adverse effect on intestinal commensal flora.

This study also points out some of the particular issues of attempting to control CDAD in a long-term care facility. The incidence of CDAD following treatment with both levofloxacin (17%) and gatifloxacin (30%) were exceptionally high. The incidence of CDAD following quinolone therapy is typically 2-5%.[1] Long-term care patients are at increased risk due to advanced age and underlying disease. In addition, appropriate isolation is difficult to maintain in long-term care facilities, which typically have lower staff-to-patient ratios and rely on health care aides to provide much of the care. Long-term care facilities often house large numbers of incontinent patients; even continent patients with limited mobility may become functionally incontinent when experiencing severe diarrhea. This can lead to significant environmental contamination with *C difficile* spores, which may be a major factor in patient-to-patient spread. Finally, a number of studies have shown that much of the antimicrobial therapy administered in long-term care is inappropriate or unnecessary.

Thus, while restricting agents with a high incidence of CDAD appears to be beneficial, controlling CDAD in long-term care is likely to require restraint in total antimicrobial use, improving infection control practices, and attention to environmental decontamination. Given the level of resources and infection control expertise available to most long-term care facilities, this is likely to be a major challenge. ■

Reference

1. Bartlett JG. Antibiotic-associated diarrhea. *N Engl J Med*. 2002;346:334-339.

MRSA With Reduced Susceptibility to Vancomycin

ABSTRACT & COMMENTARY

Synopsis: *Receipt of vancomycin antedated isolation of MRSA with reduced susceptibility to vancomycin in 25 patients.*

Source: Howden BP, et al. Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. *Clin Infect Dis*. 2004;38:521-528.

Howden and colleagues examined the case histories of 25 patients with infections due to MRSA with reduced susceptibility to vancomycin (SA-RVS). The isolates all had broth microdilution MICs of 2-4 μg/mL and, thus, would be reported as susceptible by NCCLS standards. Reduced susceptibility was confirmed by population analysis profile testing. The latter method involves enumeration of colonial growth on agar containing increasing concentrations of vancomycin with plotting of vancomycin concentration against the viable count and derivation of an area under the curve (AUC). A ratio of the AUC of the test isolate to the corresponding AUC of Mu 3, a known vancomycin heteroresistant isolate, greater than 0.9 was evidence of reduced susceptibility.[1]

Nine patients had bacteremia without endocarditis and 8 had endocarditis, while 6 had osteomyelitis or septic arthritis and 2 had empyema. All patients had received vancomycin before isolation of SA-RVS, and 16 (64%) had had a trough serum vancomycin concentration < 10 μg/mL. All but 2 patients had MRSA detected prior to detection of SA-RVS, with a median interval between the 2 events of 22 days (range, 3 days-31 months).

Of the 21 patients who received treatment for their SA-RVS infection, linezolid was given, alone or in combination, to 18, with good responses in most.

COMMENT BY STAN DERESINSKI, MD, FACP

All the isolates in this study would fit into the category of vancomycin-heteroresistant *Staphylococcus aureus* (hVISA) (*see Table 1*), although there is no standardized definition of this category. Heteroresistance is the consequence of the presence of clones with reduced susceptibility relative to the larger population of bacterial cells. A compilation of 14 published surveys suggests that 2.2% of MRSA demonstrate heteroresistance to vancomycin.[2]

The involvement of heteroresistant strains in serious infections is evidence that they retain significant virulence. The therapeutic implications of heteroresistance, however, remain poorly defined. In this study, all infections with SA-RVS were detected in patients who had received or were receiving vancomycin. Eradication of most of the infections occurred with the use of an antibiotic other than vancomycin, most frequently linezolid. Howden et al indicate that approximately two-thirds of the patients had had trough vancomycin concentrations < 10 μg/mL. This concentration (or one close to it) has, however, been somehow chosen by many as the upper limit of trough concentration allowable to avoid toxicity —a proposition for which there are no confirmatory data.

There appears to be an increasingly common general recognition that vancomycin is a "weak stick" against *S aureus*. A recent analysis of compiled data from 2 clinical trials indicates that linezolid, as an example, is supe-

rior to vancomycin in the treatment of nosocomial pneumonia due to MRSA.[3] While it is possible that this is the result of the higher lung tissue concentrations achieved with the oxazolidinone antibiotic, it is likely that the relatively poor intrinsic activity of vancomycin played a role.

It is suggested that higher doses of vancomycin than are routinely used would prove more effective. Vancomycin, however, exhibits concentration-independent pharmacodynamics.[4] The efficacy of such antibiotics depends primarily upon the proportion of time during the dosing interval that the concentration of the drug remains above the MIC of the infecting organism. For at least some concentration-independent antibiotic-bacteria pairs, it is necessary to remain above the MIC of the pathogen for 40-60% of the dosing interval. Elevating peak concentration to levels greater than 4 or 5 multiples of the MIC has no added effect on bacterial killing. Increasing the dose may, however, overcome some of the problems with tissue penetration.

Fortunately, there are several alternatives to vancomycin for many of these isolates. These include dalfopristin-quinupristin, linezolid, and daptomycin. There are, in addition, a large number of antibiotics in the pipeline with activity against Gram-positive organisms (*see Table 2*). ■

Table 1

Classification of *S aureus* Susceptibility to Vancomycin

Category	MIC
Susceptible	< 4.0 m g/mL
HVISA (SA-RVS)	1-4 m g/mL (subpopulations)
VISA	8-16 m g/mL
VRSA	> 32 m g/mL

Table 2

Some Antibiotics with Activity Against Gram-Positive Organisms That Are In Development

- Semisynthetic Glycopeptides
  - Oritavancin - InterMune
  - Dalbavancin - Vicuron (many VRE resistant)
    - T1/2 - 166 hours
- Glycolipdepsipeptide
  - Ramoplanin—Genome
- Anti-PBP2a Cephalosporins
  - RWJ-54428—Microcide/J&J
  - CAB-175—Cubist
  - BAL-5788—Basilea
  - BMS-247243—Bristol
- Carbapenem
  - CP5609
- Fluoroquinolones
  - WCK771 A
  - WCK 919
  - WQ-2932
  - DW 286 (naphthyridone)
- Glycycline
  - Tigecycline —Wyeth (minocycline derivative—also *Enterobacteriaeceae*, *B fragilis*)
- Oligosaccharide
  - Evernimicin
- DHFR Inhibitor
  - Icalaprim
- Ansamycin
  - Rifalazil

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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***

Respiratory Tract Infections

Bacterial Infections

Community-Acquired Pneumonia

In a randomized trial of oral therapies of CAP, 10 days of treatment with moxifloxacin or with amoxicillin/clavulanate plus roxithromycin each resulted in clinical cure rates of 89% (*ICAAC L-1594*).

Such completely oral therapies make outpatient antibiotic therapy of CAP readily feasible. Furthermore, a prospective, randomized trial found that outpatient care of patients with low-risk (PSI class II or III) CAP was as safe and effective as inpatient treatment. Relevant to this approach is the finding that the pathogen distribution was similar in patients with CAP across all Fine classes with the exception of *M pneumoniae*, which was more frequently identified in class I than classes II-IV. In addition, a review of hospitalized patients with CAP found that 568 had received only orally administered levofloxacin, while 500 had received an antibiotic intravenously for at least part of their course. When stratified for severity of illness, initial oral levofloxacin therapy was associated with similar clinical outcomes but with equivalent or lower lengths of stay and cost (*ICAAC L-1597, IDSA 252, 302*).

In an examination of 5 randomized and 1 noncomparative trials, successful clinical outcomes in patients with CAP due to *S pneumoniae* occurred in 276 of 297 (93%) patients who received amoxicillin/clavulanate 2000 mg/125 mg b.i.d. The success rate for 54 patients who received comparator antibiotics was 87%. Success was achieved with amoxicillin/clavulanate 2000 mg/125 mg in 24 of 25 patients infected with penicillin-resistant pneumococci and in 6 of 7 with amoxicillin MICs of 4 to 8 mg/mL (*IDSA 303*).

Another strategy is an early conversion from parenteral to oral antibiotic therapy. In one study, 187 patients hospitalized with severe CAP were randomized to receive antibiotics intravenously for either 7 days or for only 3 days followed, if clinically stable, by oral antibiotic to complete a total 7-day course. The switch to oral antibiotic administration after 3 days was associated with shorter length of stay and reduced costs, without significant differences in cure rate or mortality (*ICAAC A-1355*).

S pneumoniae

Children exposed to passive smoking had an increased rate of nasopharyngeal carriage of *S pneumoniae* (*ICAAC G-1545*).

In addition to reducing the incidence of pneumococcal disease in children younger than 5 years, administration of the pneumococcal conjugate vaccine was associated with evidence of herd immunity in a large northern California population. There was a 58% decrease in vaccine strain infections in adults aged 20-40 and a 14% decrease in those older than 60. At the same time, there was no concomitant increase in nonvaccine strain infections (*IDSA 498*).

In addition to producing herd immunity, widespread use of the conjugate vaccine may be favorably affecting antibiotic resistance rates in *S pneumoniae*. One group reported that use of this vaccine has been associated with a reduction in the prevalence of antibiotic-nonsusceptible pneumococci in the target age group. Another group found a significant increase in pneumococcal susceptibility to penicillin, erythromycin, and tetracycline following the introduction of the seven-valent pneumococcal conjugate vaccine and a concomitant decrease in infections due to the included serotypes (*IDSA 482, ICAAC G-2045*).

The Alexander Project reported that the rate of growth of multidrug resistance in *S pneumoniae* in the United States is approximately 3% per year. Three-fourths of penicillin-resistant isolates are currently also resistant to erythromycin and trimethoprim/sulfamethoxazole. In the PROTEKT study, 29% of *S pneumoniae* were resistant to 2 or more antibiotics, and 8.8% were resistant to 4 in the United States in 2001-2002 (*IDSA 202, 203*).

Increasing antimicrobial resistance is the consequence of the selective pressure exerted by antibiotic use. Consistent with this axiom, the national prevalence of penicillin-nonsusceptible *S pneumoniae*, macrolide-resistant *S pneumoniae*, and macrolide-resistant *S pyogenes* was directly correlated with the antibiotic selection pressure in each of 20 developed countries. On a smaller scale, household cephalosporin use appeared to be associated with an increased effect on transmission of resistant *S pneumoniae* among siblings when compared to penicillin class use. However, despite interventions to reduce antibiotic misuse in Tennessee, the proportion of penicillin-, cephalosporin-, and erythromycin-resistant invasive pneumococcal isolates increased between 1995 and 2001 in individuals older than 5 but remained steady in those younger than 5 (*IDSA 245, ICAAC K-1406, IDSA 483*).

Not all the news is bad, however. The SENTRY study of US pneumococcal isolates found a decrease in penicillin resistance from 22% in 2001 to 17% in 2002. Erythromycin resistance decreased from 30% to 26%. In the TRUST 7 study of 4377 *S pneumoniae* strains isolated in the United States in 2002-2003, > 99% remained susceptible to levofloxacin, gatifloxacin, and moxifloxacin (*ICAAC C2-926, IDSA 201*).

Two evaluations of the accuracy and usefulness of the Binax NOW™ urine antigen test in the diagnosis of invasive pneumococcal disease came to less than glowing conclusions. Evaluation of 134 children with suspected invasive disease found that the urine antigen test appeared to be useful for excluding pneumococcal infection but not, however, in distinguishing infection from coloniza-

tion. In addition, a retrospective review concluded that the Binax NOW™ *Streptococcus pneumoniae* urine antigen assay "provided minimal additional information to standard culture in diagnosing etiology of CAP, and empiric therapy was not modified based on the results." The NOW assay was, however, effective in detecting pneumococcal antigen in empyema fluid in 9 of 9 children and was better than culture in patients who had received antibiotics (*ICAAC D-1689, IDSA 331, 332*).

The treatment of pneumococcal disease remains in a state of evolution. Twenty-four of 101 patients with *S pneumoniae* bacteremia were managed as outpatients, with therapeutic success in each case. Treatment of patients with pneumococcal bacteremia without meningitis caused by penicillin-nonsusceptible *S pneumoniae* with penicillin did not appear to adversely affect outcome. In vitro resistance is nonetheless meaningful. Of 13 children with invasive pneumococcal disease failing azithromycin therapy, 8 were infected with strains of *S pneumoniae* with the M phenotype, 3 with the MLSB phenotype, and 2 were macrolide susceptible. Among 15 with invasive pneumococcal infection, 7 were infected with penicillin-resistant strains, 4 with penicillin-intermediate strains, and 3 with penicillin-susceptible organisms (*IDSA 251, ICAAC L-469, IDSA 793*).

Mycoplasma pneumoniae

Serological testing, when compared to PCR identification, was not reliable in the diagnosis of lower respiratory tract infection due to *M pneumoniae* in hospitalized patients (*ICAAC D-1860*).

A single dose of azithromycin was at least as effective as the same total dose divided into 5 daily administrations in a murine model of *M pneumoniae* pneumonia; placebo was inferior to either regimen (*ICAAC B-1672*).

Chlamydia pneumoniae

The activities of telithromycin and levofloxacin were each increased against *C pneumoniae* in a cell coculture system in the presence of dexamethasone (*ICAAC E-1994*).

Legionella

The residential water system was identified as the probable source of infection in approximately one-fourth of cases of community-acquired *L pneumophila* serogroup 1 (*ICAAC K-120*).

Neisseria meningitidis

Review of national data led to the conclusion that, compared with sporadic infection, outbreaks of meningococcal disease had a higher case fatality rate (21% vs 11%; $P < .001$) (*IDSA 289*).

A 6-year-old sibling of a child who died of infection due to a rifampin-susceptible strain of *N meningitidis* developed meningococcemia due to a rifampin-resistant strain within a day of completing rifampin prophylaxis (*IDSA 739*).

Bordetella pertussis

Primary immunization with the Biken DTaP was found to have an efficacy of 96% against typical *B pertussis* disease with paroxysmal cough of > 21 days, with persistent protection for at least 5-7 years (*ICAAC G-2050*).

Some reports have indicated that symptoms considered characteristic of pertussis are uncommonly observed in adults. However, in an outbreak of pertussis in adult oil refinery workers, 90% had a paroxysmal cough, one-quarter had an inspiratory whoop, and one-quarter had post-tussive vomiting. Administration of a 5-day course of azithromycin was effective in the rapid eradication of *B pertussis* in adults, but persistent cough after treatment remained a cause of considerable morbidity and loss of work productivity (*ICAAC L-1583, G-458*).

Central Nervous System Infections

Bacterial Meningitis/Ventriculitis

Both host and bacterial factors are important in the outcome of pneumococcal meningitis. None of 20 patients with pneumococcal meningitis due to serotype 1 organisms died, while 27% of those with serotype 3 and 33% with serotype 9 did so. Impaired mental status on admission and delayed antibiotic administration (> 6 hours) were independent risk factors for death among 123 adults with pneumococcal meningitis (*ICAAC L-613s, L-614*).

Adjuvant doxycycline administration in a rodent model of pneumococcal meningitis was associated with improved survival and reduced neuronal injury when compared to treatment with ceftriaxone alone. This may be the result of inhibition of matric metalloproteinases, which have been associated with the pathogenesis of bacterial meningitis (*ICAAC B-326*).

A retrospective review found that 29 of 230 (12.6%) patients with an external CSF drainage device not receiving antibiotic prophylaxis developed bacterial meningitis, 72% due to Gram-positive organisms. The median time to onset was day 5 (range, 1-17). Increased risk of infection was associated with prolonged presence of the device and of CSF leakage.

There were no associated deaths. The authors conclude that "prophylactic use of antibiotics is not indicated, provided that frequent CSF analysis is performed" (*ICAAC K-577*).

Two patients with external drainage device-related ventriculitis due to multidrug-resistant Gram-negative bacilli were successfully treated with intraventricular polymyxin B (*IDSA 330*).

Viral Encephalitis

Coronavirus OC43 was detected by PCR in CSF and nasopharyngeal secretions, in association with a 4-fold rise in antibody titer to the virus, in a patient with acute disseminated encephalomyelitis (*IDSA 836, ICAAC V-173*).

In an analysis of 27 patients with CNS West Nile virus infection, 14 had encephalitis, 7 had a Guillain-Barré-like syndrome, and 6 had aseptic meningitis. Seven patients had elevated CPK. EMG was abnormal in 12 of 13 patients. Six patients required mechanical ventilation, and 1 died (*IDSA 837*).

Bartonella Encephalopathy

Eighteen patients with serologically diagnosed cat scratch encephalopathy were identified between 1998 and 2002 in ongoing studies in Tennessee and California, representing 1.9% of encephalitis cases. The median age was 9 years (range, 4-40 years), and two-thirds had recent or concurrent lymphadenopathy. Seventy-two percent had peripheral leukocytosis. CSF in each case had normal WBC and glucose, while 39% had elevated protein. Brain imaging was normal in all but 1 case. PCR was unable to detect evidence of *B henselae* or *B quintana* in all 18 patients (*IDSA 103*).

Borrelia burgdorferi

A comparison of 24 children with meningitis due to *B burgdorferi* and 151 with enteroviral meningitis found that the former was associated with a longer duration of symptoms prior to presentation. Cranial neuropathy and papilledema were seen only in children with Lyme meningitis. The presence of > 10% neutrophils in CSF had a negative predictive value of 99% for the diagnosis of Lyme meningitis (*IDSA 804*).

Amebic Meningoencephalitis

Four children in North Texas died of amebic meningoencephalitis due to *Naegleria fowleri* after swimming in warm shallow waters during periods of drought. Two children in Arizona died of primary amebic meningoencephalitis within 24 hours of each other. It was discovered that both children had engaged in activities that may have led to nasal entry of ameba-contaminated water from the municipal water system, which was not required to chlorinate or filter. *N fowleri* was isolated from that water supply. A recent case of fatal primary amebic meningoencephalitis had been described in some detail by the CDC (*MMWR Morb Mortal Wkly Rep*. 2003;52:962) (*IDSA 755, 748*).

Tetanus

One hundred and twenty patients with tetanus were given human antitetanus immunoglobulin intramuscularly and were randomized to also receive it intrathecally or not. Intrathecal administration was associated with significantly better outcomes (*ICAAC L-179*). ■

CME Question

16. An 11-month-old boy presents with coryza and mild cough. There is no history of fever. Physical examination reveals mild respiratory distress with bilateral wheezing. Chest x-ray shows scattered, diffuse infiltrates. A clinical diagnosis of bronchiolitis is made, but a rapid test for respiratory syncytial virus (RSV) is negative. Which is the most likely cause of this illness?

a. Influenza viruses
b. Parainfluenza viruses
c. Adenoviruses
d. Metapneumovirus
e. Enteroviruses

Answer: 16(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:

Antivirals and the SARS Coronavirus

UPDATES

By Carol A. Kemper, MD, FACP

Improved Blood Donor Screening for WNV

Source: *MMWR Morb Mortal Wkly Rep*. 2004;53:281-284.

Most persons (around 80%) with WNV infection are asymptomatic, despite ongoing viremia for a median of 6.5 days. This group of asymptomatic but viremic individuals represents a risk to the safety of the US blood supply. In addition, some persons may develop symptoms only after their blood donation. Thus, screening based on reported symptoms is not sufficient.

As previously reported in this column, by March 2003, the CDC had received reports of 61 possible cases of WNV transfusion-associated infection (*Infectious Disease Alert*. 2003;23:12). As a result, in June 2003, the United States begun screening all blood donations using investigational nucleic acid-amplification tests (NATs). Two differing screening algorithms were used, including either testing small "mini-pools" of 6 or 16 individual donations, depending on the test kit used, or screening individual donations in certain areas during limited periods of seasonal WNV activity. Screening of individual donations was performed on any reactive mini-pools.

From June through December, a total of 6 million units of blood were screened using these techniques, resulting in the identification of 818 viremic blood donations. Data available on the donors for 811 of these units found that 654 people (81%) remained asymptomatic, 137 (17%) developed WNV fever, and 6 people (1%) subsequently developed WNV encephalitis or meningitis. Of the potential viremic donors, 85% were residents of 9 states: Colorado, Kansas, Nebraska, New Mexico, North Dakota, Oklahoma, South Dakota, Texas, and Wyoming.

Despite the success of this screening program, 6 cases of WNV transfusion-associated infection occurred, presumably because of an inability to detect low-level viremia in some donations. In each of the 6 cases, the recipients received components from multiple donations, although only one infected unit was later identified in each case. Four recipients developed WNV encephalitis, one developed WNV fever with a maculopapular rash, and one developed an illness not compatible with WNV although IgM antibody studies were positive. All cases were diagnosed based on positive WNV IgM Ab and later confirmed by PCR.

While additional infected units could have escaped detection but not resulted in clinically apparent disease, these data suggest that the current NAT kit tests fail to detect ~0.7% of infected donations. The estimated viral load from recalled plasma samples from 4 of the 6 donors was 0.11 plaque-forming units (pfu) per mL. Three of the recalled units tested negative for IgM Ab. Interestingly, for reasons that are not clear, the estimated level of viremia for 2003 appears significantly lower than that detected in 2002: estimated viral loads were 0.8-75 pfu/mL in 2002 vs 0.06-0.5 pfu/mL in 2003. The lowest level of viremia that can cause clinical illness is not known. ■

Azithromycin Failure as Prophylaxis or Treatment of Syphilis

Source: *Eurosurveillance Weekly*. April 1, 2004.

San Francisco—along with several other major cities in Europe, North America, and Australia—has been experiencing a minor epidemic of syphilis, especially in men who have sex with men (MSM). It is not unusual for HIV physicians in my neighborhood to have seen 5-10 new cases of syphilis within the past year, and I have personally seen 2 cases of penile chancre during the past few months (2 more than I've seen in as many years)—in which the diagnosis had either been missed or was in question.

In this report, the San Francisco Public Health Department presents the results of their investigation of treatment failure in syphilis patients receiving single-dose azithromycin therapy. It was hoped that the tolerability and feasibility of single-dose azithromycin for the treatment of high-risk STD contacts might facilitate the management of these cases, especially because azithromycin has excellent coverage against a number of other STD agents including chlamydia and chancroid. A single 1.0 gram dose of azithromycin has been used as prophylaxis for patients at high risk with other STDs and for contacts of patients diagnosed with syphilis; a single 2.0 gram dose has been used in the treatment of primary syphilis.

Unfortunately, between September 2002 and July 2003, 8 HIV-infected

MSMs failed single-dose azithromycin therapy, either for acute primary syphilis or for high-risk contact. Despite receipt of azithromycin 2.0 gram single-dose therapy for primary syphilis, one patient with a penile ulcer had positive darkfield microscopy at 5 days, a second patient with a penile ulcer had positive darkfield at 5 weeks, and a third with an oral chancre was positive at 18 days. Five additional patients with high-risk contact received a single dose of azithromycin 1.0 gram; all either seroconverted their serology or developed early syphilis after treatment. All 8 patients were subsequently successfully treated with either penicillin or doxycycline.

While animal studies show good activity of azilides against *Treponema pallidum*, other data suggest that resistance to erythromycin may be developing in certain strains. Whether this finding explains the treatment failures identified in San Francisco is unknown but is being investigated. In the absence of other good clinical data demonstrating the success of azilide therapy, azithromycin should not be considered a dependable second- or third-line agent for either the treatment of active syphilis or the prophylaxis of high-risk sexual contact. ■

United Kingdom Cracks Down on Potential Blood Donors

Source: *Eurosurveillance Weekly*. 2004;8.

As reported in this column in August 2002, public health experts in the United Kingdom were debating the merits of enhanced screening criteria for blood donations based on a "theoretical" risk of transmission of bovine spongiform encephalopathy (BSE) through blood transfusion. Successful experimental transmission of BSE has been demonstrated from sheep, fed cattle brain naturally infected with BSE, to other sheep, even in advance of symptoms of disease in the donor. However, there had been no firmer data to suggest transmission of BSE in humans. Britain, therefore, elected to recall any tissue or blood components from patients diagnosed with vCJD since 1997 and has been using only leukopoor blood because of concerns that white blood cells may carry infection since August 1999. By the end of 2002, 115 people in Britain had died of BSE (variant Creutzfeldt-Jakob disease [vCJD]); 4 of those had received blood transfusions, but this was not believed to be the source of their infection. Twenty-two people had received donations from persons who later died of BSE; none had demonstrated disease.

Based on the first possible case of transfusion-associated vCJD in a blood recipient, the UK Blood Service has decided to block the blood donation of anyone who has ever received donated blood since January 1, 1980 (effective April 5, 2004). The patient in question received a transfusion in 1996 and was diagnosed with vCJD last year; the source patient was well at the time of donation but developed symptoms of vCJD in 1999 and died the following year.

The United Kingdom will also start importing fresh frozen plasma from the United States for use in patients born after January 1, 1996. The UK officials believe this is a highly precautionary move; although ~2.5 million persons in the United Kingdom receive blood products each year, only one case of possible transfusion-associated disease has been reported. On the other hand, cases of definite or probable vCJD in the United Kingdom have continued to increase and now number 146; one case has occurred in Ireland. ■

Human and Feline Sporotrichosis in Rio

Source: Barros M, et al. *Clin Infect Dis*. 2004;38:529-535.

For the past few years, Rio de Janeiro has been experiencing the largest epidemic of feline and human sporotrichosis ever reported. From 1998 to 2001, 178 culture-proven cases of sporotrichosis occurred in persons living in various municipalities of Rio—beginning with 9 cases in 1998 and peaking at 91 cases in 2001. Human cases occurred coincident with an outbreak of feline sporotrichosis in the same areas. Further investigation demonstrated that 156 affected persons (91%) had close household or professional contact with cats with sporotrichosis, and 111 (65%) reported a cat scratch or bite before developing their infection. Five percent of those affected were veterinarians, although adult women were the most commonly affected group, possibly because they are in closer contact with pets or provided more care for the animals.

About 55% of the human cases presented with lymphocutaneous disease, 25% presented with localized cutaneous disease, 16% presented with extensive cutaneous involvement, and 3% with mucosal or conjunctival involvement. In addition, 30% of patients presented with arthralgias, 4% developed erythema nodosum, and 1% developed erythema multiforme. All of the patients received itraconazole as first-line therapy, except for 13 (7%) patients who had spontaneous remission. Spontaneous remission has been rarely reported in the past, but may have occurred more frequently in this group given the nature of the inoculation and the lack of significant underlying disease in most of the patients. ■