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INSIDE

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Community-Acquired MRSA and Influenza — A Lethal Combination

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: CDC. Severe methicillin-resistant Staphylococcus aureus community-acquired pneumonia associated with influenza - Louisiana and Georgia, December 2006 - January 2007.

After a 2 year lull with few such reports, the CDC was informed of 10 cases of severe community-acquired pneumonia (CAP) due to MRSA in previously generally healthy individuals in Louisiana and Georgia in just the 2 months of December 2006 and January 2007. The age of the patients ranged from 4 months to 48 years, with 8 being < 30 years of age; the sexes were equally represented. Two patients were current smokers and, other than one patient with hypertension and chronic hepatitis C virus infection, none suffered from chronic disease. Four of the patients either lived with someone with a history of skin infection due to MRSA or had recently had such an infection themselves. None of the 6 patients for whom the information was available had received the 2006-2007 influenza vaccine. Six had laboratory confirmed influenza, while the remainder had compatible prodromal illnesses. MRSA was isolated from sputum of 7, blood of 6, and pleural "rind" of one. Seven of the 10 had radiographic evidence of multilobar infiltrates. The median interval from the onset of respiratory symptoms to death in the 6 fatal cases was 3.5 days, with a range of 2 to 25 days.

Further testing was performed on the 5 isolates available to CDC. These 5 isolates, all from Louisiana, besides being resistant to beta-lactam antibiotics, were also resistant to erythromycin, with 2 having inducible resistance to clindamycin and 2 being resistant to levofloxacin. All carried SCC*mec* type IVa, consistent with their community origin, and belonged to the prevalent USA 300-0114 strain. All also carried genes encoding the Panton-Valentine leukocidin (PVL).

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COMMENTARY

The CDC previously described 17 patients with severe CAP due to *S. aureus* reported to them during the 2003-2004 influenza season.[1] Only one had documented receipt of influenza vaccine during 2003-2004. Twelve (93%) of 13 patients for whom data was available were hypotensive. One-fourth of patients had involvement of multiple lobes of the lung and one-fourth had radiographic evidence of cavitation or necrosis; 31% had effusions/empyema. ICU admission was required by 81%, 62% required mechanical ventilation, and 46% required chest tube placement. Five (29%) died, a median of 7 days (range, 3 to 73 days) after the onset of symptoms; one was dead on arrival at hospital. Three-fourths of the isolates tested were MRSA, and all of these carried SCC*mec* types consistent with community-acquired MRSA (CA-MRSA), and all also carried PVL genes. During that 2003-2004 influenza season, *S. aureus* was recovered from 11 (11%) of 102 children with influenza-associated deaths reported to CDC and from whom specimens for bacterial culture had been obtained; most of the children had CAP.[2]

The occurrence of CAP as a complication of influenza has in the past usually been described as presenting as a biphasic illness, a characteristic not observed in these cases. The rapidity of progression of disease has been repeatedly reported as being characteristic of pneumonia due to CA-MRSA and has been attributed to the frequent carriage of a variety of virulence factors by these strains, in particular PVL. Recent data, using molecular techniques, including the creation of isogenic strains with and without PVL in a murine model of pneumonia due to CA-MRSA provide strong evidence that this toxin plays a key role in causing severe necrotizing pneumonia as well as in sepsis-related mortality.[3] It should be noted, however, that other investigators using similar techniques but with a subcutaneous route of infection, were unable to demonstrate that PVL was of critical importance to the virulence of CA-MRSA.[4]

Reports such as this one should reinforce in the clinician the need for obtaining specimens for microbiologic diagnosis in patients admitted to hospital with severe and/or complicated CAP or who have failed an initial course of antibiotic therapy. Since there is an inevitable delay in identifying the presence of the infecting pathogen and determining its antibiotic susceptibility, a high index of suspicion for MRSA infection must be maintained in order to ensure the timely administration of appropriate antibiotic therapy. It generally requires 36-48 hours to identify an isolate as being methicillin-resistant. Waiting for this data in a disease in which, as reported in this series, the median duration from onset of symptoms to death is only 3.5 days is likely to represent a fatal delay. Only 4 of the patients in this report initially received antibiotics with reasonably reliable activity against MRSA (vancomycin in 3, each with other antibiotics, and trimethoprim-sulfamethoxazole in one). Nonetheless, while the single recipient of trimethoprim-sulfamethoxazole survived, 2 of the 3 vancomycin recipients died, with the single exception among vancomycin recipients being a patient who was also given gentamicin. Thus, it is critical that clinical clues on presentation be recovered in order to institute appropriate antibiotic therapy immediately. Suspicion of MRSA infection should be foremost in patients with risk factors for healthcare-associated infection, skin infections or exposure to someone with MRSA skin infections, and the presence of severe illness manifested by such things as multilobar pneumonia, necrotizing pneumonia or shock. While the current recommendation for both healthcare-associated and community-associated pneumonia due to MRSA is to administer either vancomycin or linezolid, accumulating information suggests that vancomycin is a relatively ineffective agent against *S. aureus*.[5,6] Furthermore, although the scientific validity of the analysis has been questioned, a

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retrospective post hoc subset analysis of 2 randomized clinical therapeutic trials in patients with healthcare-associated MRSA pneumonia reported improved survival in linezolid recipients relative to those treated with vancomycin.[7]

The 2 fatalities in vancomycin recipients also received ceftriaxone, as did most of the patients receiving initial regimens not containing vancomycin.[8] Evidence, unfortunately, indicates that exposure of *S. aureus* to subinhibitory concentrations of another beta-lactam antibiotic, nafcillin, induced mRNA for PVL, alpha-toxin, and toxic shock syndrome toxin 1 and increased toxin production. Exposure to either of the protein synthesis inhibitors, linezolid or clindamycin, on the other hand, suppressed translation of the toxin genes. Thus, administration of beta-lactam antibiotics to patients with MRSA infection could theoretically worsen outcome, making the initial therapeutic choice even more crucial.

While earlier CA-MRSA isolates were mostly susceptible to respiratory fluoroquinolones, resistance to these agents is becoming increasingly common. Thus, the 2 most commonly utilized empiric regimens for hospitalized patients with CAP of unknown etiology, a fluoroquinolone (usually levofloxacin or moxifloxacin) or ceftriaxone plus azithromycin, lack activity against many or all, respectively, CA-MRSA. ■

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IL-2 in HIV Infection: Raises CD4+ Cells, But at What Cost?

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP

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Dr. Winslow serves as a consultant to Siemens Diagnostics and is on the Speakers Bureaus of Boehringer-Ingelheim and GSK.

Synopsis: *Patients treated with an indinavir-based HAART regimen who had evidence of virologic response at 12 weeks were randomized to continuous infusion IL-2 (IV IL-2), subcutaneous IL-2 (SC IL-2) or HAART alone. Patients receiving IV or SC IL-2 showed greater increases in CD4+ lymphocyte counts than those treated with HAART alone and experienced fewer AIDS-defining events but also experienced more frequent treatment-related adverse events.*

Source: Mitsuyasu R, et al. The virologic, immunologic, and clinical effects of interleukin 2 with potent antiretroviral therapy in patients with moderately advanced human immunodeficiency virus infection: a randomized controlled clinical trial--AIDS Clinical Trials Group 328. *Arch Intern Med.* 2007; 167: 597-605.

ACTG 328 WAS A MULTICENTER TRIAL THAT STUDied HIV-1 infected adults without active AIDS-defining illnesses and with CD4+ lymphocyte counts between 50 and 350/uL. Patients were protease inhibitor (PI) and IL-2 naïve but may have received prior nucleoside analogue therapy. Patients were treated during the first 12 weeks of the study with 2 nucleosides plus indinavir. Patients with ≤ 5,000 copies HIV RNA/uL at week 12 were randomized to continued HAART alone (n = 52), HAART plus continuous infusion IV IL-2 (n = 53), or HAART plus SC IL-2 (n=54). Patients were dosed with IL-2 for 5 days every 8 weeks for up to 9 cycles. Patients receiving IV IL-2 could switch to SC IL-2 after 3 or 6 cycles if they had achieved a > 25% or > 100/uL

increase in CD4 count above baseline.

Bottom-line results showed that while there was no difference in deaths between the arms of the study (3 in the HAART-only arm, 2 each in the SC and IV IL-2 arms), there was an intriguing apparent difference in AIDS-defining events (7 vs 1 vs 0 respectively). At all time points, IL-2 recipients had significantly greater numbers of total CD4+ lymphocytes and various subpopulations including CD4 naïve cells than did HAART-only patients. No significant effect on CD8+ lymphocytes was seen in any of the 3 arms. IL-2 did not appear to elevate HIV RNA levels. Treatment related toxicities were significantly more frequent in the IL-2 arms and were most commonly fatigue, fever, chills, skin rash, nausea, vomiting, and diarrhea.

COMMENTARY

Interest in the therapeutic use of IL-2 for HIV infection has been active now for more than 20 years and clinical studies have been conducted in HIV-infected patients since the late 1980s. These early studies conducted in the pre-HAART era generally showed a positive effect of IL-2 in raising CD4 lymphocyte counts, but also raised HIV RNA levels and had either no or a negative effect on clinical outcomes and were associated with significant toxicities. Cliff Lane and his intramural clinical research group at NIAID were involved with many of the early IL-2 trials. Steve Rosenberg at NCI and the DuPont Company (who jointly developed the technology for isolating lymphokine activated NK cells harvested after IL-2 infusion) even conducted a small pilot study of IL-2 plus LAK cells in HIV patients in the late 1980s. These negative trials raised a lot of skepticism on the part of many, but some held out the hope that IL-2 could still be helpful in the treatment of HIV disease if more fully suppressive antiretroviral therapy were available to be used in combination. This ACTG 328 study was initiated in the late 1990s when the first generation of HIV protease inhibitors became available.

The results of this particular trial are intriguing because of the statistically significant apparent clinical benefit of IL-2 over HAART alone in reducing the incidence of AIDS-defining events over the course of the trial. A closer look at the 7 AIDS-defining events seen in the HAART arm showed an unusually large number of malignancies (2 KS, 2 lymphomas, 1 Castleman's Disease), which seems to be a statistical aberration. The paper did not report on other characteristics of these particular patients that may have made them unique such as presence or absence of viral load suppression.

Another interesting finding that casts some doubt on the generalizability of the study results is that while CD4+ lymphocyte counts increased in the IL-2 arms, no beneficial effect of IL-2 was seen on improving skin test reactivity, vaccine response, or in vitro lymphocyte proliferate responses to various antigens. While the results of this pilot study are intriguing, the possible clinical benefit observed needs to be confirmed in larger clinical trials (of which 2 are currently ongoing: The ESPRIT and SILCAAT Phase III trials). Even if these 2 studies eventually confirm some evidence of clinical benefit, I am skeptical that IL-2 will ever be an important agent in treatment of HIV infection due to the need for parenteral route of administration and its significant adverse effect on quality of life due to IL-2 related side effects.

Human Bocavirus Infection in Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD

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Dr. Jenson is on the speaker's bureau for Merck.

***Synopsis**: Human bocavirus was detected by quantitative polymerase chain reaction in 19% of nasopharyngeal aspirate specimens from 259 wheezing children, usually as a mixed infection with other viruses. An association with acute wheezing in children is suggested.*

Source: Allander T, et al. Human bocavirus and acute wheezing in children. *Clin Infect Dis.* 2007;44:904-910.

The possible presence of 16 different respiratory viruses, including human bocavirus, was tested by quantitative polymerase chain reaction (PCR) (16 viruses), virus culture (9 viruses), and antigen detection (7 viruses) of nasopharyngeal aspirates and also acute- and convalescent-phase serologies (7 viruses) from 259 children (range, 3 months to 15 years; median age, 1.6 years) hospitalized for acute wheezing. In addition, human bocavirus was investigated in 64 hospitalized children (rage 5 months to 14 years; median age 4.1 years) who were asymptomatic for wheezing.

At least one viral agent was detected in 95% of chil-

dren, with >1 agent detected in 34% of children. Pathogens were identified by PCR in 95% of children, virus culture in 40%, antigen detection in 28%, and serologies in 28%. Diagnosis was based on serologies in only 3% of children. Rhinoviruses (73 children, 28%), respiratory syncytial virus (RSV) (72 children, 28%), enteroviruses (69 children, 27%), nontypable rhinoviruses/ enteroviruses (31 children, 12%) and human bocavirus (49 children, 19%) were the most common agents identified. Pathogens were identified in 95% of children, with one virus in 60% and ≥ 2 viruses in 34%. Human bocavirus was detected in 49 children (19%), usually as part of a mixed infection with another agent, most commonly rhinoviruses (14 children), enteroviruses (8 children), and RSV (7 children).

An association with acute wheezing in children was suggested by finding human bocavirus more frequently among children with acute wheezing than among asymptomatic children (19% vs 0%; $P < 0.001$), the highest bocavirus loads primarily in the absence of other viral agents, and higher detection of human bocavirus DNA in acute serum samples, indicating systemic infection.

COMMENTARY

Human bocavirus was first described in 2005 after large-scale molecular screening of respiratory specimens for viral genome sequences. It is one of several recently described viruses-including human metapneumovirus and coronaviruses (SARS)-that were initially detected by screening nasopharyngeal aspirates by PCR for new viral sequences. Human bocavirus is a novel parvovirus that is related to minute virus of canine and bovine parvovirus. There are now a handful of studies that show that shedding of human bocavirus, either continuous or in association with other viral respiratory pathogens, appears to be common in children.

These results show that a viral agent is able to be identified in most children with acute wheezing, and also evidence of an association of human bocavirus with acute wheezing in children. These epidemiologic studies do not confirm a causal role for human bocavirus. The high frequency of multiple infections with 2 or even 3 viruses suggests that childhood wheezing is a common result of single or perhaps the interaction of multiple viral respiratory pathogens. Our current understanding of the role of human bocavirus in causing human disease is limited by the limits of the specimen collections that have facilitated use of microarrays, consensus PCR assays, and high-throughput sequencing to identify these viruses. Confirmation of the pathogenic role of human bocavirus awaits testing of specimen sets that includes the necessary controls. ■

2007 Revised Empiric Treatment IDSA/ATS Guidelines for CAP

SPECIAL REPORT

By Carol Kemper, MD, FACP

Dr. Kemper reports no financial relationship relevant to this field of study.

Sources: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007, 44(S2), S27-S72; www.idsociety.org/guidelines.

Pines JM. Measuring antibiotic timing for pneumonia in the emergency department: Another nail in the coffin. *Ann Emerg Med.* 2007, Epub ahead of print.

SINCE THE PUBLICATION OF THE INITIAL IDSA Guidelines for the management of community acquired pneumonia in 2003, and their implementation by JHACO and the Centers for Medicare and Medicaid Services (CMS) in 2004 as a "quality standard" for hospital care and reimbursement, hospital administrators have been scrambling to improve their *numbers*. Notably, the 2003 Guideline advocated the administration of appropriate antibiotics within 4 hours of arrival to the emergency department (ED) for patients with possible CAP. For reimbursement, hospitals were required by the Joint Hospital Commission and CMS to attain > 90% compliance with these measures. "Non-compliance" (ie, less than 90% compliance) resulted in a "low score" for the hospital which, to the horror of our hospital administrators, was published on the Internet. This score had no relevance to clinical data or the actual number of patients who received appropriate care. To improve their performance, some ED physicians received financial incentives for speedier diagnosis and treatment, and those physicians that failed to prescribe one of the 4 specified beta-lactams, or perhaps gave an extra antibiotic for poorly documented reasons, were considered "non-compliant."

As a result, some hospitals have moved toward the blanket administration of a specified antibiotic for any individual walking in to the ED with possible CAP. Administrators at one of our hospitals altered the computer ordering system so that ED physicians were given one and only one choice of initial empiric therapy, ceftriaxone and azithromycin. One administrator was overheard to say of the ED physicians "I don't want them to

think, I just want them to order the — antibiotic."

Clinicians and researchers are increasingly concerned about this misguided and potentially dangerous intrusion of government bodies into healthcare decision-making. Strict adherence to guidelines can have unintended and adverse consequences for patient care, including the inappropriate administration overuse of antibiotics, an increase in health care costs, adverse outcomes and medication reactions, and increased antibacterial resistance. Imagine the consequences for antibacterial resistance if every ED used levofloxacin for every person walking through the ER with cough and fever. In addition, evidence suggests that the all-too-frequent administration of quinolones has contributed to the rise of MRSA.

The basis for the initial recommendation (that antibiotics be administered within 4 hours) grew from a general impression that patients, especially those that are ill, probably do better the sooner they receive antibiotic therapy. However, there is notably little clinical data to support this impression. Two retrospective studies found an association between the administration of antibiotics within 8 hours of presentation and severity-adjusted outcomes; subsequent analyses found that < 4 hours was associated with a lower mortality. But retrospective data can readily be confounded by other factors, both studies actually found that patients who received antibiotics within 0-2 hours did worse, and the degree of survival benefit was small. Other studies have shown that atypical presentations of pneumonia, which may lack initial radiographic evidence of an infiltrate, resulting in possible delays in treatment, were associated with twice the mortality. But these are the very patients to which the de facto 4-hour rule might fail to apply.

Good guidelines are useful tools, and their appropriate use may result in improved outcomes. A large 5-year clinical trial found that the use of guidelines in the treatment of CAP in 28,700 patients resulted in a 3.2% lower 30-day mortality rate. However, no study has demonstrated that the implementation of a single set of "rules" in the ED has improved outcomes. For this reason, the latest IDSA guideline states "CAP guidelines should address a comprehensive set of elements in the process of care." Deviations from the guidelines are natural, and by the very nature of medicine, *should* occur 5% to 20% of the time. The 2007 modified recommendations for initial empiric antibacterial treatment include:

• For patients with CAP requiring hospitalization without healthcare associated PNA, the administration of (a) a respiratory fluoroquinolone or (b) a beta-lactam plus a macrolide (preferred beta-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients with risk factors for gram-negative infection; a respiratory fluoroquinolone should be used for PCN-allergic patients (note the wording "preferred").

• For patients admitted through the ED, the first antibiotic dose should be administered in the ED. This is a practical recommendation for which there is only limited anecdotal clinical evidence. The IDSA/ATS Committee did not feel a specific time window for delivery of the first dose of antibiotics should be recommended. Rather, a practical decision was made to administer treatment as soon as possible after the diagnosis of CAP was considered likely for those patients being admitted through the ED.

• The 2007 guidelines do account for the increasing prevalence of methicillin-resistant *Staphylococcus aureus* (CA-MRSA) as a cause of community acquired pneumonia, even in patients without identifiable risk factors. Patients hospitalized with severe CAP should be evaluated for CA-MRSA, with appropriate cultures, and administered empiric vancomycin in addition to the recombinant antibiotics for CAP.

• The newer guidelines also provide revised recommendations on duration of treatment.

• A new assessment tool with 5 parameters is provided to gauge whether a patient should be considered for admission to hospital. The previous pneumonia severity of illness (PSI) score, which was based on 20 different parameters, proved overly complex.

Infectious disease and infection control personnel have a responsibility to encourage the thoughtful implementation of the revised 2007 IDSA/ATS guidelines for the majority of patients with CAP, and thwart the use of a simple "one-size fits all" approach to patient care. ■

MRSA in Dialysis Patients

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: CDC. Invasive methicillin-resistant *Staphylococcus aureus* infections among dialysis patients - United States, 2005. *MMWR*. 2007;56:197-199.

Synopsis: *The incidence of invasive infections due to MRSA in 2005 was approximately 100 times greater in chronic dialysis patients than in the general population.*

DATA COLLECTED BY THE ACTIVE BACTERIAL CORE surveillance (ABCs) system in 2005 found that the incidence of invasive MRSA infections in patients undergoing dialysis was 45.2 per 1,000 population, an incidence far in excess of that estimated for the gener-

al population (0.2 to 0.4 per 1,000 population). This was based on active surveillance in entire state of Connecticut as well as in 23 counties in 8 other states. Cases were included in which MRSA was reported from any normal sterile site, including blood, cerebrospinal fluid, joint fluid, or pleural fluid. Thus, infections of the lung in cases in which the organism was recovered only from sputum were not included in this report.

Dialysis patients accounted for 813 (15.4%) of the more than 5,000 cases of invasive MRSA infection identified by ABCs sites during 2005. While the overall incidence, as indicated above, was 45.2 per 1,000 population, the incidence varied from a low of 27.2 at California locations to 92.0 per 1,000 population in Maryland. Patients > 50 years of age accounted for 70% of cases; 57% of patients were male and 56% were African-American. Bloodstream infections accounted for 86% of the sites infected. An invasive device or catheter was in place in approximately 85% of patients. Approximately 90% of patients were hospitalized and the in-hospital mortality was 17%.

Isolates that were available (n = 126) were examined by pulsed-field gel electrophoresis. By this technique, 80% belonged to types (USA100, USA200, USA500) that are associated with acquisition in the healthcare setting, with 92% of these being USA100. Of the 14% infections caused by MRSA types considered of community origin by molecular techniques (USA300, USA400, USA1000, USA1100), 89% were due to USA300. USA300 accounted for approximately 13% of all dialysis-related invasive MRSA infections.

COMMENTARY

As pointed out by the authors, in dialysis patients the incidence of invasive infections due to MRSA is the highest for any known population and approximately 100 times greater than in the general population. The importance of this is magnified by the fact that almost 14% of deaths in patients with end-stage renal disease are caused by infection, making this the second most frequent cause of mortality in these patients. *S. aureus* is the second most frequent cause of catheter-access-related bacteremia in dialysis patients, accounting for 29% of cases, just trailing coagulase-negative staphylococci (38%), but more frequent than Gram-negative bacilli (21%) and Gram-positive cocci other than staphylococci (10%).

The appropriate antibiotic choice in the management of hemodialysis patients with MRSA bacteremia is a matter of some discussion. There is increasing recognition of the inadequacies of vancomycin. Unfortunately, the remarkably frequent administration of vancomycin to chronic dialysis patients by nephrologists is also likely a contributing factor to the reported rise in its MICs to this organism ("MIC creep"), as well as to the detection of true VISA strains in this patient population. As implied by the authors, it also is not likely an accident that the first isolate of a fully vancomycin-resistant strain of *S. aureus* was recovered from a chronic hemodialysis patient. The use of an alternative therapeutic agent, such as daptomycin or linezolid seems preferable. In addition, the source of the infection should, if possible, be extirpated. More therapeutic choices may be available for the community-associated strains of MRSA, such as USA300, since they generally exhibit less multidrug resistance than do the classically hospital-based strains. Community-acquired MRSA (CAMRSA) have previously been identified as an increasing cause of infection in patients with end-stage renal disease by investigators at St. John Hospital in Detroit.[1]

Even more important is the issue of prevention. The incidence of invasive MRSA infection was more than 3 times more frequent in Maryland than in California, strongly suggesting that (in addition to the need for a better state nickname) nephrologists in the "Old Line State" may have much to learn from those in the "Golden State." Important to reducing the likelihood of infection due to antibiotic-resistant pathogens such as MRSA, is the need to slow the march of resistance by reducing the unnecessary use of antibiotics. In addition, the CDC has published recommendations, including standard infection control practices, for the prevention of transmission of infections among chronic hemodialysis patients.[2] In chronic hemodialysis patients, the primary determinant of risk of bacteremia is the type of vascular access device used, with the greatest risk observed with catheters, the lowest with native arteriovenous fistulas, and an intermediate level of risk with grafts. As a consequence, avoiding the use of catheters may be the most important single means of reducing infection risk in these patients. Other methods may also be suggested by some recent findings. Thus, statin use was found in a large retrospective study to be associated with marked reduction in risk of hospitalization for sepsis in patients receiving chronic dialysis therapy.[3] Similarly, aspirin therapy was associated with a decreased risk of *S. aureus* bacteremia in patients with tunneled catheters.[4] Perhaps most important will be the development of a vaccine. While Staph VAX® a bivalent vaccine containing *S. aureus* capsular polysaccharides 5 and 8 conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin, initially appeared promising, its development is now

on hold because of a failure to meet a primary endpoint in a large Phase III trial in 3,600 hemodialysis patients.[5] While work is continuing in the development of other vaccine approaches, the availability of an effective vaccine will not be achieved any time soon. ■

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Importance of Toxins in the Pathogenesis of S. aureus Infections

ABSTRACT & COMMENTARY

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

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Dr. John does research for Merck, is a consultant for Cubist, Roche, and bioMerieux, and is on the speaker's bureau for Pharmacia, GSK, Merck, Bayer, and Wyeth.

Source: Labandeira-Rey M, et al. Staphylococcus aureus Panton-Valentine leukocidin causes necrotizing pneumonia. *Science*. 2007;315:1130-1133.

A GROUP OF STAPHYLOCOCCAL INVESTIGATORS FROM Lyon, France, and Houston, Texas, have been working for years to show the importance of toxins in the pathogenesis of *S. aureus* infections. The group of Jerome Etienne and Francois Vandenesch in Lyon have already shown the propensity of strains containing the PVL toxin to produce fatal necrotizing pneumonia in children. There is debate, however, on its role in skin and soft tissue infection and in pneumonia in adults. What the group shows in this work is that, in mice, PVL alone is responsible for necrotizing pneumonia and has multiple other important interactions. This paper is likely to become a landmark citation.

PVL was discovered decades ago. It is carried in *S.aureus* by a phage. When mice are injected wild-type strains containing PVL and with PVL alone, in the hands of these investigators, a proliferative pneumonitis along with other severe symptoms occurs. PVL itself was found within tissues infected with the PVL-positive staphylococci. The workers next show that engineered strains lacking only the PVL genes caused minimal change in lung architecture.

Other staphylococcal products are affected by PVL. PVL-positive strains adhere to injured airway epithelium. The work by Magnus Hook (one of the coauthors in this paper) and colleagues had established over many years that staphylococci produce cell-surface associated structures known as MSCRAMMS. PVL actually upregulates these surface molecules probably explaining the persistence of these strains in pulmonary tissue. The upregulation of the cell-wall-anchored proteins is likely accompanied by a down regulation of secreted proteins and other toxins, both regulated by a central effector of global regulation, RNAIII. Among bacteria, this type of regulation through RNA is nearly unique, thus contributing to the challenge of understanding infection due to *S. aureus*.

Another interesting finding of the present study features Spa, staphylococcal protein A. Spa is a known virulence factor in mice. What was not known is the interaction of Spa and PVL. In the current work, deletion of Spa in PVL-positive strains was not associated with lethality, suggesting that Spa and PVL could act synergistically.

■ COMMENTARY

Men are not mice but sometimes mice are the best we can do to in order to understand pathogenesis. The scourge of community-associated MRSA infections justifies this work in mice since we have a poor understanding about why the currently circulating CA-MRSA is so virulent. Almost all community strains of MRSA are PVL positive, but there have been divergent findings about the role of PVL in pathogenesis.

The work of Labandeira-Rey et al solidifies, for the first time, evidence that PVL is absolutely crucial to pneumonitis and that its absence renders the strains tested nearly non-pathogenic. Additionally, they show that PVL has many crucial interactions with other staphylococcal genes, particularly adherence genes. Hopefully,

new targets for antimicrobial inhibition will arise out of this work. Earlier work that used strategies to inhibit MSCRAMMS showed that there were alternative adherence mechanisms that preserved virulence. The current work shows that PVL does interact with global regulators supporting a developing theme that in pathogenic bacterial global regulators may be the best next-generation of antibacterial targets. There are hints in this paper that shutting off certain of these global regulators like RNAIII could reduce toxins like PVL and markedly reduce tissue necrosis. Several labs are working on molecules that could shut off RNAIII activity in *S.aureus*. ■

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss the diagnosis and treatment of infectious diseases;

• To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• To present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

CME Questions

30. Which of the following is correct?

A. Pulmonary superinfection with *S. aureus* in patients with influenza invariably results in a clinically apparent biphasic course of illness.
B. MRSA pneumonia only occurs as a hospital-acquired infection.
C. Community-acquired pneumonia due to MRSA in patients with influenza is frequently rapidly fatal.
D. Exposure of *S. aureus* to subinhibitory concentrations of beta lactam antibiotics results in a suppression of toxin production.

31. What is one primary manifestation of PVL production by *Staphylococcus aureus*?

A. Glomerulonephritis
B. Cytokine production and sepsis syndrome
C. Lung necrosis
D. Hepatitis

32. Which of the following is correct with regard to invasive MRSA infection in dialysis patients?

A. It significantly occurs less frequently than in the general population.
B. It occurs more frequently in pateints with arteriovenous fistulas than with grafts.
C. An effective vaccine is available.
D. Its incidence was 45.2 per 1,000 population in the U.S. in 2005.

Answers: 30.(c) 31. (c) 32. (d)

In Future Issues:

Loss of vaccine-induced immunity to varicella over time.
Thrombocytopenia from vancomycin.

UPDATES

By Carol A. Kemper, MD, FACP

Plain Old Gonorrhea, Increasingly Difficult to Treat

Source: *MMWR*. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. 2007; 56:332-336.

QUINOLONE-RESISTANT NEISSERIA gonorrhea (QRNG) continues to spread with alarming frequency across the United States. Quinolones were first recommended for the treatment of GC by the CDC in 1986. The first quinolone-resistant isolates were reported in Asia and Hawaii in 1991, and sporadic cases occurred in the United States between 1991-1999. However, since 2000, there has been a steady increase in QRNG cases, first in Hawaii, then in California and other Western states, then in men who have sex with men (MSM) throughout major cities in the United States, and now it is appearing with increasing frequency in heterosexual men. In 2003, the CDC revised the treatment recommendations, such that areas experiencing > 5% QRNG no longer used quinolones for first-line treatment of GC.

Surveillance for GC resistance in the United States began in 1986 through a CDC-sponsored program called GISP. Data is presently collected from urethral swabs from 6,000 males annually presenting to 26 to 30 STD clinics throughout the United States. The GISP program provides increasingly important resistance data on STDs in an era with declining use of cultures. Quinolone resistance is defined as an MIC > 1 microgram/mL to ciprofloxacin; intermediate resistance is defined as an MIC 0.125-0.500 microgram/mL.

Since 2001, the prevalence of QRNG in MSM has increased from 1.6% to 29% in 2005; preliminary data for 2006 suggests the current rate is much higher (38%). Resistance in heterosexual men has occurred more slowly, beginning with 0.6% in 2001 and increasing to 3.8% in 2005; preliminary 2006 data suggest the current rate is closer to 6.7%. Certain cities, like Philadelphia and Miami are experiencing even greater rates of resistance, especially in gay men.

The CDC now recommends a single dose of intramuscular ceftriaxone 125 mg for uncomplicated urogenital and anorectal GC. Alternate regimens would include a single dose of cefoxitin 2 grams with probenecid, ceftizoxime 500 mg, cefotaxime 500 mg, or cefiximine oral suspension 400 mg. For persons with severe penicillin or cephalosporin allergies, intramuscular spectinomycin 2 grams can be given (but would presently require being ordered through the public health department, resulting in a delay in treatment). A single oral dose of azithromycin 2 grams is another good option for patients with uncomplicated GC with severe PCN allergy. However, the routine use of azithromycin is not recommended because of concerns regarding the rapid emergence of resistance.

A single dose of intramuscular ceftriaxone 125 mg is also recommended for pharyngeal GC; the alternate regimens above may not be adequate for pharyngeal infection. In addition, quinolones are no longer recommended for treatment of conditions such as PID that may be caused by GC.

A test of cure 2-weeks post-treatment was previously required for persons receiving quinolone therapy. Since quinolones are no longer recommended, a test of cure is not necessary for treatment of uncomplicated GC. However, a culture and susceptibility studies should be obtained in any person with persistent symptoms. Keep in mind that the SF PHD identified 3 cases of combined quinolone and cephalosporin resistance in 2003. As of 2004, the IDSA has listed GC as one of the target organisms in their "Bad Bugs, No Drugs" campaign. ■

Find the LGV

Source: McLean CA, et al. Treatment of lymphogranuloma venereum. *Clin Infect Dis*. 2007; 44:S147-S152.

BEGINNING IN 2003, CLUSTERS OF cases of lymphogranuloma venereum were reported in several European and North American cities. Previously a third-world STD, it has since been occurring with increasing frequency in the United States, especially in men who have sex with men (MSM). LGV is caused by Chlamydia trachomatis serovars L1, L2, and L3. It typically presents with small genital papules or ulcers, although these can be readily missed or mistaken for other problems in half of patients. Patients with acute infection may develop inguinal lymphadenopathy, proctitis with rectal ulcerations, anal discharge, tenesmus, and lower abdominal crampy pain. As the infection progresses, fever, malaise, weight loss, chronic anal fissures, fistulas, and deep soft tissue abscesses and adhesions can develop in 25% of untreated persons. By then, the chronic inflammation, lymphatic scarring, and deep soft-tissue changes may not be reversible. Therefore treatment during the early stage of infection is important.

Having said this, the diagnosis of LGV remains problematical, and largely requires the heightened recognition of the clinical signs and symptoms of infection. Current DNA-based screening

methods for Chlamydia fail to detect LGV (different serovar). Routine serologic testing for Chlamydia provides helpful supportive evidence if a titer is greater than or equal to 1:64 in the appropriate clinical setting. However, there is little data on the utility of this approach as a screening tool in high-risk patients. Cross-reaction with other chlamydial organisms is common, and serovar-specific testing is not readily available. Lesions and tissue from excisional biopsy of lymph nodes can be variously tested by culture, direct immunofluorescence, or nucleic acid testing, but such techniques have not been approved by the FDA for use on rectal swabs or rectal tissue biopsies.

Hence the diagnosis of LGV is to a large degree based on the prevalence of infection in your area, patient risk factors, and your clinical suspicion. Thus, any patient at risk with proctocolitis, inguinal adenopathy, or genital or rectal ulcers for which no other ready explanation exists should receive empiric doxycycline for 3 weeks. Some physicians advocate a longer course of therapy in patients with more severe symptoms. Only limited clinical data for the use of azithromycin and quinolones exists. Quinolones are probably highly effective but require a 3-week course, which is costly. Reports have found that a single dose of azithromycin 2 grams was effective in 2 patients, and this agent may be especially useful in pregnant women, although multiple doses over a > 3-week period would likely be necessary. ■

Cryptococcus gattii in North America

Source: Struck D. *Washington Post Foreign Service,* Sunday April 8, 2007, page D01; ProMED-mail post dated April 7 and April 12, 2007; www.promedmail.org.

Vancouver Island, off the coast of British Columbia, is experiencing an increasing number of unusual fungal infections in humans and pet dogs and cats due to Cryptococcus gattii. C. gattii is a yeast, distantly related to Cryptococcus neoformans, which is believed to have been brought to North America in the bark of imported eucalyptus trees. First identified in 1999 in pet dogs, and subsequently a number of porpoises with fatal pneumonia, the infection has resulted in more than 160 human infections and 8 deaths. While the infection typically occurs in persons with immune system dysfunction, such as those with HIV/AIDS, immune-competent hosts can be affected. Most of the human cases have occurred on Vancouver Island, although infections have been reported elsewhere in British Columbia, Washington, and Oregon, and a few tourists to the area have also been affected. The prevalence of infection on Vancouver Island is approximately 27 per million.

The basis for the increasing appearance of this fungal organism is not known, although some authorities have blamed global warming and a number of unusually warm summers. Epidemiologic investigation first focused attention on the eucalyptus trees in Rathtrevor Beach Provincial Park on the eastern side of the island, where the yeast was first isolated from swabs of tree bark, but has since been identified in about a 100 square km range along the eastern side of the island. The yeast may also be found in soil, water, and air. Dogs typically develop abscesses of the face and eyes, and have been identified with nasal colonization with the organism.

Cryptococcus gattii colonizing eucalyptus is not a newly recognized problem, although a cause of increasing concern in North America. It is endemic to Australia and other tropical zones, where it is frequently found in association with certain eucalyptus tree species. Rare cases of C. gattii infection are reported in Australia (5 cases per million), Eucalyptus were first brought to North America from Australia in the 19th century, ostensibly as another source of lumbar. But the trees proved to be too slow growing, and far too hard a wood for ordinary use as lumbar. At one point during the early days of the HIV/AIDS epidemic, it was thought the eucalyptus in San Francisco might be the source of Cryptococcal neoformans infection until it was recognized that the trees harbored a different species of yeast. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Long-Awaited Torcetrapib Will Not Be Released, Too Risky

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, has been in development by Pfizer for nearly 15 years. The drug has been shown to elevate HDL levels while reducing LDL levels, prompting hopes that torcetrapib would be the first in a new class of important cholesterol medications. In December, Pfizer abruptly pulled the plug on further development of torcetrapib when the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial showed an increase in death from all causes associated with the drug, including an increased rate of cardiovascular events and hypertension. A new study points out a possible mechanism for the lack of cardiovascular benefit. In the international study, 1,188 patients with cardiovascular disease underwent intravascular ultrasonography. They then received atorvastatin and were randomized to receive 60 mg of torcetrapib daily or placebo along with atorvastatin for 24 months. Atorva/torcetrapib resulted in a 61% relative increase in HDL and a 20% further reduction in LDL, resulting in an average HDL higher than LDL. But the drug combination was also associated with an increase in systolic hypertension of 4.6mm Hg, and more importantly an increase in atheroma volume of 0.12%, compared to an increase of 0.19% in the atorvastatin alone group (P = 0.72). The authors conclude that treatment with the CETP torcetrapib was associated with improved lipid endpoints, but was also associated with an increase in blood pressure and no significant decline in coronary atherosclerosis (*N Engl J Med.* 2007;356:1304-1316.). In an accompanying editorial, Dr Alan Tall holds out hope that other CETP inhibitors may not show the same adverse effects but suggests that further development of this class of drugs needs to proceed with caution (*N Engl J Med*. 2007;356:1364-1366). ■

IBS-Drug Treatment Pulled, CV Side Effects

Tegaserod (Zelnorm), Novartis Pharmaceutical's drug for irritable bowel syndrome has been removed from the market by the FDA based on recent findings of increased risk of serious cardiovascular events associated with use of the drug. Tegaserod was approved in 2002 for women with irritable bowel syndrome whose primary symptom was constipation. It was given the additional indication in August 2004 for chronic constipation in men and women under the age of 65. Withdrawal was based on analysis of 29 studies involving more than 18,000 patients that showed a small, but statistically significant increase in the risk of cardiovascular side effects (0.1% serious adverse effects with tegaserod vs 0.01% with placebo). The FDA may allow continued use of the drug in a limited number patients for whom no other treatment options are available and the benefits of tegaserod outweigh the chance of serious side effects. The FDA may consider limited reintroduction of the drug at a later date if the population patients can be identified in whom the benefit of the drug outweighs the risk. ■

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Drug Combo Better for Migraine Treatment

Naprosyn plus sumatriptan is better than either drug alone for the treatment of acute migraine according to a new report. In 2 studies, nearly 3,000 patients with a history of migraine were randomized to sumatriptan 85 mg plus naproxen sodium 500 mg, both drugs alone, or placebo to be used after the onset of a migraine with moderate to severe pain. The primary outcome was headache relief at 2 hours, absence of photophobia, absence of phonophobia, absence of nausea, and sustained pain-free response. Sumatriptan plus naproxen was superior to placebo in all measures and was superior to either drug alone in sustained pain-free response. The incidence of adverse effects was the same for the combination as for the individual medications. The authors conclude that sumatriptan 85 mg plus naproxen 500 mg as a single pill for acute treatment of migraine is more effective than either drug as monotherapy (*JAMA*.2007; 297:1443-1454.). Pozen Pharmaceuticals/ GlaxoSmithKline is developing the combination pill, which is expected to be approved later this year under the trade name Trexima. ■

Pergolide Off the Market, Heart Disease Risk

Pergolide (Permax) is being withdrawn from the market after reports of serious valvular heart disease associated with the drug. Pergolide is a dopamine agonist used for the treatment of Parkinson's disease, hyperprolactinemia and pituitary tumor (?). The action was prompted by 2 reports in the January 4, 2007, *New England Journal of Medicine* that showed increased rates of valvular dysfunction in Parkinson's patients who were taking the drug. These findings coupled with the availability of other dopamine agonists prompted the FDA's action. Valeant Pharmaceuticals is removing Permax brand pergolide as are all generic manufacturers. ■

Hormone Treatment, Does Timing Matter?

Further analysis of the Women's Health Initiative suggests that the timing of the initiation of hormone therapy may have an effect on the risk of cardiovascular disease. The analysis looked at postmenopausal women who had undergone a hysterectomy and were randomized to conjugated estrogen or placebo and women who had not had a hysterectomy who were randomized to conjugated estrogen plus medroxyprogesterone or placebo. The main outcomes were coronary heart disease (CHD) and stroke. Women who initiated hormone therapy within 10 years of menopause had a lower incidence of CHD (HR 0.76 [95% CI, 0.50-1.16]), which equates to 6 fewer events per 10,000 person-years. For women who initiated therapy 10-19 years after menopause the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for women who initiated therapy 20 years after menopause the hazard ration was 1.28 (95% CI, 1.03-1.58) or 12 excess events per 10,000 person years. CHD risk increased when patients were stratified by age as well. Hormone therapy increased the risk of stroke with no significant difference based on time since menopause or age. There was a non-significant trend for improved overall mortality in younger women. The authors conclude that women who initiated hormone therapy closer to menopause had a reduced risk of CHD, with an increase risk among women more distant from menopause although the trends did not meet their criteria for statistical significance (*JAMA*. 2007:297;1465-1477.). ■

FDA Actions

The FDA has approved Cangene's immune globulin to prevent reinfection with the hepatitis B virus in certain liver transplant patients. The product was previously approved for preventing hepatitis B infection after exposure in 2006. It is marketed as HepaGam B.

The FDA has banned rectal suppositories that contain trimethobenzamide due to lack of efficacy in preventing nausea and vomiting. The popular suppositories have been marketed under various trade names including Tigan, Tebamide, T-Gen and others. The drug will still be available as oral and injectable preparations. The evaluation which eventually led to the withdrawal is part of the FDA's ongoing Drug Efficacy Study Implementation (DESI) which evaluates older drugs previously approved based on safety data to make sure that they are also effective.

The FDA has approved Merck's combination diabetes drug Janumet, which combines sitagliptin with metformin. Sitagliptin, which is a dipeptidyl peptidase-4 inhibitor, has been marketed by Merck since last October under the trade name "Januvia." The combination is approved for the treatment of patients with type 2 diabetes; it should be dosed twice daily with meals with gradual dose escalation. ■