



March 2010: VOLUME 2, NUMBER 5

Update on *Staphylococcus aureus*

In this Issue...

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to plague healthcare providers. New data has emerged which provides additional tools for treating infections due to MRSA, as well as providing new insights into pathogenesis and potential spread of this organism. In this issue, we examine the epidemiology of healthcare-associated MRSA in patients and their caregivers after hospital discharge, new insights into MRSA pathogenesis, guidelines regarding use of vancomycin for MRSA infections, and the role of the infectious diseases consultant in treating *S. aureus* infections.



Program Information

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Length of Activity

1 hour

Release Date

March 8, 2010

Expiration Date

March 7, 2012

Next Issue

April 6, 2010

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe rates and risk factors for the spread of HA-MRSA (hospital acquired) infections from colonized patients to their caregivers in the home.
- Discuss the latest published evidence arguing against PVL toxin as an important virulence factor in CA-MRSA (community acquired) infections.
- Evaluate the role of the infectious diseases consultation as well as appropriate use and monitoring of vancomycin in the treatment of MRSA infections.

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- **John G. Bartlett, MD** – has disclosed that he has served as a consultant for Salient.
- **Sara E. Cosgrove, MD, MS** – has disclosed that she has received grants or research support from Cubist, AdvanDX, and Astellas, and served as a consultant for Theravance/Astellas, Merck, and Forest.

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COMMENTARY

Over the last decade we have seen increasing rates of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections occurring in otherwise healthy hosts and spreading among families and close contacts. Less is known about how MRSA acquisition in the hospital or healthcare setting (HA-MRSA) leads to household member transmission from index cases. As a result of the increased prevalence of CA-MRSA and increasing attention MRSA has received from the media, growing numbers of patients and family members are concerned about bringing MRSA into the home.

In addition, the U.S. Department of Veterans Affairs and some states are now requiring MRSA screening for all patients admitted to the hospital and subsequent decolonization if positive, a policy which may serve to increase anxiety and questions among family members. Household contacts of patients found to be colonized or infected with MRSA during a hospitalization often express concern to their physician about their own risk of becoming colonized or infected. The study by Lucet and colleagues¹ (reviewed herein) addresses this issue. The authors found that HA-MRSA carriage among patients after hospital discharge was relatively common (12.7%) and prolonged (mean length of carriage 246 days). Almost 20% of close household contacts of these patients acquired MRSA during the one year follow-up period; however, none of these household contacts went on to develop MRSA infection. Although the study does not address whether the household contacts were colonized with MRSA before caring for the patients after discharge, it does provide some reassurance that close household contacts of patients with HA-MRSA are unlikely to develop infection themselves.

Another prominent form of *Staphylococcus aureus* infection, CA-MRSA also has been associated with severe MRSA infections including severe skin and soft tissue infections and necrotizing pneumonias.^{2,3} An important feature of these MRSA strains is their ability to infect previously healthy individuals. Virulence factors responsible for these clinical manifestations have been debated. CA-MRSA strains have been shown to carry the gene for Panton-Valentine leukocidin (PVL), a toxin that induces leukocyte death. Such strains producing PVL have been associated with poor clinical outcome in some studies.^{4,5} However, animal models addressing the role of PVL in CA-MRSA infections have produced conflicting results,^{6,7} and some recent studies have associated PVL production with improved clinical outcomes.⁸ As reviewed herein, Villaruz and colleagues detected a mutation in the accessory gene regulator (*agr*) of *S. aureus* associated with a clinical phenotype similar to CA-MRSA.⁹ *Agr* encodes a regulatory component involved in expression of other virulence factors. When investigators corrected the mutation in *agr* and infected mice, there was no longer evidence of a clinical phenotype similar to CA-MRSA infection, despite presence of PVL. [9] Although the debate is likely to continue, these data add to the growing evidence against PVL toxin as a major virulence factor in the clinical presentation of CA-MRSA.

Although many clinicians are becoming familiar with MRSA infections, these infections are still associated with significant morbidity and mortality. In particular, *S. aureus* bacteremia (SAB) is associated with an in-hospital mortality of 20%-30%^{10,11} and a high risk of associated complications such as endocarditis, metastatic infection and recurrence.¹² Treatment of SAB is complex, and although infectious diseases consultation has been associated with better adherence to diagnostic and management guidelines, the impact of ID consultation on mortality has never been addressed. The Lahey and Reig studies, published in the last year and reviewed here, showed improved survival for patients with



SAB who were seen by infectious diseases specialists compared to those who were not.^{13,14} These findings should encourage clinicians of all disciplines to seek the advice of an infectious diseases specialist when treating patients with SAB.

A rise in the number of infections due to *S. aureus*, particularly MRSA, in the last twenty years has also led to a substantial increase in vancomycin use. Growing increased vancomycin use has prompted increased debate over the role of routine monitoring of vancomycin serum levels. In 2009, The American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists published a consensus review with recommendations for vancomycin dosing and monitoring.¹⁵ Highlights from this review include recommendations to calculate all vancomycin doses based on actual body weight (ABW), to always maintain vancomycin troughs above 10mg/L to avoid development of resistance, to consider vancomycin troughs of 15-20mg/L for all complicated infections, and to consider using a loading dose in seriously ill patients with the goal of quickly obtaining therapeutic serum levels. The recommendations also discuss the limited data suggesting the role of vancomycin as a direct nephrotoxin, and how the monitoring of vancomycin should be performed. This document should serve to improve clinicians' understanding and use of vancomycin dosing and therapeutic monitoring.

Infections due to *S. aureus* continue to pose significant problems for patients and healthcare professionals. Data published in the last year have shed light on the implications of MRSA colonization at the time of hospital discharge, virulence factors responsible for the severe clinical manifestations of CA-MRSA, the role of the infectious diseases consultant in the treatment of SAB, and proper use and monitoring of vancomycin. This information should translate to a positive impact on patient care; however, continued research is needed to address and minimize the significant impact of *S. aureus*.

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CARRIAGE OF MRSA IN HOME SETTINGS

Lucet JC, Paoletti X, Demontpion C, Degrave M, Vanjak D, Vincent C, Andremont A, Jarlier V, Mentré F, Nicolas-Chanoine MH. **Carriage of Methicillin-Resistant *Staphylococcus aureus* in Home Care Settings. Prevalence, Duration, and Transmission to Household Members.** *Arch Intern Med.* 2009;169(15):1372-1378.

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Little is known about the potential spread of healthcare-associated MRSA (HA-MRSA) strains from hospitals into the community. Prolonged carriage of HA-MRSA after discharge has been documented,^{1,2} and one retrospective study has documented transmission of HA-MRSA from a patient to household contacts after discharge from the hospital.³ Lucet and colleagues aimed to assess risk factors for carriage of HA-MRSA at time of discharge, duration of HA-MRSA carriage post-discharge, and factors associated with clearance, as well as rates and risk factors for MRSA transmission to household contacts.

This prospective study was carried out over a 14-month period from February 2003 to March 2004. The cohort was drawn from a network of 47 public teaching hospitals in the Paris area. Eligible patients were adults admitted for at least 48 hours who had undergone MRSA screening within 3 days prior to discharge a home healthcare network. Of the 1501 individuals screened for MRSA, 148 of the 191 found to be colonized with MRSA agreed to participate. These patients underwent routine surveillance for MRSA by culture of nasal swabs and swabs of any chronic wounds over the following year. Household contacts (n=188) who spent ≥ 8 hours daily with the index patient agreed to participate and underwent the same routine MRSA surveillance as the index patients.

Of the 1501 patients who were screened for MRSA, 191 (12.7%) were found to be colonized with MRSA before hospital discharge. Presence of chronic wounds, older age, longer duration of hospitalization, and neurologic or cardiovascular diagnosis were independently associated with MRSA carriage at the time of discharge. Fifty-one percent of the MRSA colonized patients cleared their MRSA within one year of follow-up at a mean of 246 days. Self-sufficiency in daily activities was the only factor independently associated with MRSA clearance (hazard ratio [HR], 0.63; 95% CI, 0.40-1.00) ($P=0.049$).

Of the 188 household contacts of index patients, 45% were a partner or spouse. Thirteen percent shared the same bed with an index patient, and 60% provided healthcare to the index patient. Thirty-six of the 188 (19.1%) acquired MRSA during follow-up. Only 4 of 36 were persistent MRSA carriers throughout study follow-up, and none of the household contacts were diagnosed with MRSA infection. Contact-related factors associated with acquisition of MRSA included older age and providing healthcare to the index patient.

In this fairly ill patient population with prolonged hospital stays, there was a high prevalence of MRSA carriage at discharge that persisted beyond a year in nearly half of patients, indicating there is a potentially large reservoir for spread of HA-MRSA outside of the hospital. This appears to justify the use of isolation precautions when patients with a history of MRSA return to the healthcare system. In addition, although there was a relatively high transmission rate to household contacts providing direct care to patients colonized with MRSA (19.1%), it appeared to be a benign occurrence, as it was not sustained over time and did not lead to infections. These findings may be reassuring to



caregivers of patients who are colonized with MRSA after hospitalization. This study is limited by lack of data on baseline MRSA carriage rates of household contacts as well as its inability to generalize to less-ill patients.

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NEW FINDINGS IN PVL GENE MUTATION

Villaruz AE, Bubeck Wardenburg J, Khan BA, et. al. **A Point Mutation in the agr Locus rather than Expression of the Panton-Valentine Leukocidin Caused Previously Reported Phenotypes in *Staphylococcus aureus* Pneumonia and Gene Regulation** *J Infect Dis*. 2009;200(5):724-734.

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Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has become an increasingly recognized cause of infections in previously healthy adults¹ and children.² Community acquisition of MRSA has been associated with complicated skin and skin structure infections as well as necrotizing pneumonias.^{3,4} Controversy exists regarding virulence factors important to the pathogenesis and clinical presentation of these infections. Panton-Valentine leukocidin (PVL), first described in 1932, is a toxin that forms pores on the surface of leukocytes, ultimately leading to their destruction.⁵ PVL production by *S. aureus* strains has been linked epidemiologically to severe skin infections and necrotizing pneumonias caused by *S. aureus*.^{6,7} However, murine models of *S. aureus* infection have showed conflicting results regarding this association. Some studies have shown similar clinical outcomes among mice infected with PVL-positive and PVL-deleted strains of *S. aureus*,^{8,9} while others have observed the opposite.¹⁰ In addition, Li and colleagues examined the lineage of the USA300 strain and found the virulence phenotype was present in its progenitor, prior to the acquisition of mobile genetic elements such as PVL.¹¹ These conflicting results led Villaruz et al to reevaluate previously studied strains of *S. aureus* to further investigate the role of PVL.

Study investigators sequenced the entire *agr* (accessory gene regulator) locus in laboratory strains of *S. aureus* used in prior studies. *Agr* encodes a signal transduction system that ultimately controls expression of genes encoding toxins and other virulence factors in *S. aureus* strains.¹² Investigators found a single base pair mutation in the *agr* P2 promoter region of a *S. aureus* strain (previously used in a murine model) which suggested a role for PVL in MRSA pathogenesis. The authors then repaired the *agr* point mutation and subsequently found no impact of PVL on gene expression or pathogenesis in a murine pneumonia model. This finding strongly suggests that the *agr* promoter mutation, as opposed to PVL, may be responsible for *S. aureus* pathogenesis.

The findings of this study add to the growing literature suggesting no or minimal role of PVL in CA-MRSA infections. Rather, a leading alternate explanation is that a mutation in the *S. aureus* gene regulator *agr* has a significant effect on *S. aureus* pathogenesis, at least in a mouse model. While this finding needs to be corroborated in further studies, these results provide new insight into understanding what clinicians see every day, and has implications for drug development against *S. aureus*.



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ID CONSULTATION FOR SAB

Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. **Infectious diseases consultation lowers mortality from *Staphylococcus aureus* bacteremia.** *Medicine (Baltimore).* 2009;88(5):263-267.

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Staphylococcus aureus bacteremia (SAB) is associated with significant morbidity and complications, including endocarditis, deep-seated abscesses, septic arthritis and vertebral osteomyelitis.^{1,2} In addition, SAB continues to carry a high in-hospital mortality rate, reported at between 20% and 30%.^{3,4} Factors associated with poor outcomes from SAB include inadequate treatment, persistent bacteremia, and failure to remove intravascular devices.^{5,6} all factors commonly addressed by infectious diseases



consultation (IDC). IDC has been shown to improve antibiotic use⁷ as well as the likelihood of cure from SAB.⁸ However; no study has documented mortality benefit from IDC in the treatment of SAB prior to the two studies discussed here.

The first study by Lahey et al prospectively followed 240 patients with SAB between 2002 and 2006. Fifty-one percent of patients were evaluated by IDC. Patients who underwent IDC were older, more likely to have healthcare-associated SAB, and more likely to have complications from SAB. There was no significant difference in rates of MRSA bacteremia between patients who underwent IDC and those who did not (42.6% and 37.3% respectively, $P=0.40$). The investigators found that patients who underwent IDC were also more likely to have follow-up blood cultures, receive appropriate antibiotics for a longer duration, and more likely to undergo interventions to drain abscesses or remove prosthetic material. All-cause and SAB-attributable mortality were lower [13.9% vs. 23.7% ($P=0.05$) and 12.4% vs. 22.1% ($P=0.05$), respectively] in the IDC group as opposed to those who did not undergo IDC. This relationship was still significant after adjustment for potential confounders. The beneficial effect of IDC on mortality was most pronounced in those individuals with endocarditis or MRSA bacteremia.

The second study by Rieg et al looked at patients in a German university hospital with SAB between 2002 and 2007. Patients from the earlier part of the cohort (2002-2004) were identified retrospectively, while those from 2005 through 2007 were identified and followed prospectively. From 2005 onward, IDC was offered routinely for all patients with SAB; therefore, a greater proportion of patients with SAB were seen by IDC during that time. Five-hundred-twenty-one SABs were evaluated, with 13% of these bacteremias due to MRSA. IDC was associated with lower in-hospital mortality (odds ratio [OR] 0.6) and 90-day mortality (OR 0.5).

A major limitation of the Lahey study is that investigators did not collect information on acute illness severity or admission to the ICU in either the IDC and non-IDC groups. This omission is important because the effect seen could simply be due to a lower severity of the acute illness in those who underwent IDC. Limitations of the Rieg study include the large number of patients lost to follow up after hospital discharge (90 patients, 17%) making it difficult to draw conclusions about 90-day mortality. In addition, investigators evaluated all-cause mortality as the primary outcome as opposed to SAB-attributable mortality. Therefore it is difficult to draw conclusions about the impact of IDC. Lastly, the majority of patients evaluated by IDC were from a later time period (2005-2007) than those who did not undergo IDC—therefore there may have been unmeasured changes in practice or improvements in medical care occurring over time that account for improved mortality.

Despite these limitations, both studies showed IDC significantly improved mortality related to SAB. These findings likely come as no surprise to infectious diseases physicians and should encourage other physicians to involve infectious diseases in the care of patients with SAB. In addition, they are likely to spark future discussions of mandatory IDC for SAB at some institutions.

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THERAPEUTIC MONITORING OF VANCOMYCIN IN ADULT PATIENTS

Rybak M, Lomaestro B, Rotschafer JC, et al. **Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.** *Am J Health-Syst Pharm.* 2009;66(1):82-98.

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Vancomycin is a glycopeptide antibiotic widely used to treat methicillin-resistant *Staphylococcus aureus* (MRSA). The practice of routinely monitoring serum vancomycin drug concentrations in the treatment of gram-positive infections has been debated for years. Controversy has focused on whether or not to monitor vancomycin levels to prevent drug toxicity, and whether drug monitoring improves clinical outcomes. This consensus guideline evaluates the existing data addressing serum vancomycin dosing and monitoring, and provides recommendations based on available evidence. Committee members conducted an exhaustive PubMed search; all relevant peer-reviewed studies published between 1958 and 2008 were evaluated. It is worth noting that few prospective or randomized trials of vancomycin monitoring exist; therefore, recommendations are often drawn from observational data, retrospective studies, and expert opinion.

Animal models and a few human studies have demonstrated that the ratio of the area under the serum drug concentration-versus-time curve and the minimal inhibitory concentration (AUC/MIC) is the best predictive pharmacokinetic parameter for vancomycin. An AUC/MIC of 345 has been correlated with clinical efficacy. Trough serum vancomycin concentrations (drawn at steady state after the fourth dose) are the best clinical surrogate for AUC, and are the recommended parameter for monitoring vancomycin effectiveness. The authors state there is no role for peak vancomycin concentration levels, therefore trough levels are the only recommended parameter to follow.

Emerging data suggests a correlation with low vancomycin levels (<10mg/L) and the development of vancomycin-intermediate susceptible *S. aureus* (VISA) and heteroresistant VISA (hVISA). Infection with these strains has been associated with worse outcomes than vancomycin-susceptible *S. aureus* (VSSA). For this reason, the authors recommend trough vancomycin concentrations always be maintained above 10mg/L.

Recent surveillance studies also report a shift in susceptibility patterns, such that increasing numbers of MRSA strains have MICs of 1-2mg/L, which may be associated with worse outcomes. Modeling studies have shown that daily doses of 3-4g of vancomycin would be necessary to attain an AUC/MIC of greater than 350 for strains with an MIC of 1mg/L. These results paired with poor tissue penetration of the drug and worse outcomes with MICs of 1-2mg/L led to the recommendation in this review that trough levels of 15-20mg/L be considered for complicated infections including endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia. Of note, modeling studies also show that attaining an effective AUC/MIC against strains with an MIC of 2mg/L is impossible in a patient with normal renal function. For this reason, the authors state alternative therapies such as daptomycin, quinupristin/dalfopristin and telavancin, should be sought in this situation.

The authors recommend obtaining at least one vancomycin trough drawn at steady state (usually before the 5th dose) for patients who are scheduled to receive vancomycin for more than 3 days. Weekly troughs are recommended for those on prolonged courses with sustained goal troughs of 15-20mg/L from complicated infections.



The authors recommend doses of vancomycin always be based on ABW. This is recommended for obese patients, although little data on dosing in obese patients exists. In addition, the authors recommend considering a loading dose of 25-30mg/kg (based on ABW) for seriously ill patients. This recommendation comes from limited data in critically ill patients in whom a loading dose was found to be both safe and associated with more rapid attainment of target trough serum vancomycin levels.

Controversy exists regarding the nephrotoxic potential of vancomycin. Data suggesting a direct causal relationship is limited, and existing studies fail to clarify whether high vancomycin levels are the cause or rather than the result of other factors driving renal insufficiency such as concomitant use of nephrotoxic agents. Rybak et al. suggest monitoring trough vancomycin levels weekly to reduce nephrotoxicity in patients receiving aggressive dosing, other nephrotoxic agents, prolonged courses, and those with baseline poor renal insufficiency.

In summary, prospective clinical trial data addressing ideal vancomycin dosing and therapeutic monitoring are lacking. However, the existing data has led to the recommendations discussed above. Highlights include keeping all vancomycin troughs above 10mg/L and pushing the trough to 15-20mg/L for invasive infections, considering alternative therapies for MRSA with a vancomycin MIC of 2mg/L, dosing all patients based on ABW, and considering a loading dose for critically ill patients. Further experience with higher vancomycin doses and higher trough levels will provide more insight to the debate over the role of vancomycin in causing nephrotoxicity.

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