Winter 2009

MRSA RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Distinct increase in MRSA over the past 20 years in eastern Ontario

Audcent et al. Clinical and subtype trends of methicillin-resistant Staphylococcus aureus *(MRSA) surveillance 1990 to 2009. IDSA 2009, Philadelphia, Pennsylvania.*

A distinct increase in methicillin-resistant *Staphylococcus aureus* (MRSA) has been detected by investigators at the Children's Hospital of Eastern Ontario (CHEO) over the last 20 years, predominantly the community-acquired (CA)-MRSA-10 (USA 300) strain.

Dr. Tobey Audcent, CHEO, Ottawa, and multicentre colleagues determined trends in prevalence of subtypes, source of isolates, clinical presentation and risk factors of MRSA isolates treated at the CHEO between 1990 and 2008. As reported at the 2009 Infectious Diseases Society of America (IDSA) meeting, "Patients with a culture-confirmed clinical or surveillance swab of MRSA were retrospectively identified through the infection control and microbiology database of a 150-bed pediatric tertiary care centre from July 1990 to September 2008. Furthermore, the demographic, risk-factor and clinical data were collected through a review of medical records using a standardized cases report form." Investigators also noted that isolates taken from infected children had been preserved and were then subjected to pulsed-field gel electrophoresis (PFGE) to identify MRSA subtypes.

Over a survey interval lasting nearly 20 years, investigators identified 102 cases of MRSA and had complete clinical data for 80 of them; PFGE typing was available for 74 cases. The most common strain identified by PFGE technology was CA-MRSA-10/USA 300 at 36% of all isolates, the majority of which were skin and soft tissue infections. The next most common strains were CA-MRSA-2/USA 100 (19%), CA-MRSA-7 (9%) and others/novel strains (38%). The most common clinical diagnosis was skin and soft tissue infections at 42% and invasive or other infections represented 18.7% of all MRSA infections. In this survey, some 34% of the isolates were associated with asymptomatic colonization. Perhaps as expected, 61% of all cases of MRSA infections at the CHEO occurred after 2005. However, the change in relative prevalence of CA-MRSA-10 compared to all other strains did not reach statistical significance.

The authors concluded that strains of MRSA other than the CA-MRSA-10 (USA 300) had higher rates of asymptomatic carriage compared with CA-MRSA-10 and that the high number of novel strains as colonizers would require further analysis.

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Int J Antimicrob Agents: www.elsevier.com

PCR assay for MRSA overly sensitive in the neonatal ICU

Sarda et al. Active surveillance for methicillin-resistant Staphylococcus aureus *in the neonatal intensive care unit.* Infect Control Hosp Epidemiol *2009;30:854-60.*

The polymerase chain reaction (PCR) assay for MRSA is overly sensitive in the neonatal intensive care unit (NICU) and PCR screening should be used in conjunction with bacterial cultures for MRSA to avoid unnecessary contact isolation.

Dr. Vanessa Sarda, University of Illinois Medical Center, Chicago, and multicentre colleagues sought to identify a screening algorithm that most successfully ensured appropriate isolation of colonized patients in the NICU. They reported, "From March to November 2007, infants in our NICU were screened for MRSA using both a real-time PCR assay and CHROMagar™ bacterial culture, and patients in the NICU were screened for MRSA on admission

and weekly thereafter until discharge." They added that healthcare workers were also screened as part of an outbreak investigation.

A total of 599 individuals were screened for MRSA by PCR assay and selective bacterial culture during the period of active surveillance. Out of 435 infants screened for MRSA during the active surveillance interval, 21 (4.8%) screened positive for MRSA with the PCR assay, yet only 11 of these infants or slightly more than half (52.4%) had concomitant bacterial cultures that were also positive for MRSA. Importantly, only those infants with positive cultures developed confirmed MRSA infection, and this occurred in two out of the 11 patients with positive MRSA cultures.

As investigators discussed, the PCR assay had a sensitivity of 100% and a specificity of 97.6% in this NICU setting, values similar to those reported in an adult population. However, the positive predictive value in the NICU was low at 52.4% (the negative predictive value was 100%). "This demonstrated that in a low-prevalence setting, even a highly specific screening test can be misleading because a high proportion of positive results (in this study, 47.6%) will be falsely positive," the authors observed.

Bacterial strain typing on initial isolates also indicated that, in general, MRSA strains identified in infants during the active surveillance period did not subsequently spread to other neonates in the ICU: only two infants had identical strains of MRSA.

"It is important to establish the true performance of MRSA PCR assays in all populations," the authors stated, "[as] false-positive PCR test results can lead to wrongful identification of outbreaks which disrupts patient care and causes a significant waste of hospital resources. We concluded that in the NICU, the PCR assay is overly sensitive with a low reproducibility rate for patients that have concomitant negative culture results... and its low reproducibility [rate] for patients with negative culture results argues for the need for confirmatory cultures to avoid unnecessary contact isolation."

Importance of active screening for hospital-acquired MRSA

Tacconelli et al. Rapid screening tests for methicillin-resistant Staphylococcus aureus *at hospital admission: systematic review and meta-analysis.* Lancet Infect Dis *2009;9:546-54.*

Active screening for hospital-acquired MRSA infection appears to be more important than the type of test used, according to Italian investigators.

Dr. Evelina Tacconelli, Università Cattolica del Sacro Cuore, Rome, Italy, and multicentre colleagues summarized the available evidence on the effect of MRSA detection by rapid screening tests on hospital-acquired MRSA infections and acquisition rates. From their review of the literature, 10 different studies were identified, and a meta-analysis was carried out for studies reporting data on the same outcome. "Primary outcomes included MRSA acquisition rate per 1000 patient-days (four studies), incidence of MRSA bloodstream infections per 1000 patient-days (three studies) and incidence of MRSA surgical-site infections per 100 surgical procedures (five studies)," the authors recorded.

Analyses revealed that compared to screening with enrichment cultures, the use of rapid screening tests was not associated with a significant decrease in MRSA acquisition rates. "Additionally, rapid screening was not associated with a significant decrease in MRSA surgical site infections when compared with no screening," they indicated. However, a significant 46% reduction of MRSA bloodstream infections was observed if intervention groups screened with rapid molecular tests were compared with unscreened control groups.

The authors concluded, "This data seem to suggest that, in institutions in which active surveillance screening with conventional cultures are currently applied, no evidence supports the application of rapid molecular tests to significantly decrease the MRSA transmission rate." They added that the use of rapid screening tests for MRSA in institutions where no active screening is currently in place might lead to significant reductions in MRSA bloodstream infections.

Combinations for serious MRSA infection

Deresinski S. Vancomycin in combination with other antibiotics for the treatment of serious methicillin-resistant Staphylococcus aureus *infections.* Clin Infect Dis *2009;49:1072-9.*

According to Dr. Stan Deresinski, Stanford University School of Medicine, California, clinicians should reconsider the use of vancomycin-based combination therapies for the treatment of infection due to MRSA.

Dr. Deresinski examined the practice of using combination antistaphylococcal therapy by identifying studies that support the practice. His research indicated rifampin has a number of characteristics that make it potentially effective when used in combination with vancomycin, including its potent bactericidal activity and ability to penetrate cells and a variety of tissues and compartments. Some preclinical studies also suggest that the combination of two agents given

together have synergy; others indicate the two agents are antagonistic. Clinically, however, there has been only one published randomized clinical trial examining the efficacy of vancomycin plus rifampin vs. vancomycin alone, as Dr. Deresinski pointed out. In that study of 42 patients with native-valve MRSA endocarditis, there was no difference in clinical outcomes between the two groups, although the addition of rifampin prolonged bacteremia by two days.

Similarly, a number of studies have suggested there is *in vitro* synergy between gentamicin and vancomycin against many MRSA strains. There are no published randomized trials comparing vancomycin given alone to the combination of vancomycin plus an aminoglycoside in patients with serious MRSA infections.

Even in doses as low as 1 mg/kg given every eight hours, gentamicin has been associated with significant nephrotoxicity, Dr. Deresinski observed. He concluded that given its potential to cause significant nephrotoxicity, and in the absence of evidence of clinical benefit, it would be difficult to justify the use of gentamicin with vancomycin for MRSA infections.

The combination of vancomycin together with rifampin and gentamicin is currently recommended for the treatment of prosthetic valve endocarditis (PVE) due to MRSA, not for the treatment of native-valve MRSA endocarditis. However, a recent study involving 86 adults with PVE due to coagulase-negative staphylococci, in which two-thirds of patients were resistant to methicillin, failed to demonstrate a difference in in-hospital mortality rates between those who were treated with vancomycin alone (27%), those who received vancomycin plus rifampin (33%) and those who were given vancomycin with gentamicin (20%). "Thus, the evidence for the recommendation of three-drug therapy for PVE due to MRSA—which carries with it the potential for increased risk of adverse reactions—is, at best, unconvincing," Dr. Deresinski suggested.

During initial empirical therapy given prior to the determination of methicillin susceptibility, vancomycin is often given together with an antistaphylococcal beta-lactam antibiotic. As Dr. Deresinski argued, even though experimental studies report a beneficial interaction between vancomycin and the beta-lactams, "Beta-lactam exposure has also been reported to cause reduced susceptibility of some strains of MRSA to vancomycin." Sub-inhibitory concentrations of beta-lactams may even enhance the production of staphylococcal toxins and as a result could have a detrimental effect in some patients.

"The combination of vancomycin with a beta-lactam antibiotic may provide benefit in definitive therapy for serious MRSA infections," Dr. Deresinski acknowledged. "In the absence of clinical trials confirming these results... the combination cannot be recommended for this purpose."

Clindamycin frequently antagonizes the antistaphylococcal activity of vancomycin; linezolid has been found to decrease the rate of vancomycin killing of MRSA by 100- to 1000-fold; nor is there adequate information supporting the use of quinupristin-dalfopristin with vancomycin.

As Dr. Deresinski observed, infectious disease experts were recently asked how they would manage a patient who was apparently experiencing failure of vancomycin therapy for a bacteremic illness caused by MRSA with a vancomycin MIC of 2 µg/mL. In response, 72% of those surveyed indicated that they would continue vancomycin and add a second antibiotic, most often rifampin or gentamicin.

Dr. Deresinski maintained, "The available data... however, would not appear to provide support for this approach, nor do they provide support for the use of such combinations for initial definitive treatment of MRSA infection." He concluded that the optimal therapy for serious MRSA infection has yet to be determined.

Treating complicated *S. aureus* skin and soft-tissue infections

Beibei et al. Linezolid versus vancomycin for the treatment of Gram-positive bacterial infections: meta-analysis of randomized controlled trials. Int J Antimicrob Agents *2009 Nov 7 [Epub ahead of print].*

Chinese investigators have determined that linezolid leads to superior clinical and microbiological outcomes in complicated skin and soft-tissue infections caused by *Staphylococcus aureus* compared with vancomycin. However, no differences in the likelihood of treatment success have been documented between the two treatments in patients with Gram-positive bacteremia or pneumonia.

Dr. Liang Beibei, General Hospital of Chinese People's Liberation Army, Beijing, and colleagues carried out a meta-analysis of nine randomized controlled trials (RCTs) to clarify whether the use of linezolid was associated with improved outcomes in infections caused by Gram-positive cocci compared with vancomycin. Among the nine RCTs identified, four were a blinded design and five were non-blinded. Data regarding treatment success of the administered antimicrobial regimens were reported for all nine RCTs.

"Success of empirical treatment in clinically assessed patients was achieved in 80% of linezolid-treated patients and in 78% of vancomycin-treated patients," investigators observed, "and the same was true for clinically assessed patients from blinded RCTs and from non-blinded RCTs." Six RCTs had data on skin and soft tissue infections; in these six trials, empirical treatment with linezolid was successful

in 89% of patients and empirical vancomycin treatment was successful in 86% of patients.

Three RCTs reported outcomes for patients with bacteremia and in these three trials, success of empirical treatment with linezolid was achieved in 76% of patients vs. 78% of patients treated with empirical vancomycin. Seven trials reported success for patients with pneumonia; there was no difference in success rates seen with linezolid (65%) vs. vancomycin (64%).

Investigators did remark that "empirical treatment with linezolid was associated with better eradication rates for *S. aureus*," although it was not associated with increased eradication of MRSA strains. Empirical linezolid was also associated with better treatment success in microbiologically evaluable patients than vancomycin.

Most drug-related adverse effects occurred at comparable rates with both study agents, were mild to moderate in severity and were reversible. Significantly more episodes of nephrotoxicity occurred with vancomycin compared with linezolid.

"This represents the largest meta-analysis of studies of linezolid and vancomycin for the treatment of Gram-positive infections to date," the authors stated, "and the improved penetration of linezolid into skin compared with vancomycin and the 100% bioavailability for patients receiving oral linezolid may be factors explaining the outcomes seen with linezolid for the treatment of Gram-positive infections."

Summary

The incidence of MRSA is increasing throughout the world, including Canada, where the predominant strain recently reported by the Children's Hospital of Eastern Ontario is community-acquired (CA)-MRSA-10 (USA 300).

Exploration of a screening algorithm for MRSA in an NICU indicates that in a low-prevalence setting, the PCR assay is associated with a high false-positive rate which could lead to unnecessary isolation of infants, and that it should be used along with MRSA cultures.

Yet there is an emphasis on the importance of active screening for MRSA on hospital admission for identifying MRSA in hospital patients rather than the type of test used. It has also been shown that only about half of patients with MRSA bloodstream infections actually receive appropriate empirical antibiotic therapy before susceptibility results are known, which clearly signals room for improvement.

In the setting of vancomycin failure, it is common to introduce combination therapy, usually with rifampin or gentamicin. Closer scrutiny of this practice has revealed little if any evidence to support it and in some instances, combination antimicrobial therapy may undermine the success of treatment with vancomycin alone.

Lastly, the largest meta-analysis to date of studies carried out with linezolid vs. vancomycin in Gram-positive SSTIs, bacteremia and pneumonia suggests that linezolid might be more effective in SSTIs and that it is not inferior to vancomycin in Gram-positive bacteremia or pneumonia in terms of overall treatment success. ❑

UPCOMING EVENTS

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