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INSIDE

Revised treatment guidelines for CAP **page 27**

What is the optimal does for heparin **page 28**

What happens to removable vena cava filters **page 29**

IVIG for myasthenia gravis and miller fisher syndrome **page 30**

MRSA in dialysis patients **page 31**

Selenium and Sepsis: It's Not Your Average Once-a-Day Vitamin

ABSTRACT & COMMENTARY

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Dr. Luks reports no financial relationship to this field of study.

This article originally appeared in the May 2007 issue of Critical Care Alert. It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, and Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington. Drs. Pierson and Thompson both report no financial relationships relevant to this field of study.

Synopsis: *A prospective randomized, placebo-controlled, multi-center trial demonstrates that a prolonged course of intravenous selenium improves mortality in patients with severe sepsis and septic shock and is associated with minimal to no side effects.*

Source: Angstwurm MW, et al. Selenium in Intensive Care (SIC): Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med*. 2007;35:118-126.

BUILDING ON THE RESULTS OF PREVIOUS PILOT STUDIES from their laboratory and a meta-analysis[1] that showed a tendency toward improved mortality in critically-ill patients following selenium administration, Angstwurm and colleagues used a randomized, placebo-controlled, multi-center trial to determine whether intravenous administration of selenium could improve outcomes in severe sepsis and septic shock. They recruited patients from 11 centers across Germany and included those men and women above the age of 18 with Acute Physiology and Chronic Health Evaluation (APACHE) III scores > 70 and at least 2 other markers of sepsis, such as elevated or decreased body temperature, tachycardia, tachypnea, leukocytosis, leucopenia or thrombocytopenia. Patients were excluded if they were pregnant, had concomitant disease with expected mortality within 2 months, hypoxic-ischemic encephalopathy, primary malignant disease, or hemorrhagic pancreatitis without infection.

Financial Disclosure

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Subjects were randomized to receive either 1000 micrograms of selenium as an initial bolus injection, followed by a 14-day continuous infusion at a rate of 1000 micrograms per 24 hours or an equal volume of normal saline. Angstwurm et al did not specify whether the infusion was continued if the patients recovered prior to the end of the 14-day period. The primary end point was 28-day mortality. Multiple secondary end points, such as the number of days of vasopressor therapy, mechanical ventilation, and hemodialysis, were examined.

After excluding 60 patients due to protocol violations and other factors, Angstwurm et al found that 28-day mortality among the 92 patients in the selenium group was 42.4%, compared with 56.8% among the 97 patients in the placebo group. This corresponds to a number needed to treat of 7, and Angstwurm et al estimate that the cost per life saved is roughly 1050 Euro (about $1400 USD). Among pre-defined subgroups, mortality was improved in patients with sepsis and disseminated intravascular coagulation, patients with APACHE III scores above 102, and those patients receiving intensive insulin therapy. Mortality was inversely correlated with whole blood selenium concentrations; mortality rates as low as 23-24% were found when drug levels were among the upper two-thirds of measured concentrations in the study. There were no major differences between the selenium and placebo groups with regard to any of the secondary end points, and there was no difference in the incidence of adverse events between the 2 treatment arms.

COMMENTARY

Given that the mortality from severe sepsis ranges as high as 50%, identifying a cost-effective, low risk, simple-to-use therapy that could reduce mortality would be of great benefit. On the surface, the trial presented by Angstwurm et al seems to provide promise in this regard. In a clinical trial that is methodologically sound apart from a lower number of subjects than one might expect in an 11-center study, Angstwurm et al demonstrate improvements in mortality using an intervention that is safe, relatively inexpensive and associated with a low number needed to treat to save one life.

While these are appealing factors, enthusiasm for the results must be tempered by a simple fact: the proposed treatment presents important logistical problems, the most important of which is the long duration over which the therapy must be administered. The selenium infusion lasted 14 days, and Angstwurm et al provide no information as to their protocol in the event patients improved before the 2 weeks had elapsed. As a result, it is not clear if the mortality benefit extends to patients who stop the infusion early and/or are converted to oral administration after their illness resolves. Given the increasing demands on hospital resources, keeping patients in the hospital for a 2-week period is infeasible and exposes the patient to risks such as nosocomial infection. The fact that 49 of the original 238 patients were dropped from the study due to protocol violations involving drug administration should also serve as a warning that the protocol may, in fact, not be an easy one to follow.

With these problems in mind, critical care providers would do well to avoid the quick urge to adopt interventions as standard practice after only one positive trial, as happened with activated protein C, intensive insulin therapy, and corticosteroids in refractory septic shock, and should instead wait for further trials on selenium with perhaps more feasible drug administration protocols. ■

Reference

1. Heyland DK, et al. Antioxidant nutrients: A systematic review of trace elements and vitamins in the critically ill patient. *Intensive Care Med*. 2005;31:327-337.

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Revised Empiric Treatment IDSA/ATS Guidelines for CAP

SPECIAL REPORT

By Carol Kemper, MD, FACP

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

This article originally appeared in the May 2005 issue of Infectious Disease Alert. It was edited by Stan Deresinski, MD, FACP, and peer reviewed by Connie Price, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Price is Assistant Professor, University of Colorado School of Medicine. Dr. Deresinski serves on the speaker's bureau for Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Dr. Price reports no financial relationships relevant to this field of study.

Sources: Mandell LA, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44:S27-S72; Pines JM. Measuring antibiotic timing for pneumonia in the emergency department: Another nail in the coffin. *Ann Emerg Med*. 2007;49:561-563..

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 into 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 health care 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 βeta-lactam plus a macrolide (preferred βeta-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. ■

What is the Optimal Dosing for Unfractionated Heparin?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

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Dr. Scherger reports no financial relationship to this field of study.

This article originally appeared in the May 15, 2007 issue of Internal Medicine Alert. It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Clinical Professor, University of California, Irvine, and Dr. Roberts is Clinical Professor of Medicine, Albert Einstein College of Medicine. Dr. Brunton is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and AstraZeneca, and serves on the speaker's bureau for McNeil, Sanofi-Aventis, and Ortho-McNeil. Dr. Roberts reports no financial relationships relevant to this field of study.

Synopsis: *Unfractionated heparin (UH) is commonly used in acutely ill hospital patients at risk for venous thromboembolism (VTE). Dosage regimens of 5000 units twice daily and three times daily are used, and have never been directly compared in a randomized clinical trial. A meta-analysis looking at both regimens shows that three times daily therapy reduced the rate of proximal deep vein thrombosis (DVT) and pulmonary embolism (PE); however, there is a small increased risk of bleeding complications. Patients at high risk for VTE should be treated with three times daily UH, while patients at lower risk may be treated with twice daily therapy.*

Source: King CS, et al. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A meta-analysis. *Chest*. 2007;131:507-516.

CLINICAL GUIDELINES NOW RECOMMEND USING prophylaxis against VTE in high risk hospitalized patients. Subcutaneous, unfractionated heparin (UH) has become the treatment of choice due to its safety and ease of monitoring and administration. Patients who are commonly treated include any acutely ill patient confined to bed, such as one with heart failure, respiratory disease, or postoperative care. Patients with a previous history of DVT or PE are at particularly high risk and should be treated.

Dosage regimens of 2 times daily and 3 times daily are used and have never been compared, according to

King and colleagues, who did an extensive review of the literature from 1966 through 2004. Five thousand units subcutaneously is the usual dosage with both regimens. King et al from the Department of Medicine at Walter Reed Medical Center in Washington, DC, performed the meta-analysis, looking at 447 articles over 38 years. All but 12 of the articles were excluded, mainly because they studied surgical and postoperative patients. A total of 7978 patients were represented in these 12 studies, with 6314 receiving 2 times daily therapy and 1664 patients receiving 3e times daily therapy.

The patients receiving 3 times daily therapy had fewer episodes of VTE than those receiving twice daily therapy. Total VTE risk was not significantly different in the 2 groups (5.4 per 1000 patient days with twice daily compared with 3.5 in the 3 times daily patients, $P = 0.87$). The risk of PE was significantly lower in the 3 times daily group (0.5 per 1000 patient days compared with 1.5 in the twice daily group, $P = .09$). Also, the risk of proximal DVT and PE was significantly lower in the 3 times daily group (0.9 per 1000 patient days compared with 2.3 in the twice daily group, $P = .05$). This reduced VTE risk is offset some by a higher risk of bleeding complications in the 3 times daily group (0.96 per 1000 patient days compared with 0.35 in the twice daily group, $P = .0001$).

COMMENTARY

While a head-to-head study of these 2 dosage regimens is needed, this careful study indicated that 3 times daily dosing of UH is superior to twice daily dosing, with some increased risk of bleeding complications. Note that the risk of bleeding in the 3 times daily group is lower than the risk of VTE, DVT, or PE in the twice daily group.

So what should we do with this important study? A prudent recommendation would be to use 3 times daily therapy for all patients at high risk for VTE, such as patients with a past history of DVT or PE, and immobile patients in bed. In patients in which the risk of VTE is lower but prophylaxis is still warranted, twice daily therapy would be appropriate to reduce the risk of bleeding complications. We can all thank King et al for a painstaking analysis of 38 years of medical literature. I would hope that funding for a head-to-head study of these regiments is forthcoming since the differences here are small and a meta-analysis of studies in which none used both regimens is far from being definitive. ■

What Happens To Removable Vena Cava Filters?

ABSTRACT & COMMENTARY

By David J. Pierson, MD

This article originally appeared in the May 15, 2007 issue of Critical Care Alert. It was peer reviewed by William Thompson, MD.

Synopsis: *Among 413 patients who underwent placement of a removable inferior vena cava filter following trauma for prophylaxis or treatment of pulmonary thromboembolism and survived to hospital discharge, subsequent removal of the filter was attempted in 116 of them and successful in only 91 (22%). Fewer patients were lost to follow-up at hospitals with policies requiring the service that placed the filters to follow them.*

Source: Karmy-Jones R, et al. Practice patterns and outcomes of retrievable vena cava filters in trauma patients: An AAST multicenter study. *J Trauma*. 2007;62:17-24.

Trauma surgeons at 21 institutions participated in this retrospective study of inferior vena cava filter (IVCF) placement and follow-up. A total of 599 IVCFs were placed at 21 hospitals during the study year, 226 (0.8% of all admissions) at 7 high-volume hospitals (> 2000 trauma cases admitted) and 373 (2% of all admissions, $P = 0.009$) at 14 low-volume institutions. Of all IVCFs in the study (both permanent and removable), 74% were placed prophylactically — that is, in patients without evidence for pulmonary thromboembolism or deep-venous thrombosis.

Of the 599 IVCFs, 446 (79%) were removable filters. Ten of the 21 participating centers had policies whereby the trauma service followed up with the patients following IVCF placement, as well as coordinated removal. In 3 centers, these aspects were the responsibility of the service placing the filter, and in the remaining 8 centers, no policies were in place. Of the 413 patients who had removable filters placed and survived to hospital discharge, filter removal was attempted in only 116 patients (28%) 50 ± 61 (mean ± SD) days after placement. Filter removal was not actually carried out in 25 of these patients because of technical difficulties or the presence of residual thrombus. Inability to remove the filter was more common with the Cordis Endovascular Optease filter (8/11 attempts)

than with the Bard Recovery (9/50) and Cook Gunter-Tulip (8/54) filters ($P = 0.01$).

Losing the patient to follow-up was the most common reason for not attempting removal of the filter, and this was significantly more frequent in hospitals where the placing service was not required to follow-up with the patient (122 of 273 patients, 45%) than in the 3 institutions having this requirement (4 of 65 patients, 6%; $P = 0.001$). Among the other patients in whom filter retrieval was not attempted, the most common reasons for this were immobility (124 patients), other ongoing risk for recurrent thrombosis (12 patients), and persistence of deep venous thrombosis (11 patients).

COMMENTARY

This was not a prospective study, and the descriptions provided for case identification, patient follow-up, complication detection, and other aspects of the methods are fairly cursory. For this reason, the reported absolute complication rates and the differences between these among the various indications, institutions, and devices should be interpreted cautiously. However, despite the study's limitations, it conveys several important messages. The use of "removable" IVCFs has become widespread. Many (if not most) such devices are being placed prophylactically rather than because of the inability to adequately anticoagulate patients with known venous thromboembolism. Despite the attractiveness of the concept of removing the filter once the acute threat of thrombosis has passed, it is clear that this is not actually taking place in many (if not most) instances.

Although it may be argued that the risk of subsequent deep-venous thrombosis and other long-term vascular complications of IVCFs may be different with current devices as compared to those of a decade or two ago, the final word on this issue is certainly not in at present. The large number of patients lost to follow-up in this study is worrisome, in that these lost patients may also not be receiving therapy with anticoagulants and may be at increased risk for complications related to the filters.

Following up patients seen at major trauma centers is a difficult and complicated problem, for numerous reasons. However, this study's finding of much greater follow-up success at institutions with protocols for follow-up of patients with IVCFs by the service that placed them indicates that such continuity of care is possible, even for these challenging patients. ■

IVIG for Myasthenia Gravis and Miller Fisher Syndrome

ABSTRACT & COMMENTARY

By Michael Rubin, MD

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Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

This article originally appeared in the May 2007 issue of Neurology Alert. It was edited by Matthew E. Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Vice Chairman, Professor of Critical Care Neurology, NewYork-Presbyterian Hospital, and Dr. Beal is Professor and Chairman, Department of Neurology, Cornell University Medical College. Drs. Fink and Beal report no financial relationships relevant to this field of study.

Synopsis: *IVIG is safe and effective for worsening MG, but has no effect on the natural course of Miller Fisher syndrome*

Sources: Zinman L, et al. IV immunoglobulin in patients with myasthenia gravis. A randomized clinical trial. *Neurology*. 2007;68;837-841; Mori M, et al. Intravenous immunoglobulin therapy for Miller Fisher syndrome. *Neurology*. 2007;68:1144-1146.

Despite reports touting the apparent benefits of intravenous immunoglobulin (IVIG) in myasthenia gravis (MG), level 1 evidence has been lacking until now. Between March 2004 and May 2005, the University Health Network Neuromuscular Clinic of the University of Toronto, Ontario, enrolled 51 MG patients with progressive weakness, 18 years of age or over, into a randomized, placebo-controlled, double-blind study, comparing IVIG to placebo (IV dextrose 5% in water, D5W). MG diagnosis was based on clinical evaluation, positive findings on single-fiber electromyography (SFEMG), previous response to treatment, and positive acetylcholine receptor antibodies and muscle-specific tyrosine kinase antibodies. Progressing weakness was defined as increasing ptosis, diplopia, dysarthria, chewing or swallowing difficulties, or limb weakness important enough to warrant change in medication. Exclusionary criteria included weakness due to intercurrent infection or medication, respiratory failure requiring intensive care admission, dysphagia with aspiration risk, recent (2 week) change in steroid dosage, renal, hepatic, or cardiac disease, hypercoagulable or hyperviscosity states, pregnancy, and lactation. Patients received either 2 G/kg of IVIG

or D5W over 2 days, were premedicated in all instances with acetaminophen and diphenhydramine, and were evaluated by clinical examination at baseline, day 14, and day 28 by the same blinded examiner. Clinical assessments included the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity and the Post-Intervention Status classification, with all anti-cholinesterase medication held for 12 hours prior to evaluation. Change in QMG Score for Disease Severity from baseline to day 14 was the primary outcome measure, whereas changes from day one to 28, and from day 14 to 28, served as secondary outcome measures, as did day 14 and 28 Post-Intervention Status, and changes in SFEMG and repetitive nerve stimulation studies from baseline to day 14. Student T test, x2, or Fisher exact test, and analysis of covariance (ANCOVA) were used for statistical analysis.

IVIG provided a small but significant improvement of QMG Score, compared to placebo, at day 14, which persisted, though it failed to reach significance at day 28. All the benefit was accrued by those with more severe disease, whose QMG score was > 10.5 at baseline. No IVIG patient worsened, compared to 4% on placebo, while 23% vs 42% experienced no change, respectively. Post-Intervention Status was also significantly improved by IVIG compared to placebo, 23% vs 8%, again appreciated only in the more severe cases, with none vs 6% worsening, respectively. No serious adverse events were experienced in either group, with headache, easily treated with over-the-counter medication, being the most common side effect.

COMMENTARY

In contrast to its proven efficacy in myasthenia gravis and Guillain-Barré syndrome, intravenous immunoglobulin (IVIG) appears to be less useful for Miller Fisher syndrome (MFS). Among 92 MFS patients seen between 1979-2005 at the Chiba University Hospital and its affiliates in Japan, and treated with IVIG (n = 28), plasmapheresis (n = 23), or supportive care alone (n = 41). Mori et al reported no significant difference between the treatment groups. Only 4 (4%) remained symptomatic one year after disease onset; one each from the IVIG and control groups, and 2 from the plasmapheresis group. They all had persistent diplopia, and one patient also experienced persistent ophthalmoplegia. MFS is a terrifying, but relatively benign condition, and does not appear to benefit from IVIG. Almost all patients recover with or without treatment. ■

MRSA in Dialysis Patients

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

This article originally appeared in the May 2007 issue of Infectious Disease Alert. It was peer reviewed by Connie Price, MD.

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.*

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

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 1000 population, an incidence far in excess of that estimated for the general population (0.2 to 0.4 per 1000 population). This was based on active surveillance in the 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 5000 cases of invasive MRSA infection identified by ABCs sites during 2005. While the overall incidence, as indicated above, was 45.2 per 1000 population, the incidence varied from a low of 27.2 at California locations to 92.0 per 1000 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 set-

ting; 92% of these being USA100. Of the 14% of infections caused by MRSA types whose community origin was considered to be 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, 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 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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