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INSIDE

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Cleansing Patients with Chlorhexidine Promotes Infection Control

ABSTRACT & COMMENTARY

By Leslie Hoffman, PhD, RN

Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

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

Synopsis: *Cleansing patients with chlorhexidine-saturated cloths reduced VRE contamination of patients' skin, the environment, and health care workers' hands, and also decreased VRE acquisition.*

Source: Vernon MO, et al. Chlorhexidine gluconate to cleanse patients in a medical intensive care unit: the effectiveness of source control to reduce the bioburden of vancomycin-resistant enterococci. *Arch Intern Med*. 2006;166:306-312.

Infection control practices often target clinician behaviors, eg, improving adherence to hand washing hygiene and other infection control practices. This study tested an alternative approach: source control. Over a 15-month period, all patients (n = 1787) admitted to a medical intensive care unit (MICU) were bathed during three sequential periods with soap and water (Phase 1), single-use, no rinse disposable cloths saturated with 2% chlorhexidine gluconate (Phase 2), and single-use, no rinse disposable cloths without chlorhexidine (Phase 3). Each study phase lasted for approximately 5 months. The study used a standard set of bathing procedures and products, eg, Dial soap (Phase 1), packets containing 2 non-medicated cloths for face and neck cleansing and 6 medicated cloths for body cleansing (Phase 2) and packets containing a similar number of non-medicated cloths (Phase 3). Vancomycin-resistant enterococci (VRE) acquisition was defined as a positive finding for VRE on a rectal culture specimen > 3 days after MICU admission with at least 1 prior negative culture.

Compared with soap and water, bathing patients with chlorhexidine-saturated cloths resulted in 2.5 $\log_{10}$ less colonies of VRE on patients' skin and less VRE contamination of health care workers' hands (risk ratio [RR], 0.6; 95% confidence interval [CI], 0.4-0.8)

and environmental surfaces (RR, 0.3; 95% CI, 0.2-0.5). The incidence of VRE acquisition decreased from 26 colonizations per 1,000 patient-days to 9 per 1,000 patient-days (RR, 0.4; 95% CI, 0.1-0.9). For all measures, the effectiveness of cleansing with non-medicated cloths was similar to that of soap and water baths. Skin condition was assessed daily. More patients had deterioration in skin condition during soap and water bathing compared to chlorhexidine (P = .02) or nonmedicated cloth (P = .001) bathing.

COMMENTARY

Today, we are facing an ever-increasing number of pathogenic bacteria with diminishing susceptibility to antibiotics. Commonly, approaches to reducing cross-contamination with resistant bacteria such as VRE have focused on improving adherence to infection control recommendations. This study evaluated a different approach—source control. The goal was to reduce microbial skin density and, thereby, patient-to-patient transmission. Chlorhexidine was selected because of its low toxicity and known effectiveness against a broad range of pathogens. To detect VRE hand carriage, culture specimens were obtained from a convenience sample of individuals exiting rooms of patients with VRE colonization and from individuals in common MICU areas. To detect environmental contamination, specimens were obtained from the bed rail, pull sheet, and overbed table.

Daily bathing with chlorhexidine produced lower bacterial counts on patients' skin, hands, and surfaces. With such an intervention, there are always concerns about development of resistant organisms and skin reactions. Resistance, evaluated using median chlorhexidine inhibitory concentrations for strains of VRE (11 strains of *Enterococcus faecalis* and 52 strains of *Enterococcus faecium*) was similar during each phase. Also, there were no adverse reactions in the 642 patients enrolled in the phase with chlorhexidine bathing. To avoid the potential of allergic reactions, the bathing procedure did not involve use of chlorhexidine on the patients' faces. Skin condition for most patients (89%) was unchanged and deterioration was more common during soap and water bathing and bathing with nonmedicated cloths. However, mean MICU stay was only 3.4 days and findings might have differed if the intervention was applied to long-stay ICU patients.

Findings of this study provide strong initial support for bathing with 2% chlorhexidine gluconate as a measure to reduce the transmission of VRE in high-risk settings such as the ICU. Studies involving a longer observation period are needed to evaluate safety and efficacy in long-stay ICU patients. ■

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Sildenafil for Pulmonary Embolism?

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In a patient with severe pulmonary embolism and clinical deterioration despite thrombolytic therapy in whom more invasive therapy could not be undertaken, administration of oral sildenafil was associated with better hemodynamics and other clinical improvement.*

Source: Ganiere V, et al. Dramatic beneficial effects of sildenafil in recurrent massive pulmonary embolism. *Intensive Care Med*. 2006;32:452-454.

A 58-YEAR-OLD WOMAN PRESENTED WITH 3 DAYS OF dyspnea and was shown by CT scan to have pulmonary thromboemboli. She was anticoagulated with low-molecular-weight heparin and was stable for 2

days, but then developed acute respiratory failure, was intubated, and transferred to the ICU. A transesophageal echocardiogram showed right ventricular dysfunction and an estimated pulmonary arterial systolic pressure of 100 mm Hg. Thrombolytic therapy was instituted, and over the next 2 days the patient was administered increasing doses of norepinephrine and dobutamine. Pulmonary arterial catheterization was performed, revealing a cardiac index of 2.1 L/min/m^2, a mean pulmonary arterial pressure of 56 mm Hg, and a pulmonary vascular resistance index of 700 dynes/cm-5/m^2. The patient's family declined a proposed transfer to another facility where surgical therapy and nitric oxide were available.

She was then given 50 mg sildenafil by nasogastric tube, and 2 hours later the cardiac index had increased to 3.2 L/min/m^2, with a decrease in mean pulmonary artery pressure to 46 mm Hg and a fall in pulmonary vascular resistance index to 425 dynes/cm-5/m^2. The patient had previously been normotensive, and systemic arterial pressure did not fall with sildenafil administration. Sildenafil 50 mg 3 times daily was administered for several weeks and then slowly withdrawn. Echocardiography showed an estimated pulmonary arterial systolic pressure of 65 mm Hg at 3 months and 80 mm Hg at 9 months.

COMMENTARY

Sildenafil, an enhancer of nitric oxide-mediated pulmonary vasodilation, is now approved by the US Food and Drug Administration for treating chronic pulmonary arterial hypertension. This case report from Switzerland illustrates the possibility of its use in selected instances of severe acute pulmonary hypertension.

There are a number of uncertainties about this case. The title of the article says "recurrent massive pulmonary embolism," but no documentation of recurrence was obtained, and it is not clear whether the patient was ever hypotensive, a criterion for most definitions of massive pulmonary thromboembolism.[1] In these days of direct visualization of thromboemboli via CT angiography, the clots are often described as "massive" based on their number and size. However, there is a difference between anatomic extent and hemodynamic effects. To my knowledge the only clinical trials of thrombolysis or other intervention in massive pulmonary embolism have used either initial or refractory hypotension to define this condition. This patient also probably had chronic pulmonary hypertension, as shown by the very high initial pulmonary arterial systolic pressure (100 mm Hg) and the markedly elevated mean pulmonary arterial pressures obtained on follow-up echocardiograms up to 9 months after the episode of thromboembolism.

These quibbles about the case notwithstanding, it seems inevitable that sildenafil will be tried in the ICU (although its use in this context is not currently approved). Its use has already been reported in right-sided heart failure due to exacerbation of chronic pulmonary arterial hypertension,[2] and there are reports of the administration of sildenafil in tandem with inhaled nitric oxide.[3,4] However, a case report does not a clinical trial make, and intensivists would be wise to await the results of further investigations before trying this potentially promising, easy-to-administer therapy in their own practices. ■

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Special Feature

Prevention of Overwhelming Post-Splenectomy Infections

By Saadia R. Akhtar, MD, MSc

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

Case Presentation

A 53-YEAR-OLD WOMAN WITH A HISTORY OF splenectomy 15 years ago for idiopathic thrombocytopenic purpura and no chronic medical problems awoke with headache, myalgias, and fever. She was seen at her local urgent care that evening where she had a temperature of 102°F with mild tachycardia but otherwise normal vital signs. Exam was unremarkable. Basic laboratory studies revealed leukocytosis with a leftward

shift (13K WBC with 10% bands) and no other abnormalities. Chest X-ray and urinalysis were normal. Blood cultures were collected and she was sent home with the diagnosis of probable viral syndrome.

Six hours later the laboratory called the urgent care with positive blood cultures growing Gram-positive diplococci. The patient was called at home. She noted over the phone that she was feeling a bit weaker and was still febrile. She was instructed to come back to the hospital. Her husband drove her in and upon arrival to the urgent care, about 30 minutes after the phone conversation, she was somnolent and mottled-appearing with a systolic blood pressure of 60. She received aggressive resuscitation with intravenous fluids, vasopressors, antibiotics and mechanical ventilatory support. Laboratory studies now revealed acute renal failure, shock liver and disseminated intravascular coagulation. Bilateral alveolar infiltrates were noted on chest X-ray. Blood cultures ultimately revealed *Streptococcus pneumoniae*.

After a 3-week ICU stay with aggressive support (including ongoing mechanical ventilation, activated protein C and continuous renal replacement therapy) the patient ultimately recovered and was able to be discharged to a rehabilitation unit. In reviewing her history, this woman had not had pneumococcal vaccine since just after splenectomy and did not recall ever having had vaccination against meningococcus or *Haemophilus*. She and her family were not aware that she was at any particular risk for severe infection.

Introduction

Overwhelming post-splenectomy infection (OPSI), also termed post-splenectomy sepsis, is a fulminant form of sepsis (frequently due to or accompanied by pneumonia and/or meningitis) occurring in asplenic patients. The term OPSI is used loosely and applied to persons who have post-surgical as well as functional asplenia. The usual pathogen is *Streptococcus pneumoniae*, although patients have increased susceptibility to infection by a variety of other organisms. Mortality is high.

OPSI first came to widespread attention in 1952 after King and Shumacker's report of sepsis and death in infants who had undergone splenectomy for hereditary spherocytosis.[1] It was initially thought that adults were at little or no risk for OPSI but it quickly became clear that this was not the case. Today, although we have a better understanding of risk, presentation, treatment and prevention of OPSI, more work needs to be done to disseminate this information and incorporate it into practice.

Splenic Function and Causes of Asplenia

The spleen is the largest lymphoid organ in the body and serves multiple immune functions. It is responsible for antibody response to a variety of antigens including capsular polysaccharides (some of this response may be via production of 2 opsonins, tuftsin which may initiate phagocytosis and properdin which is important in the alternative complement activation pathway). Filtering of blood through splenic sinusoids and the action of splenic macrophages eliminate abnormal (non-deformable or antibody-coated) erythrocytes from the circulation, including those infected with parasites. The spleen may also play a role in removing endotoxin from the circulation. Thus splenectomy reduces clearance of circulating pathogens, particularly encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type B and *Neisseria meningitidis*, parasites such as *Babesia* or *Plasmodium* species, and Gram-negative bacteria such as *Escherichia Coli*, *Pseudomonas* species and *Salmonella* species (*Salmonella* infection is usually only seen in children with sickle cell anemia). Interestingly, *Capnocytophaga canimorsus* infection (typically acquired from animal bites) occurs almost exclusively in asplenic patients.[2-4]

Asplenia may be congenital, functional, or surgical. Congenital asplenia is usually associated with other major malformations and 95% of those affected die within the first year of life. Functional asplenia occurs in a wide variety of conditions including hemoglobinopathies (sickle cell anemia, thalassemia, hereditary spherocytosis), lymphoproliferative disorders, post-bone marrow transplantation, chronic liver disease, gastrointestinal diseases (celiac sprue, inflammatory bowel disease), some autoimmune diseases (systemic lupus erythematosus), infiltrative diseases (amyloidosis, sarcoidosis) and following splenic irradiation. Surgical splenectomy is performed for management of traumatic or iatrogenic splenic injury, idiopathic thrombocytopenic purpura (ITP), hemolytic anemia, some malignancies, and for other causes of hypersplenism.[3]

Epidemiology

There are no robust population-based epidemiological studies of post-splenectomy infection. The available information is further complicated by the fact that studies employ different definitions of serious infection, include different patient populations (surgical splenectomy vs asplenia of any cause) and may precede introduction of the current pneumococcal vaccine. Taking these factors into account, lifetime risk of OPSI is sug-

gested to be about 0.5-5%.[3-6]

Risk is related to age, indication for and time after splenectomy, presence of immunosuppression for another reason and prior history of OPSI. OPSI rates are lower in adults than in children (risk may be up to 10% in children younger than age 5). Splenectomy for trauma appears to impart the lowest risk for OPSI along with splenectomy for ITP: the highest rates are in patients with thalassemia major, hereditary spherocytosis or malignancy.[3-5]

OPSI risk is greatest in the first 2-5 years after splenectomy but there are reports of OPSI occurring over 20 years after splenectomy: mean time interval between splenectomy and infection was 22.7 months in one large review of the literature.[5] Asplenic patients who are also immunosuppressed for another reason are at higher risk for OPSI (for instance, up to 25-33% in patients who underwent splenectomy for Hodgkin's disease followed by chemotherapy).[4] Finally, patients appear to be at higher risk for infection after a first episode. Kyaw et al reviewed clinical course of a cohort of 1648 patients who underwent splenectomy in Scotland and found overall risk of first serious infection (requiring hospitalization but not necessarily with septicemia or meningitis) to be 7 in 100 person-years but that of second infection to be 44.9 in 100 person-years. The majority of first infections (84%) occurred within the first 3 years after splenectomy: the majority of second episodes occurred within 6 months of the first episode.[7]

S. pneumoniae accounts for 50-90% of the cases of OPSI and *H. influenzae* for about 8%. Mortality with OPSI is highest when the causative agent is *S. pneumoniae* but overall is estimated to be 38-69%.[5,6]

Clinical Presentation of OPSI[4,6]

Patients initially develop nonspecific mild symptoms of illness such as headache, myalgias, sore throat, cough, or gastrointestinal upset. Associated fever or rigors are key findings that should prompt patients to seek medical attention immediately and should alert medical personnel to be seriously concerned. These patients quickly become toxic-appearing: the hallmark of OPSI is rapid progression, often within a few hours (and no more than 1-2 days) to fulminant sepsis and shock with tachycardia, tachypnea, hypotension, altered mental status, oliguria or anuria and evidence of disseminated intravascular coagulopathy with petechiae and purpura. Laboratory studies are those usual for sepsis and septic shock (abnormal leukocyte counts with left shifts, metabolic acidosis, evidence of end-organ injury with abnormal creatinine, elevated liver function studies, coagulopathy, etc). It is relatively common, due to the high-grade bacteremia these patients experience, for blood cultures to become positive within hours of inoculation: altogether, positive blood cultures are found in about 95% of cases of OPSI. Pneumonia or meningitis are common in children with OPSI but a specific focus of infection may not be found in adult patients.

Treatment

Asplenic patients presenting with acute febrile illnesses should have blood cultures drawn and antibiotics administered immediately (including at a physician's office prior to transfer to the emergency department).[6] Strong consideration should be given to prolonged observation in the emergency department or overnight in the hospital for all febrile asplenic patients regardless of clinical appearance.

The initial empiric antibiotic regimen should treat penicillin-resistant, beta-lactamase producing encapsulated bacteria and also provide some Gram-negative coverage: intravenous ceftriaxone at meningitis-treatment doses (2 g IV q12 hours) is recommended. Strong consideration should be given to adding vancomycin (1 g IV q12 hours) for possible high-level penicillin-resistant pneumococci. For patients with a β-lactam allergy, fluoroquinolones (such as levofloxacin) are the suggested alternative.[3] Dexamethasone should also be considered until meningitis is ruled out.[8]

Due to the relative deficiency of opsonizing antibody in asplenia, it has been suggested that administration of intravenous immune globulin (IVIG) may be beneficial. However, there are only very limited data in the form of animal studies and case reports suggesting possible benefit of IVIG in OPSI (3 days of IVIG at 0.4mg/kg/day). Granulocyte-macrophage colony stimulating factor (GM-CSF) has also been investigated and appears to increase macrophage bactericidal activity and improve outcomes in asplenic mice but clinical trials have not been undertaken.[4,6] At this time, neither of these interventions can be routinely recommended in the management of OPSI.

Prevention

Randomized, controlled trials of the efficacy of these preventive strategies are currently lacking. The recommendations are based primarily on theoretical benefit, extrapolation from other clinical settings and expert opinion. The British Committee for Standards in Hematology has published guidelines for prevention

and treatment of infection in asplenic patients (initially in 1996, revised in 2002).[9] The Centers for Disease Control and Prevention (CDC) also provides recommendations for immunization of asplenic patients.[10]

Avoid Splenectomy[9,11]

As the medical community has become more aware of the risk of OPSI, surgical approaches have changed. Trauma care has shifted over time to focus on splenic preservation rather than immediate splenectomy for blunt injuries, particularly for low-to-mid-grade splenic injuries. After defining the splenic injury by CT scan, hemodynamically stable patients without other significant intra-abdominal injuries and with limited transfusion requirements related to the splenic injury can be monitored clinically for spontaneous healing: 40-65% of blunt splenic trauma may be successfully managed in this way. Another alternative to complete splenectomy (particularly for some non-trauma indications) is partial splenectomy, with the goal of leaving 30-50% of residual tissue with an identifiable blood supply (splenic artery or short gastric vessels): this appears to preserve enough splenic function to avoid OPSI. Limited data suggest that autotransplantation of a small amount of splenic tissue (usually into the greater omentum or, less commonly, the retroperitoneum) may be another option but the efficacy of this remains unclear. A recent large survey of North American trauma surgeons revealed that only about 4% of responders were re-implanting splenic tissue during splenectomy for trauma.[12]

Immunize[9,10,13]

The CDC and most authors recommend that all asplenic patients receive polyvalent pneumococcal vaccine (PPV-23) (containing purified capsular polysaccharides from 23 serotypes of pneumococcus, accounting for about 73% of strains that have been reported to cause OPSI), *Haemophilus influenzae* type B conjugate vaccine, and quadrivalent meningococcal A, C, Y and W135 vaccine. It is recommended that patients undergoing elective splenectomy receive these vaccines at least 2 weeks prior to the surgery. If this is not possible then initial vaccination should be given at discharge (no less than 2 weeks post-procedure as functional antibody titers are significantly higher with vaccination at that time compared to vaccination in the immediate post-operative period).[14] For those patients with asplenia who have never previously been vaccinated, these vaccines may be given at any time. For patients receiving chemo- or radiotherapy, vaccination should be delayed for 6 months after completion of these treatments. (Antibiotic prophylaxis should be provided during this time, as detailed below.) Revaccination at least once after 5 years is crucial for PPV-23 and some authors recommend ongoing revaccination every 5 years. Finally, influenza vaccine is indicated yearly for asplenic individuals.

It is worth noting a few other issues and opinions regarding these immunizations. In Europe, based on prevalence of meningococcal C serotype, only the meningococcal C conjugate vaccine is recommended with suggestion that the quadrivalent vaccine be administered upon travel to other areas. Similarly, in North America, some experts suggest administration of meningococcal vaccine may not be necessary as the most prevalent serotype is B and that perhaps the vaccine should only be given prior to travel to other areas. The role of the new 7-valent conjugate pneumococcal vaccine for patients with asplenia is not clear. It has been used in patients who have failed to generate IgG to pneumococcus after receiving PPV-23 (discovered after an episode of OPSI prompted measurement of anti-pneumococcal antibodies).[15] Due to concerns about such failures of immunization, some authors also suggest routine measurement of these antibodies after vaccination of asplenic patients but there is no clear consensus about this topic.

Despite the availability of consensus guidelines and recommendations, actual immunization rates vary greatly. Several studies report immunization rates post-splenectomy at 11-75%.[16-18] Other aspects of immunization practice also vary, as demonstrated by Schatz's survey of 557 trauma surgeons in the United States and Canada (members of the American Association for the Surgery of Trauma). Response rate was about 50%. Although Schatz found an excellent rate of vaccine administration at 99.2%, he found that the timing varied considerably: One-third of surgeons vaccinated in the operating room or immediate post-operative period and one-third at hospital discharge. One-third of responding surgeons felt revaccination was unnecessary. Of the 39% that did report revaccinating, the intervals ranges from < 1 year to 10 years.[12]

Provide antibiotics[6,9]

Daily penicillin or amoxicillin prophylaxis is recommended for children with asplenia. This is based primarily on evidence for protection again pneumococcal infection in children with sickle cell anemia.[19] Some authors suggest continuing this up to age 16-21 years. It is also suggested that daily antibiotic prophylaxis be

provided for up to 5 years post-splenectomy in adults. (Usual adult dose would be penicillin or amoxicillin 500 mg daily or twice a day.) As noted above, daily antibiotic prophylaxis is also recommended for patients who must begin chemo- or radiotherapy immediately post-splenectomy: in this case, prophylactic antibiotics must be continued at least until appropriate vaccinations can be given. For penicillin-allergic patients, co-trimoxazole or a newer-generation fluoroquinolone are reasonable alternatives.

These recommendations must be tailored based on regional antibiotic susceptibility patterns: due to increasing prevalence of penicillin-resistant Streptococci, some authors suggest using amoxicillin/clavulanate or cefuroxime routinely instead of penicillin or amoxicillin. Long-term development of antibiotic resistance is clearly a concern if these recommendations are followed: this issue has not been studied or specifically addressed in the literature for this clinical scenario.

Strong consideration should also be given to providing patients with a 5-day home supply of therapeutic doses of antibiotics to be initiated at the first sign of any febrile illness or in the event of an animal bite (along with instructions to then seek immediate medical care).

Finally, it is important to be aware of the infectious risks asplenic patients may face with travel. Some authors recommend resuming daily penicillin or amoxicillin prophylaxis with travel abroad as it may be more difficult in that setting for patients to get immediate medical attention if they become ill. Malaria prophylaxis is essential for asplenic patients traveling to high risk areas. As discussed above, if immunization for meningococcus has not been given previously, it should also be considered with travel to high-risk areas.[20]

Educate Patients and Ourselves

Multiple studies have shown that, like the patient in our case presentation, up to 50% of asplenic patients are not aware that they are at increased risk of sepsis and are not familiar with the need for routine immunizations or the need to seek medical attention and start antibiotics immediately for signs of infection.[16,17,21] Repeated education of patients about their risk of life-threatening infection, recommendations for immunizations, what to do in the event of a febrile illness and travel-related infectious concerns is essential. It is also recommended that splenic patients wear a medical bracelet: per one study, < 30% of patients wear them.[22]

Similar surveys of physicians suggest deficient knowledge of risk of infection for asplenic patients.[16,22,23] For instance, Bridgen et al's survey of 122 Canadian practitioners revealed a good understanding of the risk of pneumococcal infection after surgical splenectomy (94% recognized this) but poor knowledge of the risks of infection with functional asplenia or risks of infection with pathogens other than pneumococcus. Twenty-five percent (25%) of physicians felt revaccination for pneumococcus was not indicated and 35-40% were unaware of the recommendations for vaccines against *H. influenzae* and *N. meningitides*. Prophylactic antibiotics (either daily or for use in the event of febrile illness) were provided by < 30%.

Summary

Considerable work must be done to improve our understanding of the mechanisms, epidemiology, management, and prevention of OPSI. Until that time, greater awareness by physicians and patients of the known risks and clinical features of OPSI, knowledge and compliance with immunization guidelines, lower thresholds for use of antibiotics and early medical attention and admission for asplenic patients with febrile illnesses may improve outcomes for some of these patients. ■

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CME Questions

6. When cloths medicated with 2% chlorhexidine were used for daily bathing:
a. skin irritation increased significantly.
b. skin contamination decreased but hand contamination increased.
c. fewer bacteria were found on environmental surfaces.
d. VRE infection initially decreased and then increased.
e. fewer patients acquired VRE.

7. Compared with using traditional soap and water for bathing, cleansing patients with 2% chlorhexidine gluconate resulted in:
a. shorter ICU stays.
b. decreased incidence of clinical VRE infections.
c. fewer clinical infections with MRSA.
d. All of the above
e. lower bacterial counts on patients' skin, hands, and surfaces.

8. Which of the following statements is true about the use of sildenafil in critically ill patients with pulmonary hypertension and echocardiographic evidence of right ventricular dysfunction?
a. It safely decreases pulmonary arterial pressures in such patients
b. It reverses acute cor pulmonale
c. It improves oxygenation
d. All of the above
e. It is not currently approved for use in this setting

9. Which of the following has been used as a criterion for the diagnosis of massive pulmonary embolism in clinical trials of thrombolytic and other therapy?
a. Systemic arterial hypotension
b. Pulmonary arterial hypertension
c. Occlusion of > 50% of the pulmonary vascular bed on CT scan or angiography
d. All of the above

10. Overwhelming post-splenectomy infection is typically caused by any of the following *except*:
a. *Streptococcus pneumoniae.*
b. *Babesia species.*
c. *Haemophilus influenza.*
d. *Candida albicans.*
e. *Capnocytophaga canimorsus.*

Answers: 6 (e); 7 (e); 8 (e); 9 (a); 10 (d)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

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PHARMACOLOGY WATCH

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Reversal of Atherosclerosis Via Intensive Statin Therapy

Aggressive LDL lowering with statins, so-called "very intensive statin therapy," leads to reversal of coronary atherosclerosis, according to a new study. The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, a perspective, open label, blinded end-points trial, utilized the potent statin rosuvastatin in evaluating whether very intensive statin therapy resulting in LDL cholesterols in the low 60s associated with increases in HDL cholesterol could reverse atherosclerosis. Five hundred and seven patients were initially evaluated with intravascular ultrasound (IVUS) to determine baseline atheroma burden. Patients were then treated with intensive statin therapy with rosuvastatin 40 mg daily for 24 months, which resulted in an average LDL cholesterol of 60.8 mg/dL (mean reduction, 53.2%) and increased HDL cholesterol by 14.7%. IVUS was performed again at 24 months. The mean change in atheroma volume in the most diseased 10 mm sub segment was -6.1 (10.1) mm^3, with a median of -5.6 mm^3 ($P < .001$ vs baseline). Change in total atheroma volume showed a 6.8% median reduction. Adverse events were infrequent. Specifically there were no cases of rhabdomyolysis.

The authors conclude that lowering LDL-C to levels below currently accepted guidelines, when accompanied by significant increases HDL-C, can regress atherosclerosis in coronary disease patients, and is indicated for high-risk patients with established coronary disease (*JAMA*. 2006;295:1556-1565). An accompanying editorial notes that the study had several limitations, including lack of a control group or a comparator drug. They also note that the modest plaque reduction noted in this study "may not be the best measure of the treatment's effect on hard cardiovascular end points", however, they do applaud the pioneering work using intravascular ultrasound to help understand the anatomy and pathophysiology of coronary atherosclerosis and the effect of medical therapy on atheroma (*JAMA*. 2006;295:1583-1584).

Alternative Therapy for Depression?

Patients who fail SSRI treatment for depression may respond to an alternative medication, or the addition of a second medication, according to 2 studies in the March 23 *New England Journal of Medicine*. In the first study, 727 adults with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram (Celexa) were randomized to receive sustained release bupropion

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(Wellbutrin) in a maximal daily dose of 400 mg, sertraline (Zoloft) at a maximum daily dose of 200 mg, or extended release venlafaxine (Effexor-XR) at a maximal daily dose of 375 mg for up to 14 weeks. The primary outcome was remission of symptoms based on the Hamilton Rating Scale of Depression (HRSD-17). Secondary outcomes included scores on the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16). Remission rates, as assessed by the 2 scales, respectively, were bupropion - 21.3% and 25.5%, sertraline - 17.6% and 26.6%, venlafaxine - 24.8% and 25.0%. Response rates based on the QIDS-SR-16 were bupropion 26.1%, sertraline 26.7%, and venlafaxine 28.2%. There was no significant difference with respect to outcomes, tolerability, or adverse effects among the 3 drugs.

The authors conclude that after unsuccessful treatment with an SSRI, 1 in 4 patients have a remission after switching to another antidepressant, and all 3 drugs in the trial were reasonable choices (*N Engl J Med*. 2006;354:1231-1242). Another option for treating patients who failed treatment with citalopram was explored in the second study in the same issue. In the study, 565 adults who had a nonpsychotic major depressive disorder without remission after 12 weeks of citalopram therapy were randomized to receive add-on therapy with sustained release bupropion up to 400 mg per day, and 286 were randomized to receive buspirone (Buspar) at a dose of up to 60 mg per day. The same depression rating scales were used in this study as in the previous study. For bupropion and buspiron, respectively, HRSD-17 remission rate was 29.7% vs 30.1%, QIDS-SR-16 remission rate was 30.9% vs 32.9%, and QIDS-SR-16 response rate was 31.8% vs 26.9%. Bupropion was associated with a greater change in QIDS-SR-16 score, as well as the overall lower QIDS-SR-16 score at the end of the study and a lower dropout rate to due to intolerance (12.5% vs 20.6%, $P < 0.009$).

The authors conclude that the addition of bupropion or buspirone to citalopram is useful; however, the addition of bupropion may have some advantages, including a greater reduction in the severity of symptoms in fewer side effects (*N Engl J Med*. 2006;354:1243-1252).

FDA Actions

The FDA has approved the first generic HIV/AIDS drug for use in the United States. Zidovudine, manufactured under the trade name Retrovir by GlaxoSmithKline, was initially approved in 1987, and the company has had exclusive manufacturing rights until the drug's patent expired in September 2005. The generic is made by Aurobindo Pharma LTD of India. This is the same company that recently received approval from the FDA to co-package 3 antiretroviral drugs for the treatment of HIV/AIDS outside the United States. The regimen consists of lamivudine/zidovudine combination tablet along with efavirenz tablets. The co-packaging of these products has met the clinical safety, efficacy, and manufacturing quality standards required by the FDA. The approval is part of the Presidents Emergency Plan for offering full HIV treatment regimens for targeted areas of the world that are at risk to prevent HIV transmission and to treat AIDS and associated conditions. Patents and exclusivity prevent marketing of this combination in United States.

The FDA has approved a transdermal patch for the treatment of children with attention-deficit hyperactivity disorder. The patch delivers methylphenidate, the same ingredient found in Ritalin, in a daily patch that is applied early in the morning and removed 9 hours later. Methylphenidate patch is manufactured by Shire Pharmaceuticals and Noven Pharmaceuticals under the trade name Daytrana.

Salix pharmaceuticals has received approval to market a new tablet bowel prep for colon cleansing prior to colonoscopy. The virtually tasteless sodium phosphate tablets are an alternative to traditional liquid PEG bowel preps. The recommended dose is 32 tablets taken orally with a total of 2 quarts of clear liquids, administered as 4 tablets with 8 ounces of liquid every 15 minutes. Twenty tablets are given on the night prior to the procedure, with the remaining 12 tablets administered 3 to 5 hours prior to colonoscopy. Sodium phosphate tablets will be manufactured under the trade name OsmoPrep. ■