Critical Care CME Program

Module 2

This CSA CME program's topic is critical care and will consist of eight modules. The second module appears in this issue of the *Bulletin*. The upcoming modules will appear in consecutive seasonal issues of the *Bulletin*. The test questions and evaluation for this module are at the end of this article. Submit answers to the nine questions to the CSA office with the registration page in order to receive the CME credit. Your CME certificate will be mailed from the CSA office.

Alternatively, the full text of each module of this CME program will be accessible through the CSA Web Site, **www.csahq.org**, in the Online CME Program section, and as part of the online *CSA Bulletin*. Instructions to complete Module 2 online are given in the Information pages. After completing the assessment, you may print your CME certificate. Members will need their usernames and passwords to do the modules online.

Important Information about Critical Care Module 2

The following information must be read and acknowledged before proceeding to the rest of the module. Check the acknowledgement box on the registration page.

Faculty/Disclosures

Any faculty participating in continuing medical education activities sponsored by the CSA is required to disclose any real or apparent conflict(s) of interest related to the content of their presentation(s) or any of the industry sponsors of the meeting. In addition, speakers must disclose when a product is not labeled for the use under discussion or when a product is still investigational.

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Dr. Truong has no relevant financial relationships with any commercial interests.

Registration/Instructions

Method of Participation: The physician will read and study the materials and complete a quiz and evaluation of the module. Some modules may have slides available online. To register for and complete this module:

1. First, read and study all of the module pages.
2. Complete the registration page.
3. Go to the test questions that can be found after the article.
4. Complete the quiz and the evaluation that follows.
5. Submit your quiz to the CSA office by mail or fax (650-345-3269).
6. Your CME certificate will be mailed to you.

Estimated Time to Complete the Module: One hour

Availability

Module 2: Ventilator-Associated Pneumonia

Release Date: June 30, 2008
Expiration Date: June 30, 2011

CME Sponsor/Accreditation

The California Society of Anesthesiologists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The California Society of Anesthesiologists Educational Programs Division designates this critical care educational activity for a maximum of 8 *AMA PRA Category 1 Credit(s)™*. Physicians should claim credits commensurate with the extent of their participation in the activity.

Fees

The modules are free to CSA members. Nonmembers pay $25 for each module. Each module is worth one *AMA PRA Category 1 Credit™*

Target Audience

This program is intended for all licensed physicians, including residents.

Evaluation

An evaluation of each module of this series is offered after the test questions.

Privacy Policy

CSA has a privacy policy that is a general policy for information obtained regarding all online interactive pages, including online CME activities. To review this policy, please go to www.csahq.org/privacy.vp.html.

Acknowledgement

To proceed with this module, please acknowledge that you have read everything on these introductory pages by checking the box on the registration page.

Objectives

Upon completion of this CME activity, participants will be able to:

- Discuss incidence and etiology of Ventilator-Associated Pneumonia
- Describe the precision and accuracy of various methods to diagnose VAP
- Discuss management of VAP, including role of antibiotics (monotherapy vs. combination therapy), sedation, oral hygiene, and other available tools
- Describe various methods to prevent VAP
- Discuss clinical and economic consequences of VAP

Ventilator-Associated Pneumonia

By Nitin Shah, M.D., and Co Truong, M.D.

Nitin Shah, M.D., has been a co-chair of the "preventing harm to 5 million patients" committee of Long Beach VAHS. The committee is charged with reducing VAP, catheter related infection, reduction in complications of central venous line, and Rapid Response Team (RRT). He was responsible for creating a RRT in the hospital. His research interests include performance of PVI (Pleth Variability Index) with different levels of PEEP, PtcCO2 and sedation in critically ill patients employing TOSCA monitor.

Co Truong, M.D., is a first year anesthesia resident with a special interest in critical care that she may pursue after anesthesia training.

Incidence & Etiology

Pneumonia is the sixth leading cause of death in the United States, numbering 4.8 million cases per year.[1] Ventilator-Associated Pneumonia (VAP) is a complication in the hospitalized patient, and it is the leading cause of death among patients with hospital-acquired infections.[2] VAP is defined as a parenchymal lung infection occurring more than 48 hours after initiation of mechanical ventilation (MV). The incidence of VAP ranges from 10 percent to 47 percent,[3,4] depending on the patient population and has a mortality of 25 percent to 70 percent.[1] Patients with a VAP have significantly longer stays in the ICU (26 vs. four days) and in hospital (38 vs. 13 days) without VAP.[5]

The presence of an endotracheal tube serves as an abnormal conduit between the upper and lower airway. As a result, secretions from the upper airway and the stomach are in continuity with the pool of secretions that invariably accumulates above the cuff of the endotracheal tube. Secretions are aspirated into the trachea and are disseminated into the lung with each inspiration and with suctioning. Because normal oral flora are rapidly replaced by nosocomial organisms (i.e., gram-negative rods, drug-resistant *Staphylococcus aureus*) in ICU patients, those are dispersed throughout the lungs and lead to VAP. Three distinct patterns of infection (tracheobronchitis, bronchopneumonia, and bronchiolitis) are evident from autopsy studies. The sequential steps of pathogenesis of VAP are:[1]

- Antibiotic therapy and antacid therapy alters the milieu of the mouth and stomach
- Oropharyngeal and gastric colonization by pathogenic, gram-negative organisms
- Development of subglottic secretion pool
- Aspiration of pooled secretions around the cuff of the endotracheal tube
- Aerosolization of the aspirated secretions during the inspiratory phase of the ventilator cycle
- Dispersion of the aerosolized bacteria into the lung
- Development of ventilator-associated pneumonia

Risk factors. Some of the risk factors for development of VAP include: age ≥ 60 years; severity of illness (APACHE II score > 16); acute or chronic lung disease; excessive sedation; enteral nutrition; severe burns; supine body position; Glasgow coma scale < 9; use of muscle relaxants; cigarette smoking; duration of MV.[6]

Diagnosis

VAP is considered the most common nosocomial infection in the ICU.[7] Patients who develop VAP have worse outcomes and have longer ICU and hospital stays.[8] Evaluation of patients suspected with VAP should include a thorough medical history, physical examination, and chest radiograph. Bacterial pneumonias usually present with fever, leukocytosis, purulent sputum and new infiltrate on chest x-ray. The traditional "gold standard" for the diagnosis of VAP is an open lung biopsy, which is rarely employed and is susceptible to confounding factors such as sampling error. Two studies compared autopsy evidence of pneumonia with the premortem diagnosis of VAP based on clinical findings, and they concluded that the clinical criteria for diagnosing pneumonia were just as likely to occur in the presence as in the absence of pneumonia.[9,10]

The National Nosocomial Infection Surveillance System (NNIS)[11] is a diagnostic algorithm that uses clinical microbiological data to aid in the standardization of criteria for reporting nosocomial pneumonia. The clinical pulmonary infection score (CPIS)[12] has also been used to improve consistency among clinicians in their diagnosis of pneumonia. However, in trauma patients when the results of using bronchoalveolar lavage (BAL) results were defined as the standard criterion, the NNIS criteria had a sensitivity of 84 percent and specificity of 69 percent.[11] The CPIS has also not consistently demonstrated either an improvement in diagnostic accuracy when used as an adjunct in clinical decision making, or reproducibility of scoring when used as a research tool to classify patients.[12,13]

The standard practice for the evaluation of VAP is to aspirate secretions through an endotracheal or tracheostomy tube and then to perform qualitative cultures on the aspirates. However, tracheal aspirate (TA) cultures have high sensitivity but very low specificity in the diagnosis of pneumonia.[14] The technique of Protected Specimen Brushings (PSB) was developed to collect uncontaminated secretions through a bronchoscope, but it has a reported low sensitivity and high specificity in the confirmation of pneumonia.[15] BAL is another technique that can be performed with and without a bronchoscope. A meta-analysis of 23 studies of the use of BAL in the diagnosis of VAP reported a sensitivity of 22 percent to 93 percent and a specificity of 45 percent to 100 percent.[16] A randomized trial comparing quantitative culture of BAL fluid and nonquantitative culture of endotracheal aspiration revealed similar clinical outcomes and antibiotic use.[17]

For quantitative cultures, thresholds applied for the diagnosis of VAP are 10^3 colony-forming units per milliliters (cfu/ml) for PSB, 10^4 (cfu/ml) for BAL, and 10^5 cfu/ml for TA.[18] Cfu is a measure of viable bacterial or fungal numbers.

However, qualitative measurements can also be utilized in the diagnosis of VAP. A gram-stain of secretions can be helpful in determining if aspirates originated from the upper or lower airways. Furthermore, a negative TA smear in patients whose antibiotic therapy has not been changed in three days has a negative predictive value of 94 percent for VAP.[19]

The volume of lavage fluid and prior antibiotic use will have an impact upon the accuracy of any test. Ideally, samples should be obtained prior to antibiotic treatment. Because an open lung biopsy is rarely used in the diagnosis of VAP, the other techniques will be chosen, according to the experience of the personnel performing the procedure, the risks to the patient, and the cost.

Management

There is a definite trend to start antibiotic therapy at the earliest suggestion of VAP. The imperative to start antibiotics early is based upon some studies that show that even relatively short delays in initiating antibiotic therapy are associated with an increased mortality rate.[20] However, there are other studies that conclude that there is no increase in mortality in VAP with a delayed start of antibiotics.[21] The duration of MV has been associated with increased risk for VAP. There may be a rationale for the use of a nurse-implemented sedation protocol to reduce the duration of MV and the rate of VAP as shown in a prospective, controlled study.[22]

Inadequate treatment of pathogens is the most common reason for treatment failure with initially prescribed antibiotics. Commonly reported drug-resistance pathogens are *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), but resistant *Acinetobacter* species and *Klebsiella* species are also common in many hospitals. Thus, the antibiotic selection should be based on the risk factors for multidrug-resistance (MDR) pathogens and the local hospital antibiogram. The most important risk factors for MDR organisms are duration of MV and hospitalization, and also prior antibiotic exposure.[23] Adequate initial antibiotic therapy is crucial in reducing mortality from VAP, and patients who are at greatest risk for MDR pathogens should have initial broad coverage based on the local antibiogram. Current guidelines recommend two drugs of different classes active against Pseudomonas and one for MRSA.

A recommended regimen[24] includes (1) an antipseudomonal cephalosporin (cefepime, ceftazidime), or an antipseudomonal carbepenem (imipenem, meropenem) or a B-lactam/B-lactamase inhibitor (piperacillin/tazobactam); plus (2) an antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin), or an aminoglycoside (amikacin, gentamicin, tobramycin); plus (3) either linezolid

or vancomycin. Consideration of prior antibiotic exposure within the past two weeks should be taken into account when deciding an initial empiric regimen, as this may predispose the patient to resistance to that class of antibiotics. A narrow-spectrum antibiotic is recommended for patients who do not have risk factors for MDR organisms, and may include ceftriaxone or a fluoroquinolone, or ampicillin/sulbactam or ertapenem.

Empiric combination therapy, especially for Gram-negative bacilli including *Pseudomonas aeruginosa* infection, has been recommended given the higher mortality rate associated with these pathogens.[24-27] It is believed that increased success with combination therapy is secondary to synergy between antibiotics and prevention of resistant organisms.[28-30] However, a recent meta-analysis of randomized controlled trials showed that the rates of mortality and treatment failure were similar among groups receiving monotherapy and combination therapy.[31] Further, a separate meta-analysis of monotherapy vs. combination therapy found that combination therapy did not reduce the rate of emergence of resistance organisms during treatment.[32] An observational, multicenter study concluded that initial use of combination therapy significantly reduced the likelihood of inappropriate therapy, but appropriately administered monotherapy had similar outcomes compared to combination therapy, therefore suggesting that switching to monotherapy after the susceptibility is documented is feasible and safe.[33] In addition, de-escalation of initial empiric combination therapy, when appropriate based on the patient's history and clinical status, may reduce the emergence of resistant organisms.[34] The search for prognostic markers to aid in evaluating the appropriateness of antibiotic treatment has yielded some promising results. C-reactive protein as a prognostic marker in patients with VAP was useful in evaluating for effectiveness of antibiotic therapy.[35]

Antibiotic dosages that are spaced at appropriate intervals are necessary for the effective management of VAP. Inadequate dosing and excessive duration of treatment are risk factors for the emergence of resistant organisms. With the exception of patients with nonfermenting Gram-negative bacilli VAP, patients receiving adequate initial therapy had similar clinical outcomes when treated with an eight-day course of antibiotics as compared to 15-days.[36] Increased risk for recurrence was seen in patients infected with *Pseudomonas aeruginosa* or *Acinetobacter* species who were treated only with an eight-day course of antibiotics. A recent pilot study investigating repeat BAL in guiding treatment for VAP (including nonfermenting Gram-negative bacilli VAP) showed similar outcomes in incidence of relapse, ventilator-free ICU days, ICU-free hospital days, and mortality in patients whose antibiotic duration was shortened based on BAL results.[37]

Clinical improvement following initiation of antibiotic treatment usually takes two to three days, and this is also the usual time interval for microbiologic cultures to return. Thus, if cultures are reported as negative in this time frame, it is more likely that the pulmonary insult is secondary to a noninfectious etiology and it is reasonable to stop antibiotic therapy. Also, unless the patient has declined clinically during this interval, antibiotic therapy should not be changed, unless culture results dictate otherwise.

Prevention

Prevention is crucial in reducing VAP. In order for VAP to develop, pathogens must reach the lower airways either through contiguous spread, inhalation, hematogenous routes, and, most commonly, aspiration. The presence of a nasogastric tube and supine positioning promotes aspiration of gastric contents. However, a prospective, randomized study showed that a semirecumbent position (28º vs. 10º) did not prevent the development of VAP.[38] Of note, the targeted semirecumbent position of 45º was not achieved in this study. Aspiration is also seen in cases of gastric overdistension. Thus, it is important routinely to verify positioning of nasogastric tubes and to stop feedings should residual volumes exceed greater than 200 ml. Prevention of contiguous spread can be achieved with oral care and topical antiseptics. Naturally, the first step in preventing transmission begins with good hand hygiene from healthcare personnel.[39] Oral antiseptic rinse with chlorhexidine has also been shown to be effective in preventing VAP, especially in cardiac surgery patients.[40] Because secretions from the oropharynx tend to pool above the endotracheal cuff with the potential to leak down to the lower airways, one should consider the use of subglottic secretion drainage via specially designed endotracheal tubes, which were developed and shown to be effective in preventing VAP.[41]

Because the endotracheal tube also serves as a nidus for bacteria growth, which may lead to contiguous spread to lower airways, prevention of these biofilms may also have a role in prevention of VAP. A randomized clinical trial in humans of silver-coated endotracheal tubes, which were effective in preventing VAP in a dog model, is currently being conducted.[42] Although increasing the frequency of ventilator circuit changes has not been shown to be effective in preventing VAP,[43] it is important to be vigilant regarding the risk of flushing possibly contaminated circuit condensate down the lower airways. In addition, the role of heat/moisture exchangers (HME) has come into question in the prevention of VAP. In a meta-analysis, there was a reduction in the relative risk of VAP with the use of HME.[44] However, a randomized study showed no benefit with the use of HME in the prevention of VAP.[45]

Unplanned extubation with subsequent reintubation has been associated with an increase risk for VAP.[46] Thus, the use of adequate tube fixation, patient restraints, and appropriate sedation should be implemented when necessary. Lastly, the risk of developing VAP is associated with duration of MV; hence, the use of weaning protocols should be encouraged to aid in early extubation.[47]

Clinical and Economic Consequences

Advancements in medicine have helped us to be able to take care of older and sicker patients. This has required increased use of the ventilator. As use of ventilators increases, so will the incidence of VAP. Increase of VAP will present a significant challenge because it increases morbidity, mortality and monetary cost. VAP is likely to lead to two-fold increase in ICU mortality.[27] To parse the contribution to mortality attributable to VAP (and, therefore, modifiable by the prevention of VAP) is very problematic because there are multiple factors responsible for mortality. Overall, patients in the medical ICU had a higher fatality rate than patients in the surgical ICU (18 percent vs. 10 percent, $p < .0001$); however, the mortality rate from nosocomial infection was not significantly different between medical and surgical ICU (8 percent vs. 6 percent). In a study of 1,118 patients receiving MV, VAP was associated with a one and half-fold increased risk of death (odds ratio, 1.51; 95 percent CI, 1.11-2.03), after adjusting for severity of illness, presence of organ dysfunction, and underlying disease.[48]

To determine economic consequences of VAP is extremely difficult. Many studies have tried to identify the cost related to VAP; unfortunately, the methodology used varies, and hence we are unable to compare the cost among different institutions. Relying on hospital charges will lead to overestimation of cost.[49,50] Estimated mean billed hospital charges were significantly greater for patients with VAP ($104,983 vs. $63,689) than for patients without VAP ($p < .001$).[49] Microcosting is a method used to capture costs associated with patterns of resource use. Estimated costs associated with VAP in 2001 were $5,365, using microcosting that included the cost of increased ICU length of stay, diagnostic tests, and therapeutic antibiotics directed toward treating VAP.[51]

In summary, VAP occurs in a considerable proportion of patients undergoing MV and is associated with substantial morbidity, a two-fold mortality rate, and increased cost.

References are available upon request to the CSA office at csa@csahq.org and are included in the online CSA Bulletin.

Questions

1. All the following are risk factors for the development of VAP, except:
    a. Chronic lung disease
    b. Severe burns
    c. Supine body position
    d. Cigarette smoking
    e. APACHE II score less than 16

2. In the evaluation of VAP, tracheal aspirate cultures have a higher sensitivity but lower specificity as compared to cultures from protected specimen brush.
    a. True
    b. False

3. What is the quantitative threshold applied for bronchoalveolar lavage (BAL) in the diagnosis of VAP?
    a. 10^2 cfu/ml
    b. 10^3 cfu/ml
    c. 10^4 cfu/ml
    d. 10^5 cfu/ml

4. Which of the following is not considered a commonly reported multidrug-resistant pathogen?
    a. *Pseudomonas aeruginosa*
    b. *Streptococcus pneumoniae*
    c. *Acinetobacter* species
    d. Methicillin-resistant *Staphylococcus aureus* (MRSA)

5. Antibiotics recommended in the treatment of VAP caused by *Pseudomonas aeruginosa* include all the following, except:
    a. Cefepime
    b. Meropenem
    c. Imipenem
    d. Ceftazidime
    e. Ampicillin/Sulbactam

6. Excessive duration of antibiotic treatment is a risk for the emergence of resistant organisms.
    a. True
    b. False

7. Which of the following is the most common route in pathogenesis of VAP?
    a. Contiguous spread
    b. Inhalation of aerosolized bacteria
    c. Hematogenous spread
    d. Aspiration

8. Which of the following has not shown to be effective in the prevention of VAP?
   a. Oral antiseptic rinse
   b. Frequent circuit changes
   c. Avoiding gastric overdistension
   d. Preventing subglottic secretion pool

9. Determination of cost associated with VAP is extremely difficult as multiple factors are responsible and it is impossible to standardize all of them.
   a. True
   b. False

Evaluation of Module 2

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

2. How relevant was the information in this program to your clinical practice?

Very Relevant	5	Above Average	4
Average	3	Below Average	2
Not Relevant	1		

3. How would you rate this program overall?

Excellent	5	Above Average	4
Average	3	Below Average	2
Poor	1		

4. Did you detect any commercial bias in this module? Yes No

Critical Care CME Program

In this issue of the *Bulletin*, Module 2 of the new Critical Care CME Program is available. There will be eight modules for this program. After each module is published in the *CSA Bulletin* (one per season), it is posted on the CSA Web Site at www.csahq.org. Each online module uses a self-assessment and evaluation; once these are completed, you may print your CME certificate. You may also contact the CSA office at 800-345-3691 to obtain the materials by fax or mail.

Registration

Complete this form, the test, and the evaluation, and **mail or fax** all three to the CSA office at 951 Mariner's Island Boulevard #270, San Mateo, CA 94404 or FAX to 650-345-3269. The CSA CME journal courses are also available on the CSA Web Site at www.csahq.org.

Critical Care CME Course, Module 2
Available June 30, 2008, to June 30, 2011

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