Management of MRSA Infections in the Intensive Care Unit: Focus on Pneumonia

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NEEDS STATEMENT

The purpose of this course is to provide participants with appropriate strategies for managing multidrug-resistant (MDR) organisms and methicillin-resistant *Staphylococcus aureus* (MRSA) in the intensive care setting, with a primary focus on the management of pneumonia. In addition, the course aims to familiarize readers with essential concepts from the updated "Guidelines for the Management of Adults with Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia," issued by the American Thoracic Society and the Infectious Diseases Society of America in 2005 (*Am J Respir Crit Care Med.* 2005;171:388-416).

Release Date: December 2005

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TARGET AUDIENCE

This educational program is intended for physicians, physicians assistants, and pharmacists involved in the treatment of patients with MRSA-related infections.

Despite advances in antimicrobial therapy and improvements in supportive care and prevention, methicillin-resistant *Staphylococcus aureus* (MRSA) infections remain a significant challenge in the intensive care unit (ICU). Such infections are significant causes of morbidity, mortality, and increased patient cost. Of the 2 million nosocomial infections acquired annually in the United States, approximately 60% involve antibiotic-resistant bacteria (defined as resistant to 1 or more agents).[1] Overall, more than 50% of nosocomial *S. aureus* infections are methicillin-resistant, with associated treatment costs ranging from $100 million to $30 billion, based on various estimates.[1,2] Furthermore, such infections are increasing in prevalence.[3] For these reasons, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) recently developed new guidelines for the management of nosocomial pneumonia caused or exacerbated by MRSA; however, MRSA can also invade other anatomic sites.[4]

Overview of MRSA Infections

The MRSA infections typically seen in the ICU are pneumonias, bacteremic infections, and infections of traumatic and surgical wounds. Because of their virulence, much of the study of MRSA infections is focused on the nosocomial pneumonias. These are

LEARNING OBJECTIVES

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

1. Demonstrate knowledge of the effect of MDR organisms in the intensive care unit setting.
2. Describe the distinction between hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP).
3. Identify key principles outlined in the current guidelines for the diagnosis and treatment of HAP, VAP, and HCAP, including empiric treatment, dosing, and de-escalation.
4. Identify primary clinical concerns regarding MDR organisms, particularly MRSA, with regard to infections other than pneumonia.

ACCREDITATION STATEMENTS

Physician: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Kentucky College of Medicine and McMahon Publishing Group. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.
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This program has been assigned ACPE No. 022-999-05-096-H01 and will award 1 contact hours (0.1 CEUs) of continuing pharmacy education credit in states that recognize ACPE providers. The college complies with the Criteria for Quality for continuing education programming.
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METHOD OF PARTICIPATION

There are no fees for participating and receiving credit for this activity. The participant should, in order, read the objectives and monograph and answer the multiple-choice post-test. Participation is available online at CMEZone.com. Enter the project number "CE221" in the keyword field to directly access this activity and receive instantaneous participation. Or, complete the answer sheet with registration and evaluation on page TK and mail to: Attn: Distance Education, Continuing Education Office, Colleges of Pharmacy and Medicine, University of Kentucky, 1 Quality St, 6th Fl, Lexington, KY 40507-1428. Certificates will be mailed to participants approximately 4 weeks after receipt of the mailed or faxed submissions. This credit is valid through December 31, 2006.

ESTIMATED TIME OF COMPLETION

This activity should take approximately 1 hour to complete.

SUPPORT STATEMENT

This activity is supported by an unrestricted educational grant from Pfizer, Inc.

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Expiration Date: December 31, 2006

categorized as hospital-acquired pneumonia (HAP), which includes 2 subtypes: ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP).[4]

The most common route for the acquisition of bacteremic infections is the I.V. catheter,[5,6] with MRSA one of the most common causes of catheter-related bloodstream infections (CR-BSIs). Although such infections are generally acquired nosocomially, they can also be acquired in the community[7]; for example, MRSA infections of postoperative wounds are often seen among patients admitted from nursing homes to acute care facilities.[8] Common risk factors for MRSA infections are listed in Table 1.

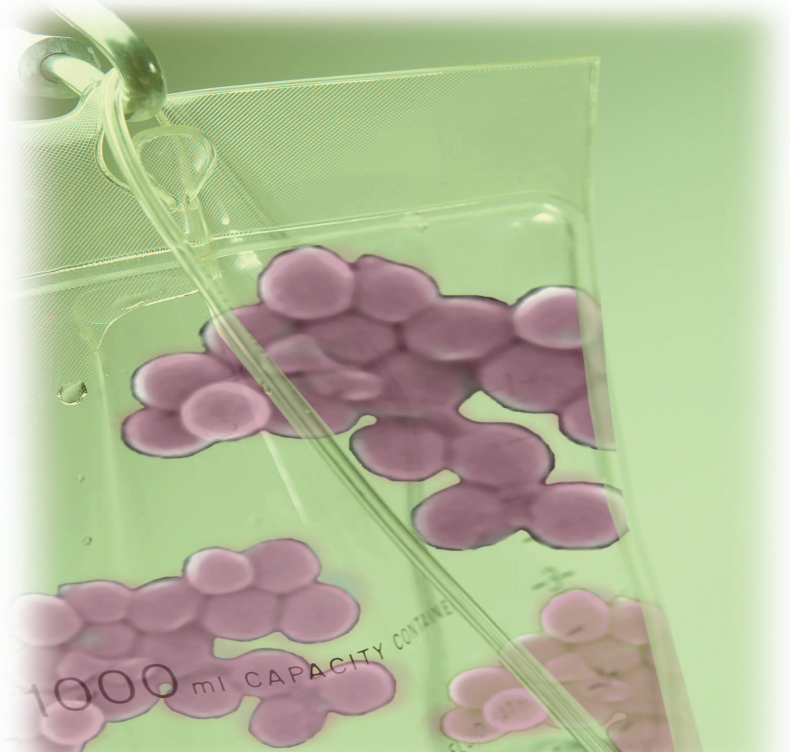

Table 1. Risk Factors For MRSA Infection

Advanced age
Male gender
Previous hospitalization
Long hospitalization
Stay in an intensive care unit
Chronic medical illness
Prior and prolonged antimicrobial use
Presence of a wound; risk increases with size
Exposure to colonized or infected patient
Presence of invasive indwelling devices

Epidemiology of MDR MRSA

MRSA is often resistant to antibiotics outside the β-lactam class. As a result, some strains may be referred to as multidrug-resistant MRSA, or MDR MRSA. Although other antibiotic-resistant pathogens exist, MDR MRSA is the most common,[3] and its prevalence is increasing. HAP caused by MDR MRSA, for example, affects 25% of all ICU patients and accounts for 50% of prescriptions for antibiotics. VAP occurs in 9% to 27% of all intubated patients; HCAP is often secondary to viral influenza.[4]

Several factors increase a patient's risk for acquiring a respiratory infection with MDR MRSA, including the following[4]:

- having received antimicrobial therapy within the preceding 90 days
- being hospitalized for >5 days
- high rates of antibiotic resistance in the community at large or within a specific hospital unit
- having known risk factors for HCAP
- having an immunosuppressive disease or receiving immunosuppressive therapy.

Among patients with trauma, head injuries, abdominal injuries, ICU stays of more than 7 days, and treatment with glycopeptide antimicrobials are associated with MDR MRSA infection.[9] In addition to MDR MRSA, other strains of drug-resistant *S. aureus* are emerging as clinical concerns. These include glycopeptide–intermediately resistant *S. aureus* and vancomycin-resistant *S. aureus* (VRSA). Although rare, infections caused by these organisms are associated with high rates of morbidity and mortality.[10,11]

Various investigators have reported similar findings regarding length of hospital stay and economic costs related to resistant infections. For example, in 1999, Heyland and colleagues demonstrated that patients with VAP are 5.8% more likely to die than are comparable intubated patients without VAP[12]; infected patients remained in the ICU on average 4.3 days longer than those who did not contract MDR MRSA infection. Cosgrove et al found that patients infected with MRSA had hospital stays 30% longer and hospital charges 35% higher than those of patients with infections that responded to methicillin.[13] Others have reported similar findings.[14]

Updated ATS–IDSA Guidelines

The ATS–IDSA guidelines published in 2005 are an updated version of those issued by the same organizations in 1996.[4] As stated earlier, the updated guidelines recognize new subcategories of HAP (VAP and HCAP) and include information about their epidemiology and pathogenesis, in addition to the modifiable risk factors associated with them. HAP, for example, is defined as a pneumonia occurring 48 hours or more after admission in a patient who did not have pneumonia at the time of admission; VAP refers to pneumonia developing more than 48 to 72 hours after endotracheal intubation.

HCAP is described as pneumonia developing in a patient in any of the following circumstances[4]:

- hospitalized in an acute care setting for >2 days within 90 days of the current infection
- residing in a nursing home or long-term care facility
- receiving I.V. antibiotic therapy, chemotherapy, or wound care within 30 days of the current infection
- receiving outpatient care in a hospital or hemodialysis clinic.

The subtypes of HAP are also differentiated according to the type of bacterial infection involved. Among gram-negative bacilli, common underlying pathogens include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter*. Among gram-positive bacteria, *S. aureus* (eg, MRSA) is common, particularly in patients with diabetes mellitus, with head trauma, or admitted to an ICU.[4]

Diagnosing HAP

The ATS–IDSA guidelines note that a definitive diagnosis of HAP is often challenging. The guidelines identify 10 points that should be addressed before a diagnosis of HAP is made (Table 2).[4]

These steps address several ambiguities in the diagnosis of HAP. For example, if HAP is suspected, a chest X-ray is typically ordered. If the X-ray shows a new or progressive infiltrate along with clinical findings suggesting infection, HAP may be present but is not confirmed. Other suspect clinical findings include a new onset of fever, purulent sputum, leukocytosis, and a decline in oxygenation. However, a diagnosis of tracheobronchitis may be appropriate if the patient has fever, leukocytosis, purulent sputum, and a positive culture of either sputum or a tracheal aspirate but no new lung infiltrate.

In mechanically ventilated patients, nosocomial tracheobronchitis is linked to a longer ICU stay and longer periods of mechanical ventilation, but not to increased mortality. However, because antibiotic treatment may prevent subsequent pneumonia, which is linked to increased mortality, physicians may want to consider antibiotic treatment in such patients, according to the guidelines.[4]

Modifiable Risk Factors

The updated guidelines identify several modifiable risk factors for HAP, including the following[4]:

- intubation, particularly nasotracheal and nasogastric intubation, and mechanical ventilation
- recumbent versus semirecumbent positioning
- enteral nutrition
- oropharyngeal colonization
- prophylactic agents to prevent stress bleeding.

Several actions are recommended to modify these risks. These include vigorous infection control measures and surveillance of ICU infections, avoidance of intubation if possible, and use of noninvasive ventilation when possible. Recommended measures also include using orotracheal and orogastric tubes instead of nasotracheal and nasogastric tubes, placing the patient in a semirecumbent position (30-40 degrees), and in some cases administering oral antiseptics and oral antibiotics to reduce the risk for the migration of colonization. Leukocyte-depleted

Table 2. Major Diagnostic Points and Recommendations

1. **Obtain comprehensive medical history and physical examination:**
   a. to define the severity of HAP.
   b. to exclude other potential sources of infection.
   c. to reveal the presence of specific conditions that can suggest the likely etiologic pathogens.
2. **Obtain chest radiograph for every patient with suspected HAP who is not intubated, preferably posteroanterior and lateral:**
   a. to determine the severity of pneumonia.
   b. to identify any complications (eg, effusions or cavitation).
3. **Measure arterial oxygenation saturation in all patients to determine the need for supplemental oxygen.**
4. **Measure arterial blood gases:**
   a. to identify metabolic or respiratory acidosis.
   b. to manage patients who require mechanical ventilation.
   c. to identify multiple organ dysfunction and gauge the severity of illness (in combination with laboratory studies such as complete blood cell count, measurement of serum electrolytes and parameters of renal and hepatic function)
5. **Obtain blood cultures in patients with suspected VAP. A positive result can indicate either pneumonia or extrapulmonary infection.**
6. **Obtain a diagnostic thoracentesis to rule out a complicating empyema or parapneumonic effusion if the patient has a large pleural effusion or if a pleural effusion develops.**
7. **Obtain samples of lower respiratory tract secretions before any changes of antibiotics by one of the following methods:**
   a. endotracheal aspiration.
   b. bronchoalveolar lavage.
   c. protected specimen brush sampling.
8. **If the patient has tracheobronchitis instead of HAP:**
   a. antibiotic therapy may be helpful in some cases.
   b. antibiotics and respiratory tract cultures are not necessary if HAP is not suspected clinically.
9. **A sterile culture of respiratory secretions virtually rules out bacterial pneumonia if no new antibiotics have been used in the prior 72 hours, although viral or *Legionella* infection is still possible. In such cases, investigate an extrapulmonary site of infection.**
10. **In a patient with ARDS and at least one sign of pneumonia, pursue further diagnostic testing.**

ARDS, acute respiratory distress syndrome; **HAP**, hospital-acquired pneumonia; **VAP**, ventilator-associated pneumonia

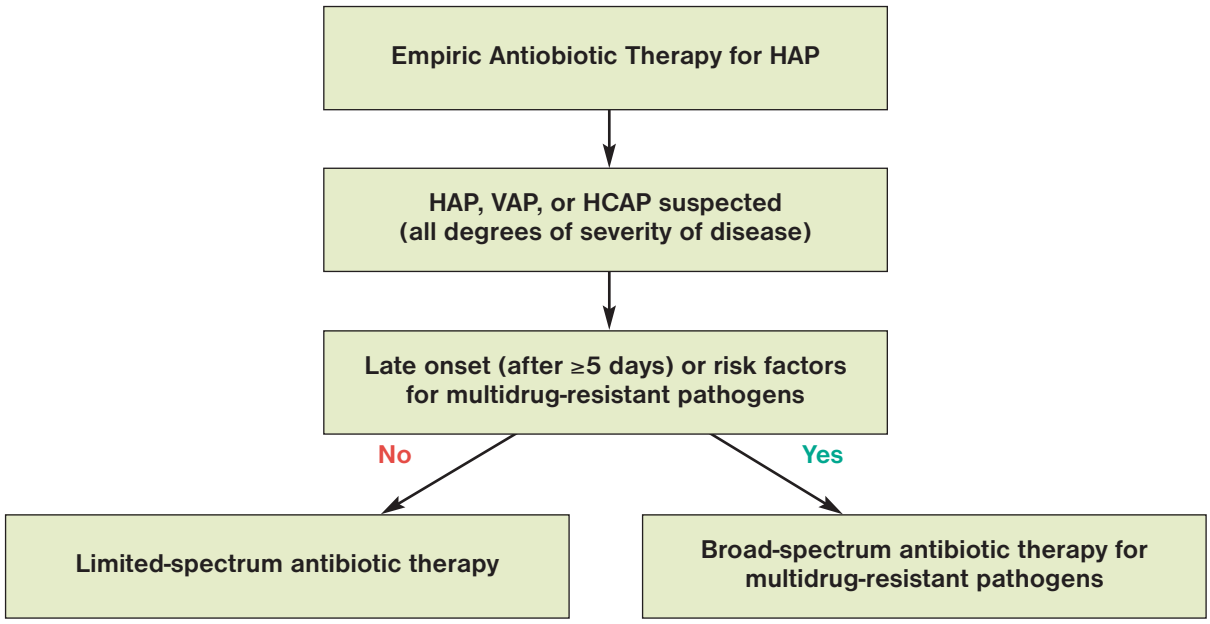

Figure. Algorithm for initiating empiric antibiotic therapy for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP).

Adapted from reference 4.

transfusions of red blood cells and rigorous glucose control in patients with diabetes should also be considered.[4]

Educating staff about these modifiable risk factors for VAP is effective in reducing its incidence.[15] In one study involving 4 hospitals, investigators found that VAP rates dropped an average of 46% after implementation of an education intervention designed to prevent VAP. In the year before the intervention, the rate was 8.75 per 1,000 ventilator days, whereas during the 18-month period following the intervention, the VAP rate dropped to 4.74 per 1,000 ventilator days ($P<0.001$). In a community hospital where the rate of compliance with the educational protocol was lowest, however, the investigators observed no change in VAP incidence rates.[15]

Antibiotic Treatment Options

The ATS–IDSA guidelines stress the importance of promptly administering empiric antibiotic therapy—because of the risk for excessive mortality associated with delayed antimicrobial treatment—and of screening patients for risks for MRSA and other MDR organisms. Patients with infection beginning within the first 4 days after hospitalization are to be considered at high risk, as are those transferred from nursing homes or cared for at facilities such as dialysis centers. According to an algorithm developed in the guidelines, patients at low risk for HAP, VAP, and HCAP can be treated with limited-spectrum antibiotics, but high-risk patients should be treated with broad-spectrum agents (Figure).[4] Limited-spectrum agents include ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin,

ampicillin-sulbactam, and ertapenem. Broad-spectrum agents include cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, amikacin, gentamicin, tobramycin, linezolid, and vancomycin.

Combination therapy is recommended for patients at high risk for infection with MDR and MRSA pathogens. This approach typically consists of 3 antibiotic agents. The guidelines recommend the following combinations: an antipseudomonal cephalosporin or carbapenem or a ß-lactam with a ß-lactamase inhibitor, plus an antipseudomonal fluoroquinolone or an aminoglycoside, plus linezolid or vancomycin. In cases of MRSA infection, regardless of the infection site, adequate tissue penetration is critical for patients to benefit from treatment. With linezolid, for example, I.V. dosing of 600 mg every 12 hours is considered necessary in adults for adequate antibiotic penetration of lung tissue.[16] With vancomycin, the comparable recommended dosage is 15 mg/kg every 12 hours in patients with normal renal function.[4]

Adequate antibiotic dosing for an appropriate length of time is essential to the successful treatment of patients at risk for MDR infections. Table 3 shows the recommended I.V. doses of antibiotics used to treat adult patients with HAP who are risk for MDR infections.[4]

The appropriate duration of therapy depends on the nature of the infection and whether the patient has shown an adequate initial response to therapy. In patients with a good initial response to treatment and in whom clinical features of the infection have resolved, the guidelines recommend shortening the duration of treatment from the typical 14 to 21 days to 7 days. This recommendation is based on findings that longer treatment is associated with recurrent colonization by resistant organisms. In patients with *P. aeruginosa* infection, however, the recommended duration of treatment is still 14 to 21 days.

After empiric treatment has begun, a response is typically seen within 48 to 72 hours. During that time, no changes in therapy are recommended unless the patient's condition is deteriorating. After day 3, if the patient has not responded, the clinician should reassess the clinical parameters. If the patient is responding, the clinician should consider the culture data obtained before antibiotic therapy was begun and de-escalate the antibiotics by using the narrowest possible treatment regimen based on the culture data. Proponents of de-escalation define it as a method of providing appropriate initial treatment to patients with serious bacterial infections while avoiding the improper use and/or overuse of antibacterial agents. The goal of this approach is to prevent the development of resistance.[17]

Protein Synthesis

A few studies have linked the prevention of protein synthesis to the effective treatment of infection with MDR organisms, although further study is needed. Blocking protein synthesis in turn inhibits the production of microbial toxin. An important in vitro proof-of-concept study demonstrated that linezolid inhibits the synthesis of proteins that are essential to cell division in several targeted organisms, including *E. coli*.[18] Quinupristin-dalfopristin has demonstrated the ability to impair bacterial protein synthesis at both the early step of peptide chain elongation and the late step of peptide chain extrusion and has bacteriostatic activity against vancomycin-resistant *Enterococcus faecium*.[19] Several classes of antibiotics—including the macrolides, tetracyclines, aminoglycosides, and oxazolidinones—have demonstrated the ability to inhibit protein synthesis.

Table 3. Initial I.V. Adult Doses of Antibiotics for Empiric Therapy of HAP, VAP, And HCAP

Antibiotic	Dosage*
Antipseudomonal cephalosporins	
Cefepime	1-2 g q8-12h
Ceftazidime	2 g q8h
Carbepenems	
Imipenem	500 mg q6h or 1 g q8h
Meropenem	1 g q8h
β-Lactam/β-lactamase inhibitor	
Piperacillin-tazobactam	4.5 g q6h
Aminoglycosides	
Gentamicin	7 mg/kg per day†
Tobramycin	7 mg/kg per day†
Amikacin	20 mg/kg per day†
Antipseudomonal quinolones	
Levofloxacin	750 mg qd
Ciprofloxacin	400 mg q8h
Vancomycin	15 mg/kg q12h‡
Linezolid	600 mg q12h

Note: Doses are those recommended for patients with late-onset disease or risk factors for multidrug-resistant pathogens.
* Dosages are for patients with normal renal and hepatic function.
† Trough levels for gentamicin and tobramycin should be <1 g/mL, and for amikacin they should be <4 to 5 g/mL.
‡ Trough levels for vancomycin should be 15 to 20 g/mL.
HAP, hospital-acquired pneumonia; **HCAP**, healthcare-associated pneumonia; **VAP**, ventilator-associated pneumonia
Adapted from reference 4.

I.V.-to-Oral Switch

The ATS–IDSA guidelines call for treating all patients who have nosocomial pneumonia with I.V. formulations of antibiotics initially. Depending on the treatment regimen, physicians can then change to oral or enteral formulations if the patients are responding and the functioning of their gastrointestinal tract is intact.[4] As examples, quinolones—such as levofloxacin—and linezolid are produced in I.V. formulations with bioavailability equivalent to that of their oral counterparts. Switching to oral therapy can reduce the costs associated with the preparation and administration of I.V. drugs and a prolonged hospital stay. Oral therapy also reduces the inconvenience and risk for new infection associated with an indwelling catheter and extended hospital stay.

Conclusion

Because of the serious nature of infection with MDR pathogens, appropriate management is critical, both for the sake of affected patients and to prevent the spread of infection. Therefore, the new ATS–IDSA guidelines for managing all subtypes of HAP will have a far-reaching effect and require the attention of those who treat patients critically ill with pulmonary and/or infectious disease. Furthermore, because several of the MDR pathogens affect organ systems such as the skin and surrounding structures, as well as the deep organs and circulatory system, the management approaches listed in the guidelines may influence the practice of clinicians beyond those involved in respiratory care. They may be useful to diabetes experts and those who treat patients susceptible to cutaneous infections, surgeons who treat deep wound infections, and providers of care to patients affected with immunosuppression.

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CME Post-test

1. **Of all *Staphyloccus aureus* infections, what percentage are methicillin-resistant?**
   a. 40%
   b. 20%
   c. 10%
   d. 50%

2. **Which of the following factors increases the risk for acquiring a respiratory infection with multidrug-resistant MRSA?**
   a. Antimicrobial therapy within the preceding 90 days
   b. Hospitalization for >5 days
   c. Immunosuppressive disease
   d. All of the above

3. **According to the ATS–IDSA guidelines, which of the following would NOT be considered HCAP?**
   a. Pneumonia developing in patients residing in nursing homes or long-term care facilities
   b. Pneuomonia developing in known injection drug users
   c. Pneuomonia developing in patients receiving I.V. antibiotic therapy
   d. All of the above would be considered HCAP.

4. **According to the ATS–IDSA guidelines, HAP is diagnosed in nonintubated patients via _____.**
   a. chest X-ray
   b. bronchoscopy
   c. sputum culture
   d. none of the above

5. **Measures recommended by the ATS–IDSA to reduce the risk for HAP include use of the following:**
   a. orotracheal and orogastric tubes
   b. nasotracheal and nasogastric tubes
   c. the semirecumbent position
   d. both a and c

6. **Which of the following is NOT a limited-spectrum antibiotic?**
   a. Moxifloxacin
   b. Cefepime
   c. Ceftriaxone
   d. Ampicillin-sulbactam

7. **Which of the following agents has demonstrated the ability to inhibit protein synthesis?**
   a. Meropenem
   b. Gentamicin
   c. Linezolid
   d. Moxifloxacin

8. **To achieve adequate tissue penetration, levofloxacin should be administered at a dose of _____ per day, according to the ATS–IDSA guidelines.**
   a. 750 mg qd
   b. 20 mg
   c. 10 mg/mL
   d. none of the above

9. **Antibiotic de-escalation is defined as _____.**
   a. reducing the cost of therapy
   b. shortening hospital stays
   c. a method for avoiding the overuse of antibacterial agents
   d. cutting antibiotic prices

10. **According to the ATS–IDSA guidelines, all patients with nosocomial pneumonia should initially be treated with _____ formulations of antibiotics.**
    a. IM
    b. oral
    c. enteral
    d. I.V.

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Answer Sheet & Evaluation Form

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2.	a	b	c	d	**7.**	a	b	c	d
3.	a	b	c	d	**8.**	a	b	c	d
4.	a	b	c	d	**9.**	a	b	c	d
5.	a	b	c	d	**10.**	a	b	c	d

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