2. CPAP can be used only with patients who have which of the following characteristics?
   A. Have high P_aCO_2 levels
   B. Can breathe spontaneously
   C. Are hypovolemic
   D. Have central sleep apnea

3. A PEEP study is being performed on a patient. When the PEEP is increased from +10 cm H_2O to +15 cm H_2O, cardiac output decreases from 4 L/min to 2 L/min. What would be the next most appropriate step?
   A. Decrease F_IO_2
   B. Administer whole blood
   C. Decrease PEEP to + 10 cm H_2O
   D. Make no changes at this time

4. The following table represents a PEEP study for a patient with ARDS. Which PEEP level represents the optimum one for the patient?

	A	B	C	D
PEEP (cm H_2O)	5	8	12	15
PvO_2 (mm Hg)	35	37	39	34
$C[a-\bar{v}]O_2$ (mL/100 mL)	3.7	3.6	3.8	4.1
Cardiac output (L/min)	7.6	7.5	7.6	6.3
Cardiac output × C_aO_2 (mL/min) (O_2 transport)	875	865	950	825

5. During mechanical ventilation with VC-CMV, the PEEP level is set at +10 cm H_2O and PIP is 34 cm H_2O. The PEEP is increased to +15 cm H_2O and PIP rises to 40 cm H_2O. The rise in PIP indicates which of the following?
   A. A normal occurrence when PEEP is increased
   B. A bronchospasm
   C. The presence of a pneumothorax
   D. That compliance had changed

6. A 38-year-old man with ARDS is undergoing mechanical ventilation. The results of an ABG analysis are pH = 7.38, P_aCO_2 = 42 mm Hg, and P_aO_2 = 55 mm Hg. The ventilator settings are: F_IO_2 = 0.9, f = 10 breaths/min, V_T = 550 mL, and PEEP = + 5 cm H_2O. On the basis of this information, which of the following might be changed to improve the patient's oxygenation status?
   A. V_T
   B. f
   C. Oxygen
   D. PEEP

7. Recent research suggests the way to establish an optimal PEEP level in a patient with ARDS is to do which of the following?
   A. Perform an inspiratory pressure-volume curve maneuver
   B. Progressively increase PEEP until cardiac output decreases
   C. Perform a recruitment-derecruitment maneuver to establish the UIPd during deflation (deflection point)
   D. Monitor PvO_2

8. Assessment for optimal PEEP is being determined in a mechanically ventilated patient. PEEP is increased progressively from 5 to 10 to 15 cm H_2O. Volume delivery remains constant at 450 mL. P_aO_2 increases progressively from 55 to 63 to 78 mm Hg. BP remains fairly constant. Mixed venous PO_2 goes from 27 to 36 to 30 mm Hg at +15 cm H_2O of PEEP. On the basis of these findings, the most appropriate action is to do which of the following?
   A. Use a PEEP of 5 cm H_2O
   B. Use a PEEP of 10 cm H_2O
   C. Use a PEEP of 15 cm H_2O
   D. Increase PEEP to 20 cm H_2O and repeat the study

9. A 70-kg man with bilateral viral pneumonia is on VC-IMV. His set V_T is 500 mL, minimum rate is 15 breaths/min with no spontaneous breaths, 40% O_2, +5 cm H_2O of PEEP, and the following ABG values: pH = 7.48, P_aCO_2 = 30 mm Hg, P_aO_2 = 98 mm Hg. Which of the following is appropriate?
   A. Increase PEEP to +10 cm H_2O
   B. Increase F_IO_2 to 0.5
   C. Increase V_T
   D. Decrease f

10. If you could select only one parameter or value that you wanted to evaluate to establish optimal PEEP in a patient, what would you select? Why?

11. The first parameter to measure after the administration of PEEP is which of the following?
   A. Heart rate
   B. BP
   C. PAOP
   D. PAP

12. A patient on CPAP of 10 cm H_2O has f = 36 breaths/min, pH = 7.23, P_aCO_2 = 54 mm Hg, P_aO_2 = 75 mm Hg (F_IO_2 = 0.5). The most appropriate action is to do which of the following?
   A. Increase CPAP to 15 cm H_2O
   B. Increase F_IO_2
   C. Begin mechanical ventilation
   D. Decrease CPAP to +5 cm H_2O

13. A patient has a P_aO_2/F_IO_2 ratio of 150 and severe sepsis. Compliance is reduced, and chest radiograph reveals bilateral infiltrates. Which of the following statements are true about this patient?
   1. The patient has moderate ARDS.
   2. This type of patient will probably have an improvement in oxygenation with a recruitment maneuver.
   3. Low V_T and therapeutic PEEP ventilation should be used with this patient.
   4. Protective lung strategies should be started as soon as possible.
   A. 1 only
   B. 2 and 3 only
   C. 1 and 4 only
   D. 1, 2, 3, and 4

14. It is better to use the inspiratory limb of an SPV curve for determining LIP and UIP than to use the deflation limb of the curve.
   A. True
   B. False

15. The purpose of setting an adequate PEEP level in ARDS is to:
   A. Avoid overdistention of the lung
   B. Prevent alveolar collapse at end exhalation
   C. Increase perfusion of the lung
   D. Improve ventilation

16. A patient with ARDS has an ideal (predicted) body weight of 53 kg. An acceptable V_T using a protective lung strategy would be:
   A. 150 mL
   B. 320 mL
   C. 530 mL
   D. 630 mL

17. During mechanical ventilation of patients with ARDS it is strongly recommended that P_{plat} not exceed 30 cm H_2O.
   A. True
   B. False

18. A 38-year-old woman with ARDS is on +15 cm H_2O of PEEP and an F_IO_2 of 0.85. Ventilation is acceptable, but P_aO_2 is only 54 mm Hg. What might the respiratory therapist recommend for improving the patient's oxygenation?
A. Set the F_IO_2 at 0.5
B. Set the PEEP to +10 cm H_2O
C. Change the patient to the prone position
D. Recommend an increase in $\dot{V}_E$

19. The improvement in ventilation-perfusion matching and oxygenation seen with prone positioning has been associated with which of the following factors?
A. Relieving the weight of the heart, great vessels, and part of the abdominal contents from the lungs
B. Increase in perfusion to the nondependent portion of the lungs when the patient is positioned face down
C. Clearance of secretion from the airways
D. Improvement in chest wall compliance in the prone position

20. Which of the following indicates that a patient is ready to be weaned from PEEP/CPAP?
1. P_aO_2 is 80 mm Hg on 30% O_2
2. The patient is stable and has no active infections
3. C_L is 37 mL/cm H_2O
4. P_aO_2/ F_IO_2 ratio is 300
A. 1 only
B. 1 and 2 only
C. 2 and 4 only
D. 1, 2, 3, and 4

21. The inflection point on the deflation curve (deflection point) using the pressure-volume loop for a patient with ARDS is 8 cm H_2O. At what value would PEEP be set?
A. 6 cm H_2O
B. 8 cm H_2O
C. 10 cm H_2O
D. Cannot be determined from this information

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CHAPTER 14

Ventilator-Associated Pneumonia

OUTLINE

KEY TERMS

- Biofilm
- Bronchial alveolar lavage
- Clinical Pulmonary Infection Score
- De-escalation
- Early-onset pneumonia
- Fiberoptic bronchoscopy
- Gastroprotective agents
- Health care–associated pneumonia
- Hospital-acquired pneumonia
- Kinetic therapy
- Late-onset pneumonia
- Multidrug-resistant microorganisms
- Nosocomial infections
- Polymicrobial infection
- Protected specimen brush
- Superinfections

LEARNING OBJECTIVES

On completion of this chapter, the reader will be able to do the following:

1. Define ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP).
2. Differentiate between early-onset VAP and late-onset VAP and describe the overall incidence of VAP.
3. Discuss the prognosis, including morbidity and mortality rates, for patients diagnosed with VAP.
4. Identify the most common pathogenic microorganisms associated with VAP.
5. List nonpharmacological and pharmacological therapeutic interventions that have been shown to increase the risk for development of VAP.
6. Describe the sequence of events that are typically associated with the pathogenesis of VAP.
7. Discuss the advantages and disadvantages of using clinical findings versus quantitative diagnostic techniques to identify patients with VAP.
8. Briefly describe the criteria for starting empirical antibiotic therapy for patients without evidence of multidrug-resistant (MDR) infections and for those patients with risk for developing MDR infections.
9. Define de-escalation of antibiotic therapy and how it can be used to reduce the emergence of MDR pathogens.
10. Discuss how ventilator bundles can be used to prevent VAP and the emergence of MDR pathogens in the clinical setting.

One of the most frequent hospital-acquired infections encountered in critically ill patients receiving mechanical ventilation is *ventilator-associated pneumonia (VAP).* VAP is defined as pneumonia that develops 48 hours after a patient has been placed on mechanical ventilation. It is an important subset of **hospital-acquired pneumonia** (HAP), which is pneumonia that occurs 48 hours or longer after admission to the hospital and results from an infection that was not incubating at the time of admission. HAP is differentiated from **health care–associated pneumonia** (HCAP), which afflicts patients who have resided in a long-term care facility or received acute care in an acute-care hospital for a specified time before developing pneumonia (i.e., ≥2 days within 90 days of the infection) (Key Point 14.1).

Most often VAP is caused by bacterial infections, but it can be caused by fungal infections or may be associated with viral epidemics (e.g., severe acute respiratory syndrome [SARS]) (Box 14.1). VAP that develops between 48 and 72 hours after

Key Point 14.1 VAP is one of the most frequent hospital-acquired infections in critically ill patients receiving mechanical ventilation.

Key Point 14.2 Successful management of VAP requires early diagnosis and appropriate use of antibiotic therapy to avoid the emergence of multidrug-resistant microorganisms.

BOX 14.1 Commonly Isolated Pathogenic Organisms From Nosocomial Pneumonias

Gram-Negative Aerobes
Pseudomonas aeruginosa
Klebsiella pneumoniae
Escherichia coli
Enterobacter spp.
Serratia marcescens
Acinetobacter calcoaceticus
Proteus mirabilis
Haemophilus pneumoniae

Gram-Positive Aerobes
Legionella pneumophila
Staphylococcus aureus
Streptococcus pneumoniae

Gram-Negative Anaerobes
Bacteroides fragilis

Fungi
Candida albicans

Others
Severe acute respiratory syndrome (SARS) virus
Influenza A virus

tracheal intubation is usually classified as **early-onset pneumonia**, whereas pneumonia that develops later than 72 hours is considered **late-onset pneumonia**.[1,2]

Despite major advances in the management of ventilator-dependent patients, VAP continues to complicate the course of treatment of a significant number of patients receiving invasive mechanical ventilation.[3] Development of VAP is associated with prolonged hospital stays, increased health care cost, and mortality rates that range from 25% to 50%.[3-7]

Guidelines for the management of patients with VAP focus on early diagnosis, appropriate antibiotic treatment, and various strategies to prevent the transmission of pathogenic organisms to patients receiving mechanical ventilation. Although there has been considerable debate among clinicians regarding the most effective means of diagnosing and treating VAP, it is agreed that successful management of VAP requires early diagnosis and appropriate use of antibiotic therapy to avoid the emergence of **multidrug-resistant** (MDR) **microorganisms** (Key Point 14.2). Effective infection control procedures and surveillance techniques are also necessary to prevent the transmission of nosocomial infections. Careful handwashing with antimicrobial agents, proper disinfection and sterilization of respiratory therapy equipment, along with the adherence to standard and disease-specific precautions, and implementation of clinical protocols, such as "VAP bundles," can significantly reduce the incidence of VAP.[8]

It is beyond the scope of this text to review every clinical study that has been conducted on VAP. A list of selected articles is provided at the end of the chapter for readers interested in further detail on specific studies about the management of patients with VAP, HAP, and HCAP.

EPIDEMIOLOGY

VAP is one of the most common **nosocomial infections** encountered in the intensive care unit (ICU).[5] The highest risk for the development of VAP occurs early in the course of the hospital stay. Cook and colleagues estimated that the risk for development of VAP is about 3% per day during the first 5 days of receiving mechanical ventilation, 2% per day for days 5 through 10, and 1% thereafter.[9]

The incidence of VAP ranges from 8% to 28% for all intubated patients.[3,5,10] Clinical studies have consistently demonstrated that critically ill patients with VAP have significantly higher mortality rates than mechanically ventilated patients without pneumonia. The overall attributable mortality rate for VAP ranges from 5% to 48%, depending on the infecting organism(s), underlying disease, comorbidities, and prior antimicrobial therapy.[3,11-15]

The prognosis for patients with early-onset VAP is generally better than those who develop pneumonia later in the course of treatment.[9] The reason for the better prognosis for early-onset VAP is related to the fact that these patients are typically infected with antibiotic-sensitive bacteria, whereas patients with late-onset VAP (i.e., >5 days) are more likely to be infected with MDR pathogens.

Causes and Risk Factors

VAP has been linked to the aspiration of oropharyngeal secretions and esophageal/gastric contents, direct inoculation of infectious material into the trachea and lungs during endotracheal intubation, inhalation of infected aerosols, embolization of biofilm that can be found in the endotracheal tubes (ETs) of patients receiving prolonged mechanical ventilation, exogenous penetration from the pleural space, and the hematogenous spread of extrapulmonary infections to the lung.[5,16]

Box 14.1 lists the most prevalent aerobic gram-negative and gram-positive bacteria that have been identified as potential pathogens responsible for VAP. Historically, aerobic gram-negative bacilli have accounted for nearly 60% of all VAP infections with *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, and *Acinetobacter* occurring at the highest frequency (Key Point 14.3).[17] More recent studies have shown that gram-positive bacteria are becoming increasingly more common in VAP, with methicillin-resistant *Staphylococcus aureus* (MRSA) being the predominant gram-positive organism isolated.[3,7,18] **Polymicrobial infections** (i.e., infection by multiple pathogenic

Key Point 14.3 Aerobic gram-negative bacilli have accounted for the majority of all VAP infections.

microorganisms) constitute nearly 50% of all VAP infections, although pathogenic anaerobic infections are not typically found in these mixed-type infections.[3]

Various independent factors contribute to the development of VAP or may increase the frequency of complications in these patients. Box 14.2 lists several host-related factors and therapeutic interventions that have been identified as risk factors for VAP. Notice that these factors are generally related to the characteristics of the patient populations affected (e.g., age of the patient, diagnosis at admission, severity of the illness, presence of comorbidities) and the effect of using various pharmacological interventions and respiratory therapy modalities in the treatment of ventilator-dependent patients.

Older patients are at greater risk for developing VAP than are younger patients. Patients treated for trauma, burns, multiple organ failure, or impaired levels of consciousness typically have the highest risk for development of VAP. The presence of comorbidities may actually predispose patients to infections with specific organisms. For example, patients with chronic obstructive pulmonary disease have increased risk for *Haemophilus influenzae*, *Streptococcus pneumonia*, and *Moraxella catarrhalis*, whereas patients with cystic fibrosis are susceptible to *P. aeruginosa* and *S. aureus* infections.[3] MRSA is particularly prevalent in patients with diabetes or head trauma and those who have been hospitalized for prolonged periods in the ICU.[7] VAP is also recognized as a major complication of acute respiratory distress syndrome (ARDS). It has been estimated that 35% to 70% of patients with ARDS develop pneumonia, which can lead to sepsis and multiple organ failure. The mortality rate for ARDS patients with VAP is significantly higher than in patients without VAP.[3,19]

Therapeutic interventions are generally categorized as pharmacological and nonpharmacological. Examples of pharmacological interventions that can lead to the development of VAP or complicate the course of treatment for these patients include concurrent steroid therapy, inappropriate antimicrobial therapy, overuse of sedatives and paralytics for mechanically ventilated patients, and the use of histamine-2 antagonists and **gastroprotective agents**, such as antacids.

Inappropriate use of antibiotics in the hospital setting is particularly troublesome because it has been associated with the selection of MDR pathogens (Key Point 14.4).[3,18,20] It has been suggested that prolonged antibiotic administration to ICU patients for a primary infection may favor selection and subsequent colonization with resistant pathogens responsible for superinfections.[3] This is an important issue for patients with late-onset VAP because, as mentioned previously, these patients are at a higher risk for being infected with MDR pathogens. Imprudent use of sedatives and paralytics can also increase the incidence of VAP by impairing the patient's level of consciousness, which can ultimately blunt the patient's cough reflex and increase the chances of aspiration. Box 14.3 lists the most common risk factors for MDR infections.

Key Point 14.4 Inappropriate use of antibiotics in the hospital setting has been associated with an increased emergence of multidrug-resistant pathogens.

BOX 14.2 Conditions and Risk Factors Predisposing to Colonization and Ventilator-Associated Pneumonias[40,45]

- Alcoholism
- Antibiotic therapy
- Diabetes mellitus
- Hypoxemia
- Bronchoscopy
- Intubation
- Tracheostomy
- Chest tube thoracostomy
- Hypotension
- Nasogastric tubes/enteral feedings
- Acidosis
- Malnutrition
- Azotemia
- Preceding viral infection
- Leukocytopenia
- Surgery
- Leukocytosis
- Underlying illness
- Underlying pulmonary disease
- Nasal intubation
- Gastric alkalinization
- Supine position
- Immunosuppression
- Radiation/scarring
- Malignancy
- Coma
- Circuit/airway manipulation ($\leq$72-hour circuit changes)
- Severe illness (Acute Physiology and Chronic Health Evaluation [APACHE]) $\geq$18

BOX 14.3 Common Risk Factors for Multidrug-Resistant Infections[7]

- Antimicrobial therapy in the preceding 90 days
- Current hospitalization for 5 or more days
- High frequency of antibiotic resistance in the community or a specific hospital unit
- Presence of risk factors for health care–associated pneumonia
- Hospitalization for 2 or more days in the preceding 90 days
- Residence in a nursing home or extended care facility
- Home infusion therapy (including antibiotics)
- Chronic dialysis within 30 days
- Home wound care
- Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

Nonpharmacological interventions associated with the increased risk for VAP include the need for an ET or tracheostomy tube (TT) during ventilation; routine care of ventilator circuits, humidifiers, and nebulizers; and the use of respirometers, reusable electronic ventilator probes and sensors, bronchoscopes, and endoscopes.[5] The most important of these nonpharmacological factors that has been found to be associated with VAP is the use of an ET or TT during mechanical ventilation. The incidence of VAP is 6- to 21-fold higher in patients who are intubated receiving mechanical ventilation compared with the incidence in patients receiving noninvasive mechanical ventilation. This has led some clinicians to suggest that "endotracheal intubation–associated pneumonia" might be a more appropriate name for this type of pneumonia.

Respiratory therapy equipment has long been implicated as a source of nosocomial infections. Indeed, epidemics of HAP and VAP are most often associated with contamination of respiratory therapy equipment, bronchoscopes, and endoscopes. Instituting stringent infection control procedures can reduce the incidence of nosocomial infections in hospitals and other health care facilities; however, ensuring that all of the clinical staff members adhere to the prescribed infection control policies remains a formidable task. Surveillance of ICU patients at high risk for bacterial pneumonia also can be an important part of determining trends and identifying outbreaks.[21] Additional details on various nonpharmacological strategies that can be used to reduce the incidence of VAP are presented later in this chapter.

PATHOGENESIS OF VENTILATOR-ASSOCIATED PNEUMONIA

The pathogenesis of VAP most often involves colonization of the aerodigestive tract with pathogenic bacteria and aspiration of contaminated secretions into the lower airways, followed by colonization of the normally sterile lower airways and lung parenchyma with these infectious microrganisms.[15] The upper airways of healthy individuals typically contain nonpathogenic bacteria, such as the viridans group of streptococci, *Haemophilus* spp., and anaerobes.[5] Aerobic gram-negative bacilli, most notably virulent forms of *P. aeruginosa* and *Acinetobacter*, are rarely found in the respiratory tract of healthy individuals because of anatomical barriers, the cough reflex, mucociliary clearance mechanisms, and innate cellular and humoral immune factors (e.g., leukocytes, immunoglobulins).

During critical illnesses, particularly in patients with an ET and receiving mechanical ventilation, there is a dramatic shift in the flora of the oropharyngeal tract to gram-negative bacilli and *S. aureus*.[5,7] This shift in flora may be attributed to factors that compromise host defense mechanisms, including comorbidities, malnutrition, reduced levels of mucosal immunoglobulin A, increased production of proteases, exposed and denuded mucous membranes, elevated airway pH, and an increased number of airway receptors for bacteria as a result of acute illness and prior antimicrobial use.[5,22-24] Aspiration of the contaminated oropharyngeal secretions and, in some cases, gastroesophageal contents can occur because the patient is unable to protect the lower airways. Impaired level of consciousness, gastroesophageal reflux, a blunted gag reflex, and abnormal swallowing can all contribute to the risk for aspiration.[15] After these offending organisms penetrate and colonize the lower airways, they can overwhelm already compromised pulmonary cellular and humoral immune defense mechanisms and eventually lead to VAP.[15]

DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA

The lack of a precise definition for the diagnosis of VAP has caused considerable debate among clinicians.[25-27] It has been suggested that clinical criteria involving patient symptoms and signs, chest radiographs, and baseline hematologic studies can be effective for starting empirical antibiotic therapy; however, simply relying on clinical findings to guide therapeutic interventions can be subjective (i.e., high interobserver variability), resulting in a failure to accurately diagnose VAP and leading to inappropriate antibiotic therapy if the infection is polymicrobial in origin or if a drug-resistant organism is present.

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) presented recommendations in 2005 to address these concerns regarding the management of VAP. The ATS/IDSA recommendations provided a list of clinical criteria that could be used in the diagnosis of VAP.[7] The guidelines further advised that invasive microbiological procedures, such as quantitative cultures of lower respiratory secretions obtained by **bronchial alveolar lavage** (BAL) or **protected specimen brush** (PSB) procedure, are often necessary to ensure effective treatment of patients with VAP.[7]

In 2011, the Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network proposed an updated definition that was designed to improve the reporting criteria for VAP used by institutions. Although the CDC surveillance definition incorporates the general features of the ATS/IDSA definition, several points are noteworthy. For example, the CDC surveillance definition uses the term *ventilator-associated event* to describe a range of conditions and complications that occur in mechanically ventilated patients, including VAP.[27] As Table 14.1 shows, a ventilator-associated event can be categorized as a ventilator-associated condition, an infection-related ventilator-associated complication, and possible pneumonia or probable pneumonia. The CDC surveillance definition relies on the use of only objective data, clearly defined time criteria, and the exclusion of radiographic imaging to diagnose the presence of pneumonia in ventilated patients.[26,27]

Clinical Diagnosis

VAP should be suspected when a patient on mechanical ventilation demonstrates radiographic evidence of new or progressive infiltrates and one or more of the following findings: fever, leukocytosis, purulent tracheobronchial secretions, decreased oxygenation, increased minute ventilation, decreased tidal volume, and increased respiratory rate.[3] Table 14.2 provides a list of clinical criteria that can be used in the clinical diagnosis of VAP. Fever and the presence of pulmonary infiltrates on chest radiographs are nonspecific findings that can be associated with numerous other conditions, including chemical and radiation pneumonitis, atelectasis, pulmonary embolism and infarction, lung contusion, ARDS, and drug or hypersensitivity reactions.[16,25]

TABLE 14.1 Centers for Disease Control Surveillance Paradigm for Ventilator-Associated Events

Concept	Name	Definition
New respiratory deterioration	Ventilator-associated condition (VAC)	≥2 Calendar days of stable or decreasing daily minimum positive end-expiratory pressure or daily minimum fraction of inspired O_2, followed by a rise in daily minimum positive end-expiratory pressure of ≥3 cm of water or a rise in the daily minimum percentage of inspired O_2 by ≥20 points sustained for ≥2 calendar days
New respiratory deterioration with evidence of infection	Infection-related ventilator-associated complication (IVAC)	VAC plus a temperature of <36°C or >38°C or a leukocyte count of ≤4000 or ≥12,000 per cubic millimeter, plus 1 or more new antibiotics continued for at least 4 days within 2 calendar days before or after onset of a VAC, excluding the first 2 days of mechanical ventilation
New respiratory deterioration with possible evidence of pulmonary infection	Possible pneumonia	IVAC plus Gram staining of endotracheal aspirate or BAL showing ≥25 neutrophils and ≤10 epithelial cells per low-power field or a positive culture for a potentially pathogenic organism, within 2 calendar days before or after onset of a VAC, excluding the first 2 days of mechanical ventilation
New respiratory deterioration with probable evidence of pulmonary infection	Probable pneumonia	IVAC plus Gram staining of endotracheal aspirate or BAL showing ≥25 neutrophils and ≤10 epithelial cells per low-power field, plus endotracheal aspirate with $\geq 10^5$ colony-forming units per milliliter or BAL culture with $\geq 10^4$ colony-forming units per milliliter, or endotracheal aspirate or BAL semiquantitative equivalent, within 2 calendar days before or after onset of a VAC, excluding the first 2 days of mechanical ventilation

BAL, Bronchoalveolar lavage.
From Klompas M: Complication of mechanical ventilation: the CDC's new surveillance paradigm, *N Engl J Med* 368:1472–1475, 2013.

TABLE 14.2 Clinical Criteria Used in the Diagnosis of Ventilator-Assisted Pneumonia (VAP)[27,29]

	POINTS		
Variables	0	1	2
Temperature (°C)	≥36.1 to ≤38.4	≥38.5 to ≤38.9	≥39 to ≤36
WBC count (μL)	≥4000 to ≤11,000	<4000 to >11,000	—
Secretions	Absent	Present, nonpurulent	Present, purulent
P_aO_2/F_IO_2	>240 or ARDS	—	≤240 and no ARDS
Chest radiography	No infiltrate	Diffuse or patchy infiltrate	Localized infiltrate
Microbiology	No or light growth	Moderate or heavy growth; add 1 point for same organism on Gram stain	—

ARDS, Acute respiratory distress syndrome; P_aO_2, arterial oxygen pressure; *WBC,* white blood cell.
From Porzecanski I, Bowton DL: Diagnosis and treatment of ventilator-associated pneumonia, *Chest* 130:597–604, 2006.

Some clinicians emphasize certain findings over others using a "weighted" approach to clinical diagnosis.[25] The **Clinical Pulmonary Infection Score** (CPIS) is an example of this type of approach. The CPIS includes six clinical assessments, with each item given a score of 0 to 2 points (see Table 14.2). Assessment criteria include fever, leukocyte count, quantity and purulence of tracheal secretions, oxygenation status, type of radiographic abnormality, and results of a tracheal aspirate culture and Gram stain. (Note that a modified CPIS in which the endotracheal aspirate culture and Gram stain results are excluded is also available. In this case the score will range from 0 to 10 instead of 0 to 12).[26-29] When all six criteria are used, a score greater than 6 is considered evidence of the presence of VAP.[27] It is generally accepted that measurements of CPIS should be performed at the beginning of antibiotic therapy and after 2 to 3 days to evaluate the effectiveness of the treatment course. Although some investigators

Case Study 14.1

Patient Case—VAP

A 65-year-old man is admitted to the intensive care unit after thoracic surgery. He has an endotracheal tube and has been receiving pressure-controlled mechanical ventilation for 48 hours. The attending physician suspects that the patient may have ventilator-associated pneumonia (VAP). The following clinical data were obtained during an initial assessment. What is his Clinical Pulmonary Infection Score and does he demonstrate enough evidence of VAP to warrant the initiation of antibiotic therapy?

Temperature = 39.5°C
White blood cell count = 12,000 cells/mm^3
Localized infiltrates on chest radiograph
Purulent secretions
P_aO_2/F_IO_2 = 300

have found considerable interobserver variability and a lack of specificity to guide antibiotic therapy, a case can be made that measurement of the CPIS may reduce the mortality rate associated with VAP.[28,29] The measurement of CPIS may also provide information that can allow the clinician to aggressively treat patients with VAP while limiting the course of antibiotic therapy and thus controlling for the development of bacterial resistance[25] (Case Study 14.1).

Bacteriological (Quantitative) Diagnosis

As mentioned, many clinicians have concerns about simply using clinical findings to guide antibiotic therapy in VAP. They think this approach can result in the unnecessary use of broad-range antibiotics, which in turn can lead to the emergence of MDR strains of microorganisms and higher mortality rates for patients afflicted with VAP. Numerous studies have shown that obtaining quantitative cultures of specimens from the lower respiratory tract by conventional **fiberoptic bronchoscopy** or nonbronchoscopic techniques can significantly improve the diagnosis of VAP and facilitate decision making regarding the management of these patients.[3,30,31]

Fiberoptic bronchoscopy allows the clinician to have direct access to the lower airways. The most common bronchoscopic techniques used to obtain samples from the lower airways and the lung parenchyma involve BAL and PSB sampling. Selection of the sampling site is usually based on the location of the infiltrate on chest radiographs or by direct visualization of inflammation and purulent secretions in the airway.[3,31] Note that relying on chest radiographs when selecting the appropriate sampling area can be challenging if diffuse pulmonary infiltrates are present.

A variety of nonbronchoscopic techniques have been described.[32] The most commonly used nonbronchoscopic techniques include mini-BAL, blinded bronchial sampling, and blinded PSB. The advantages of using these techniques over conventional bronchoscopy are that nonbronchoscopic techniques are noninvasive and less expensive than bronchoscopy and can be performed by individuals not qualified to perform fiberoptic bronchoscopy.[3] These techniques also typically do not result in compromised gas exchange, which often occurs during fiberoptic bronchoscopy. The primary disadvantage of using the nonbronchoscopic techniques is that samples are obtained blindly and can therefore increase the chances of a sampling error because of lack of direct visualization of the sampling site.[33]

Once the sample is obtained, it should be processed without delay according to clearly defined procedures for bacteriological analysis to prevent the loss of viability of the pathogenic organisms or overgrowth by contaminants. Bacteriological studies include quantitative culture techniques and microscopic analysis of the cultures using an appropriate stain (e.g., Gram stain) to differentiate pathogens from oropharyngeal contaminants.[3] In patients with VAP, pathogens are usually present at concentrations of 10^5 to 10^6 colony-forming units (CFU)/mL, whereas contaminants are generally present in concentrations of less than 10^4 CFU/mL. (Baselski has provided a complete description of the standard laboratory procedures for processing bronchoscopic samples in suspected cases of VAP.)[31] Direct microscopic and histological examinations of BAL and PBS samples can be used to identify the presence or absence of bacteria in the lower respiratory tract.

TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA

Treatment of VAP can be challenging, even under the best of conditions. It should be apparent from the aforementioned issues related to diagnosing VAP that developing an effective strategy for the management of these patients ultimately depends on establishing a reliable diagnosis. Initiating empirical antibiotic therapy should be based on whether the patient has any of the risk factors for MDR pathogens. The ATS/IDSA Guidelines for the Management of Adults with HAP and VAP provide a series of pathways to guide clinicians on the initiation of empirical antibiotic therapy in addition to strategies that can be used to reduce the emergence of MDR pathogens. Information that should also be reviewed when designing an antibiotic regimen includes the predominant pathogens identified for the specific clinical setting and local patterns of antibiotic susceptibility, cost and availability of the antibiotics used, and any formulary restrictions.[7]

The algorithm shown in Fig. 14.1 is a summary of current management strategies recommended for patients with suspected VAP. **De-escalation** of antibiotic therapy or, more specifically, focusing the types and duration of antibiotics used (i.e., broad-range antibiotics vs. limited-spectrum antibiotics) can be accomplished once quantitative data on lower respiratory tract and blood cultures are available[7] (Key Point 14.5). It is important to understand that successful treatment of patients with VAP requires serial clinical and microbiological assessments. More specific information about the use of various antibiotic dosing schedules, including combination therapy, can be found in the ATS/IDSA Guideline listed in the references at the end of this chapter[7] (Case Study 14.2).

STRATEGIES TO PREVENT VENTILATOR-ASSOCIATED PNEUMONIA

Implementing an effective infection control program in the ICU is essential to reduce the incidence of VAP. The first step in the development and implementation of an effective program is

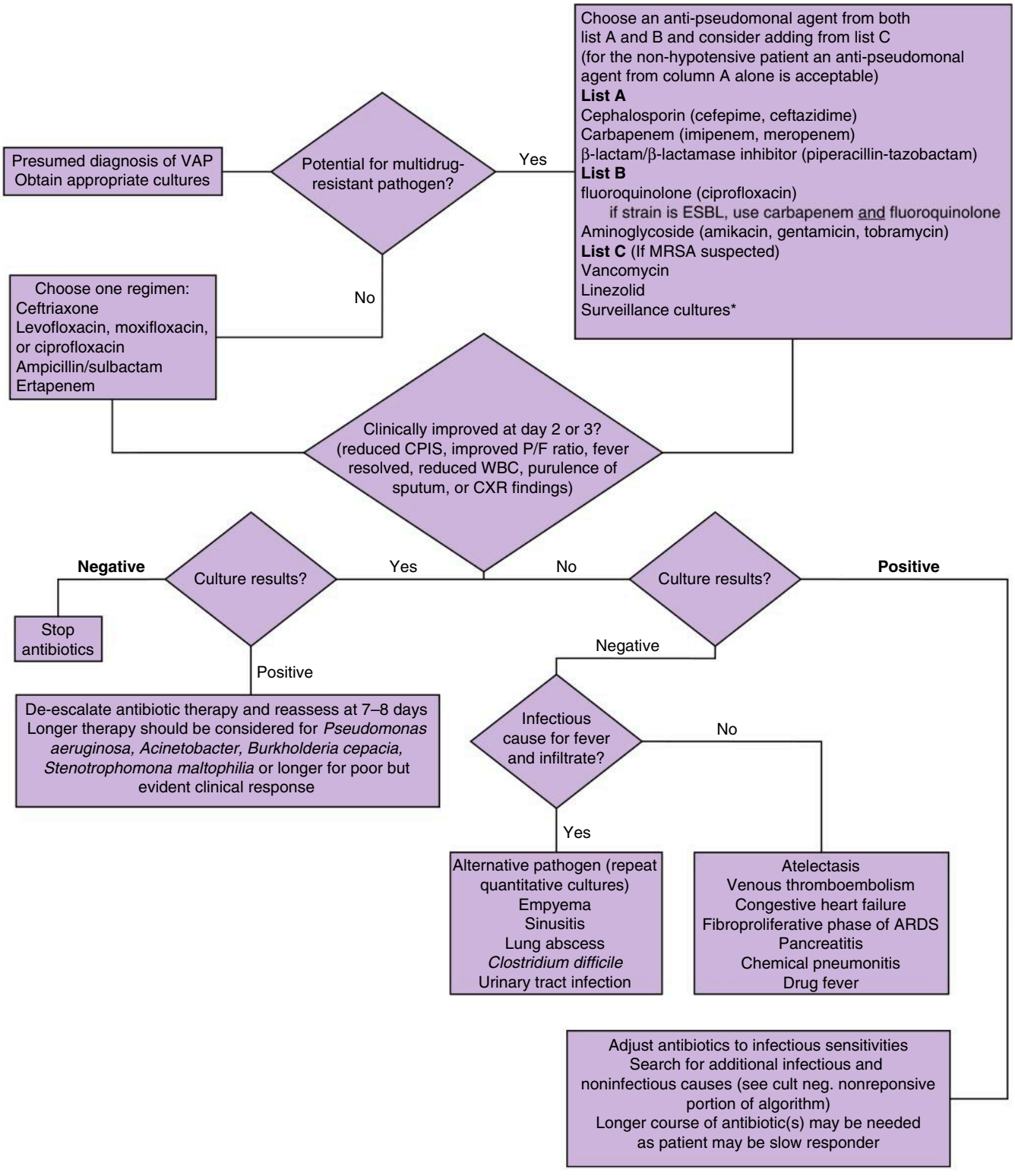

Fig. 14.1 Algorithm illustrating antibiotic regimens used for the management of patients with ventilator-associated pneumonia.[7,52] (Adapted from the *American Journal of Respiratory and Critical Care Medicine*[5] with permission. In Koenig SM, Truwit JD: Ventilator-associated pneumonia: diagnosis, treatment, and prevention, *Clin Micro Rev* 19:637—657, 2006. *ARDS,* Acute respiratory distress syndrome; *CPIS,* Clinical Pulmonary Infection Score; *CXR,* chest x-ray; *ESBL,* extended-spectrum β-lactamase; *MRSA,* methicillin-resistant *Staphylococcus aureus; P/F* ratio, PaO2/FIO2 ratio; *WBC,* white blood cell. *Antibiotic choice can be tailored to the pathogens' last sensitivity report if quantitative endotracheal aspirate (QEA) surveillance cultures are obtained twice weekly and if the growth level exceeds 100,000 CFU/mL.)

Key Point 14.5 De-escalating antibiotic therapy can be accomplished once quantitative data on lower respiratory tract and blood cultures are available. De-escalation of antibiotic therapy is an important method that can be used to reduce the incidence of MDR pathogens because it reduces unnecessary use of antibiotics.

Case Study 14.2

Exercise

Patient Case—Methicillin-Resistant *Staphylococcus aureus*

A 55-year-old woman with a 35-pack-year history of smoking cigarettes is admitted into the intensive care unit after a cholecystectomy. She has a history of diabetes mellitus and has been mechanically ventilated via an endotracheal tube for 5 days. Her chest radiograph demonstrates localized infiltrates in the right middle lobe. Her white cell count is 15,000 cells/mm^3, and the results of bronchoalveolar lavage show the presence of methicillin-resistant *S. aureus*. Briefly describe the appropriate antibiotic course that should be initiated for this patient.

recognition that it is a high-priority task. Ensuring that everyone on the clinical staff is familiar with the established infection control policies and procedures is critical. Staff must consistently follow these procedures for all patients and recognize the consequences of lapses in continuity of care. Adequate physical and human resources must be provided to establish surveillance mechanisms to track the local incidence of VAP and other nosocomial infections. The findings of the surveillance team must be effectively communicated to the clinical staff on a regular basis, and the program must be updated to reflect the most current evidence-based clinical studies, the use of new technology, and changing patterns of disease in the local environment.[2]

Box 14.4 lists strategies that can be implemented to prevent VAP. Many of these strategies are incorporated into *ventilator bundles*, which are viewed as evidence-based practices that can significantly reduce the incidence of VAP. As mentioned, these strategies are generally categorized as nonpharmacological and pharmacological procedures.[34-37] The following is a brief discussion of each of these strategies that can be used to reduce the incidence of VAP.

Nonpharmacological Interventions

Handwashing

Routine handwashing with soap and water and alcohol-based hand rubs is the most important prevention strategy to reduce the risk for clinicians transmitting infectious microorganisms from one patient to another or from a contaminated site to a clean site on the same patient[38] (Key Point 14.6). Hand decontamination should be done before and after contact with an intubated patient and before and after performing any procedure in which handling

BOX 14.4 Methods to Reduce the Risk for Nosocomial Pneumonias in Mechanically Ventilated Patients[34-37]

Nonpharmacologic

- Noninvasive ventilation
- Handwashing and use of accepted infection control procedures and practices
- Semirecumbent positioning of patient
- Appropriate circuit changes (when grossly contaminated)
- Consider using silver-coated antimicrobial endotracheal tubes
- Heat-moisture exchanges when possible
- Continuous aspiration of subglottic secretions (CASS)
- Appropriate disinfection and sterilization techniques
- Kinetic beds
- Identifying a dedicated person/group for monitoring nosocomial ventilator-associated pneumonia (VAP) rates
- Use of closed-suction catheters and sterile suction technique
- Avoiding large gastric volumes
- Extubating and removing nasogastric tube as clinically indicated
- Avoiding contamination with ventilator circuit condensate
- Use single patient items such as monitors, O_2 analyzers, resuscitation bags
- Careful use of inline small-volume nebulizers
- Consider use of expiratory-line gas traps or filters
- Oral rather than nasal intubation
- Daily screening of patients for discontinuation of invasive mechanical ventilation and endotracheal extubation

Pharmacological

- Stress ulcer prophylaxis with sucralfate instead of histamine-2 antagonists in high-risk patients for prevention of stress ulcers (still controversial)
- Possible prophylactic intestinal decontamination (antimicrobial administration)
- Avoid central nervous system depressants
- Implementation of a sedation interruption protocol

Methods to Improve Host Immunity

- Maintain nutritional status
- Avoid agents that impair pulmonary defenses (aminophylline, anesthetics, certain antibiotics, corticosteroids, sedative narcotics, and antineoplastic agents)
- Minimize use of invasive procedures when possible
- Remove or treat disease states that affect host defenses when possible (acidosis, dehydration, hypoxemia, ethanol intoxication, acid aspiration, stress, thermal injury, diabetic ketoacidosis, liver failure, kidney failure, heart failure)

Key Point 14.6 Routine handwashing with soap and water and alcohol-based hand rubs is the most important prevention strategy to reduce the risk for nosocomial infections.

items contaminated with respiratory secretions can occur.[32] Wearing gloves and gowns reduces the rate of nosocomial infections, but this practice appears to be most effective when used with patients with specific antibiotic-resistant pathogens.[2]

Semirecumbent Patient Positioning and Enteral Feeding

Enteral feeding may predispose a patient to VAP by elevating the gastric pH, which can lead to gastric colonization with pathogenic bacteria and cause gastric distention. This in turn can lead to an increased risk for reflux and aspiration. Following some basic guidelines can reduce aspiration of gastric contents. Routine verification of the proper placement of the enteral feed tube is important.[39,40] Intermittent feedings may also be preferable to continuously feeding because preventing overdistention of the stomach can limit gastropulmonary colonization.[35]

Aspiration occurs more often in patients placed in the supine position than in patients in the semirecumbent position (i.e., 30–45 degrees from the horizontal position).[35,40-42] When it is feasible and the patient can tolerate it, placing a patient in semirecumbent position is a low-cost, low-risk procedure effective in reducing the aspiration of gastric contents compared with the supine position.

Noninvasive Ventilation

Clinical studies have clearly demonstrated that endotracheal intubation is a modifiable risk factor for the development of VAP. Avoiding ET intubation and use of noninvasive positive pressure ventilation (NIV) has been shown to significantly lower the nosocomial pneumonia rate in select groups of patients (e.g., acute exacerbations of chronic obstructive pulmonary disease or immunocompromised patients with pulmonary infiltrates and hypoxemic respiratory failure).[7] Using NIV is also associated with a lower rate of other nosocomial infections such as urinary tract infections and catheter-related infections.[43] When it is clinically appropriate, NIV should be preferentially used over invasive ventilation.[36]

Selection, Changing, and Suctioning of the Endotracheal Tube

It is important to recognize that the type of ET selected and site of insertion are important factors to consider when initiating invasive mechanical ventilation. Advances in ET construction have resulted in the development of different cuff materials and shapes that attempt to reduce leakage of secretions around an inflated cuff.[43] Polyurethane and silicon ET cuffs decrease the formation of longitudinal channels, which can occur with standard polyvinyl cuffs. Changing the shape of the ET cuff also has been shown to reduce leakage. Tapered or cylindrical designs have been shown to reduce fluid leakage compared with ET tubes with the standard globular cuff design.[43]

Maintaining adequate ET cuff pressure is also an important factor that must be considered to avoid aspiration of oropharyngeal secretions. There appears to be a higher risk for aspiration pneumonia among patients with persistent intracuff pressures below 20 cm H_2O.[44] Increasing the cuff pressure (e.g., to 20–25 cm H_2O) decreases but does not completely eliminate this aspiration. Furthermore, it is important to recognize that using higher cuff pressure is not without its own problems of potential airway injury (see Chapter 8).

The use of oral rather than nasal intubation is recommended because sinusitis is a particular concern in nasally intubated patients and is associated with VAP.[42,44] Furthermore, there is an increased risk for VAP when patients are reintubated. The risk and benefits of reintubation should be considered before changing an ET. If the tube is changed, it is important to avoid contamination of the lower airways with oropharyngeal secretions by properly suctioning around the ET cuff before deflating the cuff or replacing the ET. The CDC recommends using a new suction catheter with each open-suction procedure and using sterile water to rinse the catheter when suctioning is performed. The use of sterile gloves is also appropriate for this procedure.[44-47]

Recent studies have demonstrated that antimicrobial-coated ET tubes can reduce the incidence of VAP by delaying bacterial colonization and **biofilm** formation on the tube's inner lining. Laboratory studies have suggested that silver is an ideal coating because it is nontoxic and antimicrobial, and it has antiadhesive properties.[26] It is important to mention, however, that although these devices can delay biofilm formation, the antibacterial efficacy of the coating decreases over time. In addition, removal of the biofilm can be difficult because routine tracheal suctioning is not effective. Berra and colleagues introduced a novel device called the *Mucus Shaver* to overcome this limitation. The Mucus Shaver consists of an expandable silicon rubber balloon with shaving rings that adhere to the surface of the ET. This device has been shown to be effective in the removal of biofilm and thus allows the ET tube to retain its antimicrobial efficacy.[45]

Continuous Aspiration of Subglottic Secretions (CASS)

Secretions that pool around the ET cuff are reservoirs of potentially pathogenic bacteria (Key Point 14.7). Efforts to reduce silent aspiration of secretions above and below the ET cuff have led to the development and use of specialized ETs (Fig. 14.2). These specialized ETs have a dorsal lumen above the ET cuff that allows for continuous or intermittent suction of tracheal secretions that accumulate above the patient's subglottic area.[49,50] CASS has been shown to reduce the incidence of nosocomial pneumonias.[46] Early studies by Valles and colleagues reported that continuous aspiration of subglottic secretions reduced the incidence of VAP by nearly 50%.[50] Interestingly, these investigators also found that episodes of VAP occurred later in patients receiving continuous aspiration (12.0 ± 7.1 days than in the control patients (5.9 ± 2.1 days).[50] Rello and colleagues also showed a five times greater likelihood of VAP when continuous aspiration of subglottic secretions was not used.[46]

At present, the CDC makes no specific recommendation about how often continuous inline suction catheters should be changed. Studies have not shown differences in VAP rates between once-daily and no routine changes in closed-suction catheters. It may be appropriate to leave the catheter inline until it is visibly contaminated or no longer functional.

Care of the Tracheostomy Tube

TTs placed by the percutaneous route can predispose the patient to the development of pneumonia, possibly from contamination

Key Point 14.7 Secretions that pool around the ET cuff are reservoirs of potentially pathogenic bacteria.

Fig. 14.2 Specialized continuous-suction endotracheal tubes.

during the insertion procedure. In cases in which the patient has a TT, the caregiver should wear a gown, use aseptic technique, and replace the tube with one that has been sterilized or given high-level disinfection.[44] These types of pneumonia are associated with prolonged ventilation and ICU stay but not increased mortality. A common pathogen associated with percutaneous tracheotomy is *Pseudomonas* spp.[47]

Ventilator Circuit Management Strategies

Manipulation of the ventilation circuit may increase the risk for patient aspiration and VAP.[51,52] Most clinicians agree that reducing ventilator circuit changes is cost-effective and, more important, lessens the risk for VAP.[35,36,48,51] Circuits do not need to be changed unless they are nonfunctional or if they are visibly soiled with secretions or blood.[36,44,51,52]

Using certain types of humidifiers during mechanical ventilation can be another potential source of pathogenic bacteria. Heat-moisture exchangers have the ability to filter bacteria and may be a more effective method of reducing VAP during mechanical ventilation than heated-wire circuits and heated humidifiers.[36,44,47] It is important to recognize that patients with thick, tenacious secretions are not good candidates for using these devices because heat-moisture exchangers might not provide adequate humidification and increase the risk for endotracheal occlusions causing asphyxiation.[36,44,53]

For heated wick or pass-over humidifiers, the CDC recommends the use of sterile water.[47] (NOTE: Although bubble humidifiers are now used only rarely during mechanical ventilation, it is safe to assume that the same advice would be appropriate for these devices, too.[53]) Draining of condensate in the ventilator circuits that use heated humidifiers should be performed in a manner that avoids accidentally allowing circuit condensate from spilling into the patient's ET.

Small-volume nebulizers (SVNs) are sometimes used in the ventilator circuit for the administration of medications. The CDC recommends that between treatments, the SVN be disinfected, rinsed with sterile water, and air-dried.[44] Only sterile solutions should be used to fill SVNs, and whenever possible, unit-dose vials of medication should be used[44] (Key Point 14.8).

Kinetic Therapy

Immobility in critically ill patients can lead to atelectasis and reduced bronchopulmonary secretion clearance. Several investigators have suggested that **kinetic therapy** or the use of automated rotating beds may be effective in reducing the incidence of VAP, particularly in surgical patients or patients with neurological problems.[39] Whether kinetic beds offer significant advantages over standard ICU patient-turning strategies will require additional studies.[39,44,47] At present, the CDC has no recommendation regarding "kinetic" therapy or continuous lateral rotational therapy.

Pharmacological Interventions

Oropharyngeal Decontamination

The CDC currently recommends the development and implementation of an oral hygiene program for patients in acute care and long-term care facilities that are at high risk for nosocomial pneumonias. Although there has been a debate regarding the benefits of oral hygiene in preventing VAP, studies have demonstrated that using an oral cleansing agent such as chlorhexidine can modulate oropharyngeal colonization and ultimately decrease the incidence of VAP.[54]

Stress Ulcer Prophylaxis

Gastrointestinal bleeding and stress ulcers in critically ill patients are associated with increased morbidity and mortality. Use of prophylactic treatment, such as H_2-antagonists and antacids, may reduce the risk for stress ulcers. However, as the acidity of gastric contents decreases, gastric colonization by potentially pathogenic organisms increases (Key Point 14.9). The use of sucralfate may be beneficial in reducing gastric colonization. Sucralfate is a prophylactic agent that does not affect gastric pH.[36] Current findings are controversial, and the use of sucralfate is not recommended at this time for patients at high risk for gastrointestinal bleeding.[37] In patients with ARDS, sucralfate was associated with an increased risk for VAP.[37] The CDC currently has no specific recommendations about the use of sucralfate, H_2-receptor antagonists, or antacids for stress-bleeding prophylaxis.[47]

***Key Point* 14.8** Ventilator circuits do not need to be changed unless they are nonfunctional or if they are visibly soiled with secretions or blood.

Key Point 14.9 Administering type histamine-2 antagonists and antacids may reduce the risk for stress ulcers, but they can also increase the risk for gastric colonization by potentially pathogenic organisms.

Selective Digestive Tract Decontamination

There is substantial interest in topically treating the oropharynx and stomach of patients on mechanical ventilation with antibiotics. The goal is reducing the number of potentially pathogenic organisms that may colonize the stomach. This, in turn, might reduce the incidence of VAP. Selective digestive tract decontamination may reduce VAP and ICU mortality when a combination of topical and intravenous prophylactic antibiotics is used. However, this is not without the long-term risk for the development of antibiotic-resistant organisms.[36]

Prophylactic Antibiotics

The use of both topical and systemic prophylactic antibiotics may reduce respiratory infections and overall mortality rates in critically ill patients.[36] Inadequate and delayed initial treatment contributes to the risk for VAP and is often associated with a delay in writing the medical order.[55,56]

Antibiotics have a "bimodal" effect in the development of VAP. Within the first days of mechanical ventilation, antibiotics protect against pneumonia development, especially against types caused by endogenous flora. But exposure to antibiotics has a significant risk factor for colonization and infection with nosocomial, MDR pathogens that are associated with significant mortality, such as *P. aeruginosa* and MRSA.[40,55,56]

There are currently no recommendations from the CDC regarding the routine use of systemic antimicrobial agents to prevent VAP or nosocomial pneumonias.[40,47] On the other hand, judicious use of appropriate antibiotics may reduce patient colonization and subsequent infections with MDR bacteria.[40]

Sedation Interruption and Daily Assessment of Readiness for Endotracheal Extubation

Reducing the duration of mechanical ventilation and length of ICU stay are important outcomes in the care of critically ill patients.[57,58] Pain and anxiety experienced by patients receiving mechanical ventilation often require sedation and analgesia. (See Chapter 15 for more details regarding the use of sedative and analgesics.) Although strategies used to administer these drugs vary considerably, it has been suggested that implementing a routine of daily sedative infusion interruption can lead to a reduction in the duration of invasive mechanical ventilation and length of stay in the ICU and therefore reduce the risk for VAP.[57,59,60]

SUMMARY

- Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops 48 hours after a patient has been placed on mechanical ventilation.
- VAP is the most common nosocomial infection encountered in the ICU.
- Guidelines for the management of VAP focus on early diagnosis, appropriate antibiotic treatment, and various strategies to prevent the transmission of pathogenic organisms to patients receiving mechanical ventilation.
- The prognosis of patients with early-onset VAP is better than those patients with late-onset VAP.
- The most prevalent microorganisms in VAP are gram-negative bacilli. Recent studies have shown an increased incidence of MDR infections, particularly MRSA.
- Several host-related risk factors can contribute to the development of VAP. These factors are related to the age of the patient, diagnosis at admission and severity of the illness, and presence of comorbidities.
- Overuse of sedatives and paralytics, in addition to the use of gastroprotective medications for stress ulcers, can increase the risk for VAP.
- Inappropriate use of antibiotics is associated with the emergence of MDR pathogens.
- Nonpharmacological interventions, such as ETs and routine care of ventilator circuits, are potential sources of infectious material.
- Avoiding ET intubation and using noninvasive mechanical ventilation have been shown to lower the incidence of VAP.
- Ventilator circuits do not need to be changed unless they are nonfunctional or if they are visibly soiled with secretions or blood.
- Including a routine of daily sedative infusion interruption in ventilator bundles can lead to a reduction in the duration of invasive mechanical ventilation and length of stay in the ICU and therefore reduce the risk for VAP.

REVIEW QUESTIONS *(See Appendix A for answers.)*

1. What is the incidence of VAP among ICU patients receiving mechanical ventilation?
A. 1% to 5%
B. 8% to 28%
C. 25% to 46%
D. 50%

2. Which of the following bacterial infections has been increasingly shown to be associated with VAP?
A. Haemophilus influenzae
B. *Escherichia coli*
C. Methicillin-resistant *Staphylococcus aureus*
D. *Legionella pneumophila*

3. Which of the following would be considered host-related risk factors for the development of VAP?
1. Malnutrition
2. Shift in oropharyngeal flora to gram-negative bacilli
3. Gastric alkalization
4. Enhanced gag reflex
A. 1 and 2 only
B. 2 and 3 only

C. 1, 2, and 3 only
D. 4 only

4. In patients with VAP, bacterial contaminants are typically less than:
A. 10^4 CFU/mL
B. 10^6 CFU/mL
C. 10^8 CFU/mL
D. 10^{12} CFU/mL

5. Which of the following have been implicated in the pathogenesis of VAP?
1. Colonization of the oropharynx by viridian species of *Streptococcus*
2. Presence of an ET tube
3. Impaired level of consciousness
4. Reduced airway pH
A. 1 and 3 only
B. 2 and 3 only
C. 1, 2, and 3 only
D. 1, 2, 3, and 4

6. The CDC definition of probable ventilator-associated pneumonia is based on which of the following criteria?
1. Oxygenation status
2. Total leukocyte count
3. Microbiological analysis of lower airway secretions
4. Chest radiographs
A. 1 and 2 only
B. 2 and 3 only
C. 1, 2, and 3 only
D. 1, 2, 3, and 4

7. Which of the following would not be considered a risk factor for VAP?
A. NIV
B. High-frequency use of antibiotic use in the community
C. Residence in an extended care facility
D. Home wound care

8. Which of the following statement is *false* regarding using sucralfate as a prophylactic agent for the treatment of stress ulcers?
A. It does not affect gastric pH.
B. It is the most effective agent to treat stress ulcers in ARDS patients.
C. Sucralfate should not be used with patients who are at high risk for gastrointestinal bleeding.
D. The CDC does not have specific recommendations for the use of sucralfate in stress-bleeding prophylaxis.

9. Which of these nonpharmacological strategies has not been shown to reduce the incidence of VAP?
A. Semirecumbent positioning of the patient
B. Use of closed-suction catheters and sterile suction techniques
C. Nasal rather than oral ET intubation
D. Maintaining adequate ET cuff pressure

10. Which of the following methods does not improve a patient's immune response to infections?
A. Maintain nutritional status
B. Rely on the use of invasive procedures when possible
C. Avoid agents that impair pulmonary defense (e.g., sedative narcotics, anesthetics, aminophylline)
D. Treat disease states that affect host defenses (e.g., acidosis, dehydration, hypoxemia)

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CHAPTER 15

Sedatives, Analgesics, and Paralytics

OUTLINE

KEY TERMS

- Analgesics
- Anesthetic
- Anterograde amnesic
- Depolarizing agents
- Miosis
- Nondepolarizing agents
- Paralytics
- Pruritus
- Ramsay Sedation Scale
- Sedatives
- Train-of-four monitoring

LEARNING OBJECTIVES

On completion of this chapter, the reader will be able to do the following:

1. List the most common sedatives and analgesics used in the treatment of critically ill patients.
2. Discuss the indications, contraindications, and potential side effects associated with each of the sedatives and analgesic agents reviewed.
3. Describe the most common method for assessing the need for and level of sedation.
4. Describe the Ramsay scale.
5. Discuss the advantages and disadvantages of using benzodiazepines, neuroleptics, anesthetic agents, and opioids in the management of mechanically ventilated patients.
6. Discuss the mode of action of depolarizing and nondepolarizing paralytics.
7. Explain how the train-of-four method is used to assess the level of paralysis in critically ill patients.
8. Contrast the indications, contraindications, and potential side effects associated with using various types of neuromuscular blocking agents.
9. Recommend a medication for a mechanically ventilated patient with severe anxiety and agitation.

Sedatives, analgesics, and paralytics are often required for the treatment of patients requiring mechanical ventilation in the intensive care unit (ICU). The importance of these drugs in the management of critically ill patients requires critical care therapists to have a working knowledge of the indications and contraindications, mode of action, potential adverse effects, and most appropriate methods to monitor the effects of these drugs.

Sedatives are used to reduce anxiety and agitation and promote sleep and anterograde amnesia; **analgesics** are used to lessen pain; **paralytics** are used to facilitate invasive procedures (e.g., surgery, endotracheal intubation), prevent movement, and ensure the stability of artificial airways. Paralysis may also be used to facilitate less conventional mechanical ventilation strategies.[1-3] (Key Point 15.1)

***Key Point* 15.1** Sedatives are used to reduce anxiety and agitation and to promote sleep; analgesics are used to lessen pain. Paralytics are used to facilitate endotracheal intubation, prevent movement, and ensure the stability of artificial airways.

A variety of pharmacological agents are available for achieving sedation and paralysis of mechanically ventilated patients. The most common sedative drugs used in the ICU include (1) benzodiazepines (e.g., diazepam, midazolam, lorazepam), (2) neuroleptics (e.g., haloperidol), (3) anesthetic agents (e.g., propofol), and (4) opioids (e.g., morphine, fentanyl). Paralysis can be achieved with neuromuscular blocking agents (NMBAs) that are classified

as depolarizing and nondepolarizing, depending on their mode of action. Succinylcholine is the only example of a depolarizing NMBA in widespread use; the most commonly used nondepolarizing NMBAs include pancuronium, vecuronium, and atracurium.

Maintaining an optimal level of comfort and safety for the patient should be a primary goal when administering sedatives, analgesics, and NMBAs. It is important therefore to recognize that although these agents can dramatically improve patient outcomes in mechanically ventilated patients, they can also precipitate significant hemodynamic, autonomic, and respiratory consequences in these patients. As discussed in Chapter 12, appropriate use of sedation protocols can lead to improved outcomes in critically ill patients (e.g., continuous sedation interruption during weaning and discontinuation of mechanical ventilation can lead to a reduction in the duration of mechanical ventilation and length of ICU stay).

SEDATIVES AND ANALGESICS

Sedation practices vary considerably because of institutional bias and because the requirements for sedation can vary greatly among patients.[4] As mentioned, sedation is generally prescribed for critically ill patients to treat anxiety and agitation and prevent or at least minimize sleep deprivation. Agitation and sleep deprivation can result from a variety of factors, including extreme anxiety, delirium, pain, and adverse drug effects. Sedation is also often required for mechanically ventilated patients who are being treated with less conventional modes of ventilation, such as high-frequency ventilation, inverse inspiratory-to-expiratory ratio ventilation, and permissive hypercapnia.[5]

The Joint Commission has defined four levels of sedation: minimal, moderate, deep, and anesthesia (Box 15.1). It is important to recognize that sedation needs may vary considerably during the course of a patient's stay in the ICU. For example, deeper levels of sedation and analgesia may be required during the initial phases of mechanical ventilation, especially in cases in which the patient is asynchronous or "fighting" the mechanical ventilatory mode being used. Conversely, minimal levels of sedation and analgesia are usually required during the recovery phase of an illness. Indeed, weaning a patient from mechanical ventilation can be severely hindered if the patient is oversedated.[6] It should be apparent therefore that reliable and accurate methods for assessing the need and level of sedation and analgesia are essential for the successful management of critically ill patients.[7]

Monitoring the Need for Sedation and Analgesia

Several techniques have been proposed to assess the level of sedation in adults and children. Examples of scoring systems validated for use in critically ill patients include the **Ramsay Sedation Scale** (RSS), the Sedation-Agitation Scale, and the Richmond Agitation Sedation Scale. Although considerable debate exists over the best technique, it is generally agreed that patients should be assessed regularly to ensure they are relaxed and are not complaining of pain (Key Point 15.2).

The RSS is shown in Table 15.1.[8] Notice that it is a graduated single-category scale. The grade assigned by the observer depends on the patient's response to stimuli. The advantages of using this type of single-category scale are that it is relatively easy to perform and provides a numerical value that can be used as a target for achieving adequate sedation. For example, a score of 2 to 4 on the

BOX 15.1 Levels of Sedation

Minimal Sedation
Patients can respond to verbal commands, although cognitive function may be impaired. Ventilatory and cardiovascular functions are unaffected.

Moderate Sedation (Conscious Sedation)
The patient can perform purposeful response after repeated or painful stimulation. (NOTE: Reflex withdrawal from painful stimulus is not considered a purposeful response.) Spontaneous ventilation is adequate, and cardiovascular function is usually maintained.

Deep Sedation
The patient is not easily aroused but can respond to painful stimulation. Spontaneous ventilation and maintenance of patent airway may be inadequate. Cardiovascular function is usually maintained.

Anesthesia
This level involves general anesthesia, spinal, or major regional anesthesia; local anesthesia is not included. Patient cannot be aroused, even by painful stimulation. Ventilatory assistance is typically required (i.e., artificial airway and positive pressure ventilation). Cardiovascular function may be impaired.

Modified from the American Society of Anesthesiologists: ASA standards, guidelines and statements. October 2007.

***Key Point* 15.2** Pain assessment and response to therapy should be performed regularly and systematically documented.[7]

TABLE 15.1 Ramsay Sedation Scale

Score	Description
1	Patient is awake but anxious, agitated, and restless
2	Patient is awake, cooperative, oriented, and tranquil
3	Patient is semiasleep but responds to verbal commands
4	Patient is asleep and has a brisk response to a light glabellar tap or loud auditory stimulus
5	Patient is asleep and has a sluggish response to a light glabellar tap or loud auditory stimulus
6	Patient is asleep and has no response to a light glabellar tap or loud auditory stimulus

RSS indicates adequate sedation. There are several disadvantages associated with using this type of graded scale. Most notably, it does not provide guidance on selection of the most appropriate sedative and is a subjective, nonlinear scale that does not allow for consideration of changing physiological and psychological needs of a patient during the course of his or her illness.[1]

Benzodiazepines

Benzodiazepines have been the drugs of choice for treatment of anxiety in critical care.[1] Preferential use of these drugs by critical care physicians is probably related to their relatively low cost and the ability of these drugs to produce anxiolytic, hypnotic, muscle relaxation, anticonvulsant, and **anterograde amnesic** effects. Anterograde amnesia relates to preventing acquisition and encoding of new information that can potentially lead to memories of unpleasant experiences and posttraumatic stress disorder.

Benzodiazepines exert their effects through a nonspecific depression of the central nervous system (CNS). This is accomplished when these drugs bind to benzodiazepine sites on the *γ-aminobutyric acid (GABA) receptor complex* on neurons in the brain. Binding of benzodiazepines to the GABA receptor complex increases the chloride permeability of the neuron, which in turn hyperpolarizes the neuron, making depolarization less likely.[9]

Benzodiazepines vary in potency, onset of action, uptake, distribution, and elimination half-life. The intensity and duration of action for the various benzodiazepines can be affected by a number of patient-specific factors, including age, underlying pathology, and concurrent drug therapy. Prolonged recovery from benzodiazepines typically occurs in patients with renal and hepatic insufficiency.[7]

Benzodiazepines generally produce only minimal effects on cardiovascular function; however, they can cause a significant drop in blood pressure when initially administered to hemodynamically unstable patients (e.g., patients with hypovolemic shock). Similarly, benzodiazepines normally do not adversely affect the respiratory system; however, they can produce hypoventilation or apnea by causing a reduction in ventilatory drive in patients with chronic obstructive pulmonary disease when combined with opioids.

Reversal of the effects of benzodiazepines can be accomplished with flumazenil (Romazicon), which prevents the sedative effects of these drugs by competitively binding to benzodiazepine receptors. It is a short-acting drug that is administered intravenously. Administration of flumazenil is generally reserved for patients admitted to the emergency department for suspected benzodiazepine overdose. The most common side effects of flumazenil include dizziness, panic attacks, and cardiac ischemia, and it may lead to seizures in patients receiving long-term benzodiazepine or tricyclic antidepressant therapy.

Diazepam

Diazepam (Valium) has a rapid onset of action because of its high lipid solubility and ability to traverse the blood-brain barrier relatively quickly. The average onset of action for diazepam when it is administered intravenously is 3 to 5 minutes.[9] It is metabolized in the liver to active metabolites that have relatively long half-lives (40–100 hours). These active metabolites are ultimately eliminated by the kidney. Therefore diazepam elimination can be decreased in older patients, neonates, and patients with compromised hepatic and renal function, resulting in prolonged clinical effects and delayed recovery from sedation.[10]

Intravenous (IV) administration of diazepam is the most reliable method to maintain sedation in critically ill patients because absorption through the oral and intramuscular routes can vary considerably. Continuous infusion of diazepam is not recommended. Instead, a bolus dose of the drug is administered at the start of an infusion, followed by a series of smaller boluses with close titration to produce the desired plasma concentration of the drug.[11]

Midazolam

Midazolam (Versed) has a rapid onset of action and short half-life, making it an ideal sedative for the treatment of acutely agitated patients (Key Point 15.3). Note that although it does have a short half-life, prolonged sedation can occur as a result of the accumulation of the drug and its metabolites in the peripheral tissues when it is administered for longer than 48 hours.[1]

***Key Point* 15.3** Midazolam and diazepam should be used for rapid sedation of acutely agitated patients.[7]

Midazolam causes a reduction in cerebral perfusion pressure, but it does not protect against increases in intracranial pressure for patients receiving ketamine.[1] Although midazolam does not cause respiratory depression in most patients, it depresses the sensitivity of upper respiratory reflexes and can reduce the ventilatory response in patients with chronic obstructive pulmonary disease and in patients receiving narcotics.[12]

Midazolam typically causes only minimal hemodynamic effects (e.g., lower blood pressure, reduction in heart rate) in euvolemic subjects and is usually well tolerated in patients with left ventricular dysfunction. It can produce significant reductions in systemic vascular resistance and blood pressure in patients who depend on increased sympathetic tone to maintain venous return.[1]

Lorazepam

Lorazepam (Ativan) is the drug of choice for sedating mechanically ventilated patients in the ICU for longer than 24 hours. It has a slower onset of action compared with diazepam and midazolam because of its lower lipid solubility and longer time required to cross the blood-brain barrier. Its lower lipid solubility coupled with decreased distribution in peripheral tissues may account for its longer duration of action in some patients compared with diazepam and midazolam.[13]

Potential adverse drug interactions are less likely with lorazepam than with other benzodiazepines because it is metabolized in the liver to inactive metabolites. Continual use of lorazepam, however, has been associated with several side effects, including lactic acidosis, hyperosmolar coma, and a reversible nephrotoxicity. These latter side effects have been attributed to the use of the

Case Study 15.1

Patient Case—Discontinuing Lorazepam

A 50-year-old man with moderately severe pulmonary fibrosis is admitted to the emergency department with an irregular heart rate and signs of agitation. He reports that he is exhausted and unable to get a good night's sleep. He has been treated with lorazepam (Ativan) for anxiety and insomnia for 6 months. He explains to the attending physician that he stopped taking his medication because "it makes me feel too tired to get anything done." What are some common side effects associated with abruptly discontinuing taking the lorazepam?

solvents (e.g., propylene glycol, polyethylene glycol) in the manufacture of lorazepam.[9] Lorazepam acts synergistically with other CNS depressants and should be administered with caution in patients receiving these drugs.[13] Case Study 15.1 provides more information about several potential harmful effects associated with long-term use of lorazepam.

Dexmedetomidine

Dexmedetomidine is an α_2-adrenoreceptor agonist used for short-term sedation and analgesia in the ICU. It has been shown to reduce sympathetic tone (i.e., sympatholytic activity), with attenuation of the neuroendocrine and hemodynamic response to anesthesia and surgery.[14,15] It has been shown to reduce the need for anesthetic and opioid requirements.[14] In a randomized controlled study designed to determine the efficacy of dexmedetomidine versus midazolam and propofol (Dipravan) in ICU patients, Jakob and colleagues found that dexmedetomidine had effects similar to those of midazolam and propofol to maintain light to moderate sedation. They also showed that dexmedetomidine appeared to reduce the duration of mechanical ventilation compared with midazolam. Compared with midazolam and propofol, dexmedetomidine reduced the time to extubation. Another interesting finding was that it reduced delirium in patients compared with propofol and improved patients' ability to communicate pain compared with midazolam and propofol. The study did find, however, that more adverse effects were associated with dexmedetomidine compared with midazolam and propofol.[15]

Neuroleptics

Neuroleptics are routinely used to treat patients demonstrating evidence of extreme agitation and delirium. Disorganized thinking and unnecessary motor activity characterize delirium; it is often seen in patients who have been treated in the ICU for prolonged periods (i.e., ICU syndrome) (Key Point 15.4).

***Key Point* 15.4** The presence of delirium can delay liberation of patients from mechanical ventilation.

Haloperidol is a butyrophenone that causes CNS depression. Although it is the drug of choice for the treatment of delirium in ICU patients, it can cause some potentially serious side effects. It possesses antidopaminergic and anticholinergic effects. It can induce α-blockade, lower the seizure threshold, and evoke Parkinson-like symptoms (i.e., extrapyramidal effects, such as muscle rigidity, drowsiness, and lethargy). Dose-dependent cardiac dysrhythmias, including QT prolongation and torsades de pointes, have also been reported to occur, particularly in patients receiving high-dose bolus administration of haloperidol.[16]

The onset of action of haloperidol is 3 to 20 minutes after an initial dose is administered intravenously. Additional doses of the drug can be administered if the patient continues to be agitated. Despite the potential side effects noted previously, haloperidol has been demonstrated to be a safe drug for the treatment of delirium in ICU patients.[17]

Anesthetic Agents

Propofol is an IV, general **anesthetic** agent that possesses sedative, amnesic, and hypnotic properties at low doses, although it has no analgesic properties.

Propofol produces significant hemodynamic effects. Most notably, it causes reductions in systemic vascular resistance with a concomitant fall in blood pressure and bradycardia during the initial induction phase. Propofol reduces cerebral blood flow and intracranial pressure (ICP), making it a useful sedative for neurosurgical patients. In fact, propofol has been shown to be more effective than fentanyl in reducing ICP in patients with traumatic brain injury. Additionally, propofol and morphine administered simultaneously allow greater control of ICP than does morphine alone.[9]

Propofol has a rapid onset and short duration of sedation once it is discontinued. The rapid awakening from propofol allows interruption of the infusion for neurological assessment. Slightly longer recovery times can occur with prolonged infusion. Clearance appears to be unaffected by renal and hepatic dysfunction (Key Point 15.5).

***Key Point* 15.5** Propofol is an ideal sedative when rapid awakening is important, such as when neurological assessment is required, or for extubation.[7]

Adverse effects associated with propofol administration include hypotension, dysrhythmias, and bradycardia. It has also been shown to cause elevation of pancreatic enzymes. Propofol infusion syndrome in ICU sedation is characterized by severe metabolic acidosis, hyperkalemia, rhabdomyolysis, hepatomegaly, and cardiac and renal failure. Propofol is available as an emulsion in a phospholipid vehicle, which provides 1.1 kcal/mL. This fact is important to keep in mind because propofol is a source of triglycerides and supplemental calories in patients receiving parenteral nutrition.[1] Prolonged use (>48 hours) has also been associated with lactic acidosis and lipedema in pediatric patients.

BOX 15.2 Side Effects of Opioids

- Nausea, vomiting, constipation
- Respiratory depression
- Bradycardia and hypotension
- Myoclonus (muscle twitching), seizures
- Histamine release, immunosuppression
- Physical dependence

Opioids

Opioids (or opiates) are endogenous and exogenous substances that can bind to a group of receptors located in the CNS and peripheral tissues. Opioids are generally classified as naturally occurring, synthetic, and semisynthetic, or, as discussed later, may be classified on the basis of their activity at opioid receptors.[1] Morphine sulfate is a naturally occurring opioid agonist; fentanyl citrate is a synthetic analog of morphine.

Although the primary pharmacological action of opioids is to relieve pain, these drugs can also provide significant secondary sedative and anxiolytic effects, which are mediated through two types of opioid receptors: mu (μ) and kappa (κ) receptors. The μ receptors are responsible for analgesia, and the κ-receptors mediate the sedative effects of these drugs.

It is well recognized that opioids can cause a number of serious side effects (Box 15.2). The severity of these side effects depends on the dosage administered in addition to the extent of the patient's illness and integrity of organ function (i.e., renal, hepatic, and hemodynamic function).

Reversal of the aforementioned side effects can be accomplished with the opioid antagonist naloxone hydrochloride (Narcan). Naloxone has a short onset of action (~30 seconds) and usually lasts about 30 minutes. When used to facilitate opioid withdrawal, a continuous IV infusion is required. It is important to understand that administering smaller doses of naloxone will reverse the respiratory depressant effects of opioids while not interfering with the analgesic effects of these drugs. Using larger doses will not only reverse respiratory depression but also reduce the analgesic effects.

Morphine

Morphine is a potent opioid analgesic agent that is the preferred agent for intermittent therapy because of its longer duration of action. It can produce significant effects on the CNS and alter the control of breathing even in normal healthy individuals. Some of the potential side effects of morphine include reductions in minute ventilation ($\dot{V}_E$), periodic breathing, and even apnea by altering respiratory activity of the pontine and medullary respiratory centers in the brainstem.[1] Morphine's effects on the CNS also include reductions of cerebral blood flow, ICP, and cerebral metabolic activity, drowsiness and lethargy, miosis, and suppression of the cough reflex.[18]

The effects of morphine on the gastrointestinal tract include reduction of lower esophageal sphincter tone and propulsive peristaltic activity of the intestine, which in turn leads to constipation. Morphine can also increase the tone of the pyloric sphincter and ultimately lead to nausea and vomiting by delaying the passage of contents through the gastrointestinal tract.[1]

Morphine can alter vascular resistance by causing decreases in sympathetic tone and increases in vagal tone. Reduction in vascular tone can lead to significant hypotension in patients who rely on increased sympathetic tone to maintain blood pressure. Increases in serum histamine levels can also occur with the injection of morphine and ultimately add to the peripheral vasodilation and hypotension. Increased serum histamine levels are associated with **pruritus** and bronchospasm in patients with asthma and in individuals with hypersensitive airways.

In the ICU, the IV route of delivery is the most effective method of administering morphine for sedation. It can be delivered as a bolus or as a continuous infusion when prolonged sedation and analgesia are required. The onset of action of morphine is slower than that of other opioids because of its lower lipid solubility and slower transit time across the blood-brain barrier. It is metabolized to active metabolites, including morphine-6 glucuronide, which can result in prolonged clinical effects. The presence of renal or hepatic diseases can further impair the clearance of morphine and its metabolites.

Fentanyl

Fentanyl citrate (Sublimaze) is a synthetic opioid that is approximately 100 to 150 times more potent than morphine.[19] Its high lipid solubility and short transit time across the blood-brain barrier produce a rapid onset of action. Fentanyl has a longer half-life than morphine and can accumulate in the peripheral tissues after prolonged infusion. In cases of prolonged infusion, clearance can be delayed, resulting in long-lasting effects (e.g., respiratory depression), particularly in patients with renal failure.

Fentanyl is normally administered as a loading dose followed by a continuous infusion to maintain its analgesic effect because of its short duration of action. Fentanyl transdermal patches are available for patients who require long-term analgesia. Although these patches can provide consistent drug delivery in hemodynamically stable patients, the extent of absorption varies depending on the permeability, temperature, perfusion, and thickness of the patient's skin.[9] Different sites should be used when reapplying patches. Fentanyl patches are not indicated for the treatment of acute analgesia because it takes approximately 12 to 24 hours to reach peak effect. Once the patch is removed, a similar lag period occurs before the effects completely disappear.

Fentanyl has minimal effects on the cardiovascular system and does not cause histamine release as does morphine. It also has minimal effects on the renal system compared with other opioids. Therefore fentanyl is the opioid of choice for patients with unstable hemodynamic status and renal insufficiency (Key Point 15.6). It can cause respiratory depression in some patients because of a biphasic elimination response that occurs when the drug is mobilized from peripheral tissues.

***Key Point* 15.6** Fentanyl is preferred for patients with hemodynamic instability and renal insufficiency.[7]

Box 15.3 summarizes the agents discussed in this section (Case Study 15.2).

BOX 15.3 Sedatives, Neuroleptics, Anesthetic Agents, and Opioids Used in Mechanically Ventilated Patients

Sedatives (Benzodiazepines)

Diazepam (Valium)
- Rapid onset of action
- Relatively low cost
- Half-life of 36 hours (or 1—3 days); multiple doses result in prolonged effect, especially in older patients and in patients with hepatic dysfunction

Midazolam (Versed)
- Onset of action in 2 to 2.5 minutes
- High cost
- Half-life of 1 hour
- Prolonged action with impaired hepatic function
- Metabolized in the liver

Lorazepam (Ativan)
- Onset of action in 5 to 20 minutes
- Low cost
- Half-life of 6 to 15 hours

Other Sedatives
- Chlordiazepoxide (Librium)
- Dexmedetomidine (Precedex)
- Alprazolam (Xanax)
- Triazolam (Halcion)
- Flurazepam (Dalmane)

Neuroleptics

Haloperidol (Haldol)
- Onset in 3 to 5 minutes
- Half-life 18 to 54 hours

Anesthetic

Propofol (Diprivan)
- Onset of action in 1 minute
- High cost
- Half-life from less than 30 minutes to 3 hours

Opioids (Narcotic Analgesics)

Morphine Sulfate
- Moderate onset of action
- Low cost

Fentanyl Citrate (Sublimaze)
- Rapid onset of action
- Moderate cost
- Short duration of action, but longer half-life than morphine
- Less cardiovascular effect than morphine; more potent than morphine; may produce increased muscle tone (e.g., chest and abdominal wall rigidity)

Others

Hydromorphone (Dilaudid)
- Rapid onset of action
- Moderate cost
- Acceptable morphine substitute

Paralytics

The following are the most common reasons for using NMBAs in patients on mechanical ventilation:
- Patient-ventilator asynchrony that cannot be corrected by adjusting ventilator settings (Key Point 15.7)

***Key Point* 15.7** It is important to recognize that ventilator asynchrony may be the result of an inappropriate ventilator setting or the presence of auto-PEEP.

Case Study 15.2

Patient Case—Agitated Patient

A 30-year-old woman admitted to the intensive care unit after a motor vehicle accident is anxious and in obvious pain. She is listed as being in guarded condition because of fluctuation in her arterial blood pressure. She has become increasingly combative to the attending staff and made several unsuccessful attempts to remove her endotracheal tube. What would be an effective pharmacological agent to treat this patient's symptoms?

- Facilitation of less conventional mechanical ventilation strategies (e.g., inverse I/E ratios, high-frequency ventilation, permissive hypercapnia)
- Facilitation of intubation, ensuring stability of the airway during transport, or repositioning
- Dynamic hyperinflation that cannot be corrected
- Adjunctive therapy for controlling raised ICP
- Reduction of oxygen consumption and carbon dioxide production[1]

As mentioned earlier, the two classes of NMBAs available for paralyzing patients on mechanical ventilation include depolarizing muscle relaxants and nondepolarizing muscle relaxants. **Depolarizing agents** (succinylcholine) resemble acetylcholine in their chemical structure. These drugs induce paralysis by binding to acetylcholine receptors and causing prolonged depolarization of the motor end plate. **Nondepolarizing agents** (pancuronium, vecuronium, atracurium, and cisatracurium) also bind to acetylcholine receptors but cause paralysis by competitively inhibiting the action of acetylcholine at the neuromuscular junction (Box 15.4 and Case Study 15.3).

Choosing the most appropriate muscle relaxant depends on a number of factors, such as its onset of action and how fast the patient can recover from its effects once it is discontinued, the patient's physical condition and organ function (particularly renal and hepatic function), and the pharmacodynamics and cost of the drug.

Regardless of the NMBA used, it is important to understand that these drugs do *not* possess sedative or analgesic properties

BOX 15.4 Paralytics Used in the Intensive Care Unit

Depolarizing Agents
- Succinylcholine (Anectine)

Nondepolarizing Agents
- Pancuronium (Pavulon)
- Vecuronium (Norcuron)
- Atracurium besylate (Tracrium)
- Cisatracurium (Nimbex)
- Rocuronium (Zemuron)

Case Study 15.3

Patient Case—Asynchrony

A respiratory therapist notes that a patient is using accessory muscles during mechanical ventilation. The ventilator graphics indicate the presence of patient-ventilator asynchrony. The respiratory therapist checks for appropriate settings of flow, sensitivity, and ventilator mode and rules out the presence of auto-PEEP. After talking with the physician, it is agreed that the patient may require the use of a pharmacological intervention. What would be appropriate for this patient?

(i.e., reduce anxiety or provide pain relief) and must therefore be used in conjunction with adequate amounts of sedatives and analgesics to ensure patient comfort. Furthermore, monitoring the effectiveness of neuromuscular blockade is essential to ensure patient safety (Key Point 15.8).

***Key Point* 15.8** Neuromuscular blocking agents do *not* possess sedative or analgesic properties.

Monitoring Neuromuscular Blockade

Monitoring neuromuscular blockade can be accomplished using visual, tactile, and electronic assessment of the patient's muscle tone. Observing the patient's skeletal muscle movements and respiratory effort can provide an easy method to determine whether the patient is paralyzed; however, more sophisticated electronic monitoring is typically required to determine the depth of paralysis.

A common method used to assess the depth of paralysis is an electronic technique referred to as **train-of-four** (TOF) monitoring.[20,21] With this technique, two electrodes are placed on the skin along a nerve path, often near a hand, foot, or facial nerve. An electrical current consisting of four impulses is applied to the peripheral nerve over 2 seconds, and the muscle contractions (twitches) produced provide information about the level of paralysis (Box 15.5).

BOX 15.5 Assessment of the Train-of-Four Response

- *One or two twitches:* The paralyzing agent is providing adequate effect.
- *Three twitches:* The paralyzing agent is moderately effective.
- *Four twitches:* The paralyzing agent needs to be readministered if continued paralysis is required.

From Mathewson HS: Prolonged neuromuscular blockade [editorial], *Respir Care* 38:522–524, 1993.

Although there has been considerable debate about how to perform the test and interpret the results (i.e., the number of twitches elicited with the TOF stimulation), the Society for Critical Care Medicine recommends that one or two twitches indicates that an adequate amount of NMBA is being administered.[22] It is important to recognize that TOF monitoring can provide valuable information to enable the clinician to maintain the desired depth of paralysis. Variability can occur among individuals performing the test and thus significantly affect the veracity of the result. When it is performed accurately and in a consistent manner, however, TOF monitoring can reduce the amount of NMBA administered to a patient and thus avoid complications such as the development of prolonged paralysis and muscle weakness.[21]

Depolarizing Agents

Succinylcholine

Succinylcholine chloride (Anectine) is the only depolarizing NMBA in widespread use. It is a short-acting (5–10 minutes) depolarizing muscle relaxant that has an onset of action of approximately 60 seconds. Succinylcholine (diACh) is most often used to facilitate endotracheal intubation. Its use in the ICU has declined during recent years because of the introduction of newer paralyzing drugs that have minimal cardiovascular side effects. It is important to know, however, that diACh is the recommended drug for inducing paralysis in hemodynamically stable critically ill patients because of its relatively low cost, rapid onset of action, and short duration of action.

The most common side effects associated with diACh include transient hyperkalemia; cardiac dysrhythmias; anaphylactic reactions; prolonged apnea; postoperative myalgias; increased intragastric, intracranial, and intraocular pressures; myoglobinuria; and sustained skeletal muscle contraction. (Hyperkalemia induced by the injection of diACh can be particularly problematic in patients with congestive heart failure who are also receiving diuretics and digitalis.) diACh can also precipitate malignant hyperthermia in susceptible individuals. Malignant hyperthermia is a rare but potentially fatal disorder characterized by sustained skeletal muscle depolarization. It occurs at a rate of 1:50,000 in adults and 1:15,000 in the pediatric population.[20-23]

diACh is inactivated by the action of pseudocholinesterase. Therefore prolonged action of diACh can occur if the serum pseudocholinesterase concentration is low or inhibited. Low concentrations of the enzyme occur during pregnancy, chronic renal failure, or severe liver damage and after starvation. The enzyme can be inhibited by anticholinesterases, organophosphates, azathioprine, cyclophosphamide, and monoamine oxidase inhibitors.[13]

Nondepolarizing Agents

Pancuronium

Pancuronium (Pavulon) was one of the first nondepolarizing NMBAs used for prolonged paralysis of patients being mechanically ventilated in the ICU. Paralysis is achieved by administering a loading dose. Sustained muscle paralysis is accomplished by administering a maintenance dose.

Pancuronium is a quaternary ammonium compound—more specifically, an aminosteroid muscle relaxant that has a slow onset

and prolonged duration of action. It is metabolized by the liver by acetylation and eliminated through the kidney. The most serious side effect attributed to pancuronium includes prolonged paralysis after discontinuation of the drug, particularly in patients with renal and hepatic failure. The prolonged duration of action may be partially explained by the fact that it is metabolized in the liver to an active 3-hydroxy metabolite that retains up to 50% of the activity of the parent compound.[23]

Other significant side effects associated with pancuronium, which result from its vagolytic effect, include tachycardia, increased cardiac output, and elevated mean arterial pressure. Its sympathomimetic activity can also lead to alterations in the ventilation-perfusion relationship as a result of pulmonary vasoconstriction.[23]

Vecuronium

Vecuronium bromide (Norcuron) is an intermediate-duration, nondepolarizing aminosteroid NMBA that does not possess the vagolytic properties of pancuronium.[24] The intermediate duration of action for vecuronium may be explained by its metabolism to minimally active metabolites.[19]

Initial data suggested that vecuronium was an effective means of producing prolonged paralysis in patients with renal insufficiency because of its hepatic and biliary elimination. Subsequent reports, however, suggested that prolonged paralysis may occur in patients with renal and hepatic insufficiency because of accumulation of vecuronium and its 3-desacetyl metabolite.[25]

Atracurium and Cisatracurium

Like vecuronium, atracurium besylate and its stereoisomer, cisatracurium besylate (Nimbex), are intermediate-duration, nondepolarizing muscle relaxants that do not have the hemodynamic side effects of pancuronium. Atracurium has been shown to cause mast cell degranulation and histamine release at higher doses, which in turn can lead to peripheral vasodilation and hypotension. Cisatracurium has been shown to cause only minimal mast cell degranulation and subsequent histamine release.[22] The lack of cardiovascular side effects may be explained on the basis that atracurium and cisatracurium are benzylquinolones that are metabolized to hemodynamically inactive metabolites in the plasma by ester hydrolysis and Hofmann elimination. One of the breakdown products of the Hofmann elimination of atracurium, laudanosine, has been associated with CNS stimulation and can precipitate seizures when it accumulates in the plasma.

The pharmacokinetic profiles of atracurium and cisatracurium make these drugs ideal NMBAs for patients with renal and hepatic insufficiency. Recovery from neuromuscular blockade typically occurs in 1 to 2 hours after continuous infusions are stopped. However, long-term use of these drugs can lead to the development of tolerance, which in turn may necessitate significant dosage increases. Additionally, muscle weakness can occur with prolonged use of these types of agents[13] (Case Study 15.4).

Case Study 15.4

Patient Case—Neuromuscular Blocking Agent

A 45-year-old man is admitted to the emergency department for injuries sustained from a fall that occurred while he was working to repair the chimney on his house. His admission diagnosis includes a fractured right radius and contusion to his right upper thorax. There is no evidence of head trauma. The patient's respiratory rate is 30 breaths per minute, his blood pressure is 140/85 mm Hg, and his pulse rate is 110 beats/min. The resident on-call physician requests that a neuromuscular blocking agent (NMBA) is administered to accomplish intubation of this patient. Which NMBA would be appropriate for this patient?

SUMMARY

- Selection of the most appropriate drug for sedating or paralyzing a patient should be based on several criteria, including the patient's condition, the drug's efficacy and safety profile, and the cost of administering the drug over a prolonged period.
- Although historically the selection of sedatives, analgesics, and NMBAs has been based on personal preference, recent clinical practice guidelines have helped define more clearly the most appropriate drugs and strategies for clinicians treating ICU patients with these drugs.
- Sedation is generally prescribed for the treatment of anxiety and agitation and to prevent or at least minimize sleep deprivation.
- The ideal sedative should have a rapid onset, have a relatively short active effect, and be easily titrated. Its effects should be reversible and have minimal, if any, effects on vital organ function.
- A common reason for using NMBAs is to alleviate patient-ventilator asynchrony that cannot be resolved with ventilator adjustment.
- Two classes of NMBAs are available for paralyzing patients on mechanical ventilation: depolarizing muscle relaxants and nondepolarizing muscle relaxants.
- Choosing the most appropriate NMBA depends on the patient's physical condition and the selected drug's onset of action and how fast the patient can recover from its effects once it is discontinued. NMBAs do not possess sedative or analgesic properties and therefore should be used in conjunction with adequate amounts of sedatives and analgesics to ensure patient comfort.
- Maintaining an optimal level of comfort and safety for the patient should be a primary goal when administering sedatives, analgesics, and NMBAs.

REVIEW QUESTIONS *(See Appendix A for answers.)*

1. Which of the following is an appropriate short-acting, depolarizing agent to use for intubation of a patient?
   A. Pancuronium
   B. Succinylcholine
   C. Vecuronium
   D. Fentanyl
2. A patient on mechanical ventilation exhibits severe anxiety and agitation. Talking with the patient does not successfully

relieve his symptoms. The nurse is concerned that the patient is sleep deprived. Which of the following would be an appropriate medication to suggest?
A. Opioid
B. Paralyzing agent
C. Sedative
D. Neuromuscular blocking agent

3. A patient in the ICU has a Ramsay score of 6. Which of the following is a patient indication resulting from this score?
A. Patient responds to a painful stimulus
B. Patient has irreversible brain injury
C. Patient requires an additional dose of paralyzing agent
D. Patient is heavily sedated

4. While performing an assessment of the level of sedation of a patient, the following is observed: Patient is asleep; patient has a brisk response to a light glabellar tap or loud auditory stimulus. These criteria would suggest that the patient would rate a score of _____ on the Ramsay scale.
A. 1
B. 2
C. 4
D. 6

5. A patient with chronic CO_2 retention and lung cancer is being treated with morphine for pain. She is anxious and keeps trying to get out of bed, despite the use of restraints. The nurse gives midazolam (Versed) and shortly thereafter notes that the patient's respirations become irregular and periods of apnea occur. Which of the following is the most appropriate treatment for this patient?
A. Flumazenil (Romazicon)
B. Caffeine
C. Noninvasive positive pressure ventilation
D. Reduction of morphine administration

6. A patient is receiving mechanical ventilation as a result of an apparent tetanus infection. The patient is having tetanic contractions. What medications would be appropriate for this patient?
1. Paralytic agents
2. Analgesics
3. Sedatives
4. Diuretics
A. 1 and 2 only
B. 2 and 3 only
C. 1, 2, and 3 only
D. 2, 3, and 4 only

7. A patient receiving morphine postoperatively by a self-actuating morphine pump complains of nausea. Which of the following is the appropriate response?
A. Nausea is not a common side effect when administering opioids, so you should ignore the patient's complaint.
B. Notify housekeeping.
C. The morphine should be stopped.
D. Contact the nurse and the physician.

8. Which of the following is a nondepolarizing NMBA?
1. Pancuronium
2. Vecuronium
3. Atracurium
4. Succinylcholine
A. 1 and 3 only
B. 2 and 4 only
C. 1, 2, and 3 only
D. 1, 2, 3, and 4

9. Which of the following is not correctly matched?
A. Diazepam, Valium
B. Propofol, Dipravan
C. Midazolam, Versed
D. Fentanyl, Ativan

10. Describe the technique of TOF monitoring.

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CHAPTER 16

Extrapulmonary Effects of Mechanical Ventilation

OUTLINE

KEY TERMS

- Cardiac tamponade
- Cardiac transmural pressure
- Oliguria
- Polyneuritis

LEARNING OBJECTIVES

On completion of this chapter, the reader will be able to do the following:

1. Explain the effects of positive pressure ventilation on cardiac output and venous return to the heart.
2. Discuss the three factors that can influence cardiac output during positive pressure ventilation.
3. Explain the effects of positive pressure ventilation on gas distribution and pulmonary blood flow in the lungs.
4. Describe how positive pressure ventilation increases intracranial pressure.
5. Summarize the effects of positive pressure ventilation on renal and endocrine function.
6. Describe the effects of abnormal arterial blood gases on renal function.
7. Name five ways of assessing a patient's nutritional status.
8. Describe techniques that can be used to reduce complications associated with mechanical ventilation.

EFFECTS OF POSITIVE PRESSURE VENTILATION ON THE HEART AND THORACIC VESSELS

The physiological effects of mechanical ventilation are well documented. Laboratory and clinical studies have demonstrated that positive pressure ventilation can significantly alter cardiovascular, pulmonary, neurological, renal, and gastrointestinal (GI) function. (See Chapter 17 for information on the pulmonary effects and complications of mechanical ventilation.) Thus every attempt should be made to minimize its adverse effects. Understanding the

physiological effects and potential complications of positive pressure ventilation is therefore essential for clinicians involved with ventilator management.

ADVERSE CARDIOVASCULAR EFFECTS OF POSITIVE PRESSURE VENTILATION

Positive pressure ventilation can significantly change physiological pressures in the thorax. The extent of these changes depends on the amount of positive pressure applied to the airways and a patient's cardiopulmonary status (Key Point 16.1).

The Thoracic Pump Mechanism During Normal Spontaneous Breathing and During Positive Pressure Ventilation

It has been known for several decades that positive pressure ventilation can reduce cardiac output. This phenomenon can be understood in part by comparing intrapleural (i.e., intrathoracic) pressure changes that occur during normal spontaneous or negative pressure breathing with those occurring during positive pressure ventilation.

During spontaneous breathing, the fall in intrapleural pressure that draws air into the lungs during inspiration also draws blood into the major thoracic vessels and heart (Fig. 16.1). With this increased return of blood to the right side of the heart and the stretching and enlargement of the right heart volume, the right ventricular (RV) preload increases, resulting in an increased RV stroke volume (SV; i.e., Frank-Starling mechanism). Conversely, during a spontaneous (passive) expiration, intrapleural pressure rises (i.e., becomes less negative), causing a reduction in venous return and RV preload, which in turn leads to a decrease in RV SV). Note that these pressure changes affect left heart volumes in a similar fashion.

The effects on intrathoracic pressures and venous return are quite different when positive pressure is applied to the airway (Fig. 16.2). During inspiration, increases in airway pressure are transmitted to the intrapleural space and the great vessels and other structures in the thorax. As the airway pressure rises, the intrapleural pressure rises and intrathoracic blood vessels become compressed, causing the central venous pressure (CVP) to increase. This increase in CVP reduces the pressure gradient between systemic veins and the right side of the heart, which reduces venous return to the right side of the heart and thus RV filling (preload). As a result, RV SV decreases.[1,2]

Notice that vascular pressures within the thorax generally increase in proportion to increases in mean airway pressure ($\bar{P}_{aw}$) and intrapleural pressure (i.e., the higher the $\bar{P}_{aw}$, the greater the effects). This phenomenon is particularly evident when one considers the effect of adding positive end-expiratory pressure (PEEP) during positive pressure ventilation. Because PEEP further increases $\bar{P}_{aw}$ during positive pressure ventilation, it is reasonable to assume that reductions in venous return and cardiac output are greater during positive pressure ventilation with PEEP than with positive pressure ventilation alone. Furthermore, the addition of PEEP during an assisted breath decreases cardiac output more than when PEEP is used with intermittent mandatory ventilation (IMV) or continuous positive airway pressure alone.

Increased Pulmonary Vascular Resistance and Altered Right and Left Ventricular Function

During inspiration with high tidal volumes (V_Ts) or when high levels of PEEP are used, the pulmonary capillaries that interlace the alveoli are stretched and narrowed. As a result, resistance to blood flow through the pulmonary circulation increases (Fig. 16.3). This increases RV afterload (i.e., pulmonary vascular resistance [PVR] and the resting volume of the right ventricle). In normal healthy individuals, RV SV is maintained in the face of increased PVR because RV contractile function is not severely impaired. However,

***Key Point* 16.1** The physiological effects of positive pressure ventilation depend on the amount of pressure applied to the airways and the patient's cardiopulmonary status.

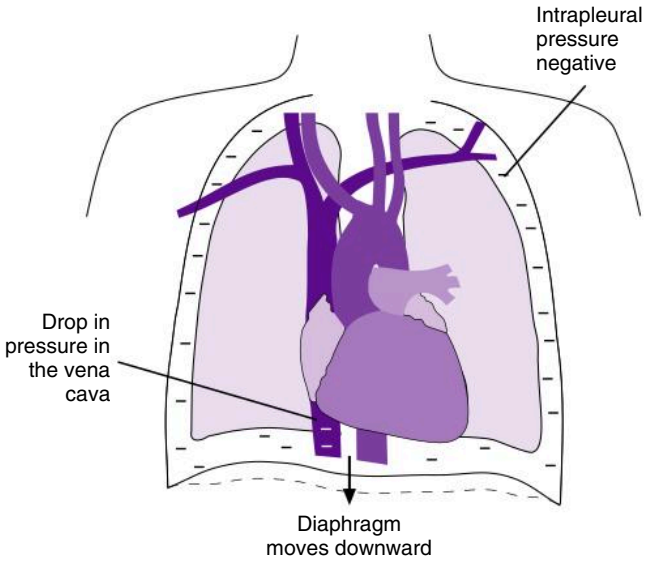

Fig. 16.1 The negative intrapleural pressures that occur during spontaneous inspiration are transmitted to the intrathoracic vessels. A reduction in pressure in the vena cava increases the pressure gradient back to the heart, and venous return increases.

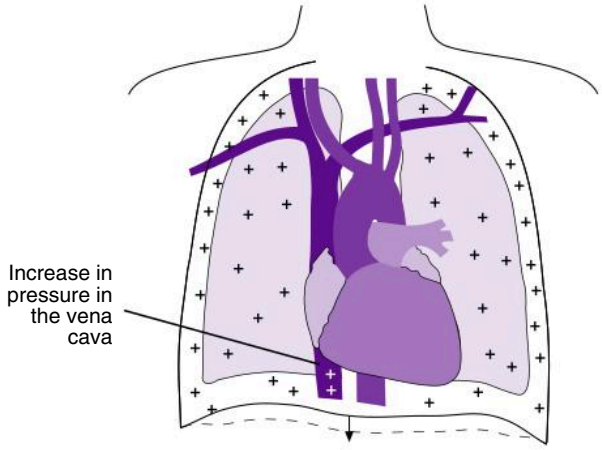

Fig. 16.2 Positive pressure ventilation increases lung and intrapleural (intrathoracic) pressures. This positive pressure is transmitted to the intrathoracic vessels. A rise in the pressure in the vena cava reduces venous return to the heart.