

Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults

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Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are important causes of morbidity and mortality, with mortality rates approaching 62%. HAP and VAP are the second most common cause of nosocomial infection overall, but are the most common cause documented in the intensive care unit setting. In addition, HAP and VAP produce the highest mortality associated with nosocomial infection. As a result, evidence-based guidelines were prepared detailing the epidemiology, microbial etiology, risk factors and clinical manifestations of HAP and VAP. Furthermore, an approach based on the available data, expert opinion and current practice for the provision of care within the Canadian health care system was used to determine risk stratification schemas to enable appropriate diagnosis, antimicrobial management and nonantimicrobial management of HAP and VAP. Finally, prevention and risk-reduction strategies to reduce the risk of acquiring these infections were collated. Future initiatives to enhance more rapid diagnosis and to effect better treatment for resistant pathogens are necessary to reduce morbidity and improve survival.

Key Words: Guidelines; Hospital-acquired; Pneumonia; Ventilator-associated

EXECUTIVE SUMMARY

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are important causes of morbidity and mortality in Canada, and they warrant a comprehensive management guideline. Furthermore, the economic impact of HAP and VAP is significant and has been a burden on health care resources. The present document, initiated and prepared jointly by the Association of Medical Microbiology and Infectious Disease Canada and the Canadian Thoracic Society, is an evidence-based guideline for the management of HAP and VAP. Group members represented the areas of

Des lignes directrices cliniques pour la pneumonie nosocomiale et la pneumonie sous ventilation assistée chez les adultes

La pneumonie nosocomiale (PN) et la pneumonie sous ventilation assistée (PVA) sont d'importantes causes de morbidité et de mortalité, les taux de mortalité avoisinant les 62 %. Dans l'ensemble, la PN et la PVA constituent la deuxième cause d'infection nosocomiale en importance, mais la principale cause documentée à l'unité de soins intensifs. De plus, la PN et la PVA produisent le plus fort taux de mortalité imputable à une infection nosocomiale. C'est pourquoi on a préparé des lignes directrices probantes détaillant l'épidémiologie, l'étiologie microbienne, les facteurs de risque et les manifestations cliniques de la PN et de la PVA. De plus, une démarche axée sur les données disponibles, l'opinion d'experts et les pratiques courantes de prestation des soins au sein du système de santé canadien ont permis de déterminer les schèmes de stratification des risques afin de favoriser un diagnostic pertinent, la prise en charge antimicrobienne et la prise en charge non antimicrobienne de la PN et de la PVA. Enfin, on a colligé des stratégies de prévention et de réduction des risques afin de réduire le risque d'acquies ces infections. De futures initiatives en vue de favoriser un diagnostic plus rapide et d'assurer le meilleur traitement des pathogènes résistants s'imposent pour réduire la morbidité et accroître le taux de survie.

infectious diseases, respiratory, critical care and pharmacy. A standard grading system was used to classify each recommendation according to its strength (A-E) and quality of the evidence (1-3) (Table 1).

The present document covers the epidemiology, etiology, clinical manifestations of disease, risk factors for infection, strategies and approaches to diagnosis, antimicrobial and nonantimicrobial therapies in HAP and VAP and, finally, the role of prevention and risk reduction. Mention has also been given to the impact of antimicrobial resistance on pathogens associated with HAP and VAP, and future considerations that

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TABLE 1
Infectious Diseases Society of America – United States Public Health Service grading system for rating recommendations in clinical guidelines

Category/grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
1	Evidence from ≥ 1 properly randomized, controlled trial
2	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments
3	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Adapted from reference 367

should be addressed regarding these two very important infectious diseases. Key issues and recommendations have been included at the end of each section.

The present guideline emphasizes rapid diagnosis, immediate empirical antibiotic therapy and avoidance of unnecessary use of antibiotics by way of streamlining and de-escalation. The use of patient risk stratification based on initial clinical presentation has been deemed an important feature in the treatment strategies described. Furthermore, these principles may not be applicable to immunosuppressed patients. However, this is a guideline and clinicians should always be cognizant of local epidemiology, antibiotic resistance issues and underlying immunosuppression. It should not replace the value of experienced clinical judgment.

The following are the highlights of the present document:

1. HAP and VAP together are the second most common cause of hospital-acquired infection and have been associated with a higher mortality than any other nosocomial infection.
2. HAP and VAP are associated with longer attributable lengths of stay in hospital and greater hospital expenditures compared with patients without HAP or VAP.
3. HAP and VAP may be caused by a variety of aerobic and anaerobic Gram-positive cocci and Gram-negative bacilli.
4. Many patients at risk for HAP and VAP have underlying medical conditions that put them at higher risk for acquiring antibiotic-resistant organisms (AROs).
5. The presence of specific host, environmental or pharmacological factors may enhance the propensity of patients to develop HAP and VAP.
6. HAP or VAP should be suspected in all patients, whether ventilated or not, if two or more of the

following clinical features are present: temperature greater than 38°C or less than 36°C; leukopenia or leukocytosis; purulent tracheal secretions and decreased partial pressure of oxygen in arterial blood (PaO₂).

7. Patient risk stratification based on clinical presentation, time of onset following admission to the hospital, and the potential for resistant pathogens can be applied to individuals with HAP and VAP.
8. Initial empirical antibiotic therapy for HAP and VAP should begin within 24 h of diagnosis and be modified accordingly as microbiological and clinical response data become available. Strong consideration should be given to abbreviating antibiotic courses to seven days for most pathogens to reduce the risk for the emergence of resistant organisms.
9. Attention to judicious use of fluids, nutritional support and careful management of mechanical ventilatory support can contribute to improved outcomes in patients with HAP and VAP.
10. An effective infection control program should be implemented to control the spread of AROs.

INTRODUCTION

HAP and VAP are important causes of morbidity and mortality in Canada and around the world. The economic impact of HAP and VAP is also significant and may be attributed to increased lengths of stay in the hospital.

HAP is defined as an inflammatory condition of the lung parenchyma caused by infectious agents not present or incubating at the time of hospital admission; that is, conditions that develop more than 48 h after admission (1,2). For epidemiological purposes, the Centers for Disease Control and Prevention state that all patients older than 12 months of age who meet at least one of the criteria listed in Table 2 are considered to have HAP (3). HAP has been subdivided into pneumonias that occur on the ward and those that arise in the intensive care unit (ICU) (ICU HAP). The term 'early-onset' is used if HAP occurs within the first 96 h of admission to the hospital and 'late-onset' if HAP arises beyond this time (4,5). Incidentally, it is this division that assists in the microbiological identification of pathogens that cause HAP (2). It has been suggested that patients with late-onset HAP are associated with an increasing prevalence of resistant nosocomial pathogens, although studies have contradicted this hypothesis.

VAP, on the other hand, is a subset of HAP and includes all patients receiving mechanical ventilation at the time of infection. VAP occurs almost exclusively in the ICU and represents approximately 86% of all ICU HAP (6). The American Thoracic Society criteria (2) for the diagnosis of VAP are pneumonia in a patient mechanically ventilated for greater than 48 h with at least two of the following criteria: fever (body temperature increase of greater than 1°C or body temperature greater than 38.3°C), leukocytosis (25% increase and a value greater than $10.0 \times 10^9/L$) or leukopenia (25% decrease and a value less than $5.0 \times 10^9/L$), and purulent tracheal secretions (greater than 25 neutrophils per high-power field). In addition, one or more of the following criteria must also be met: new or persistent infiltrates on chest radiographs, the

TABLE 2
Centers for Disease Control and Prevention criteria for nosocomial pneumonia

Pneumonia must meet one of the criteria (only in patients >12 months of age)

- 1. Rales or dullness to percussion on physical examination of chest and any of the following:**
 - new onset of purulent sputum or change in character of sputum;
 - organism isolated from blood culture;
 - isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing or biopsy.
- 2. Chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation or pleural effusion and any of the following:**
 - new onset of purulent sputum or change in character of sputum;
 - organism isolated from blood culture;
 - isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing or biopsy;
 - isolation of virus or detection of viral antigen in respiratory secretions;
 - diagnostic single antibody titre (IgM) or four-fold increase in paired serum samples (IgG) for pathogen.

Ig Immunoglobulin. Adapted from reference 3

same microorganism isolated from pleural fluid and tracheal secretions, or radiographic cavitation or histopathological demonstration of pneumonia and positive cultures obtained from bronchoalveolar lavage (BAL) (greater than 10^4 colony forming units [cfu]/mL) (2).

The diagnosis of HAP and VAP is a challenge, and the precise role of testing, especially when using an invasive technique, is controversial (7). Although antimicrobials are the mainstay of the management of HAP and VAP, the optimal therapeutic agent(s) are controversial and numerous non-antimicrobial interventions such as fluid and nutritional support may also affect outcome.

The ultimate goal of the present guideline is to provide a framework to make informed decisions regarding the diagnosis and management of HAP and VAP. Diagnostic and treatment algorithms demonstrate that patient risk stratification based on the clinical presentation and risk for resistance organisms can promote successful outcomes and improve antimicrobial stewardship, curtailing the overuse of antimicrobials.

The present guideline and the recommendations provided, albeit evidence-based, should always be tempered by the judgment of a well-informed physician and only assist in the decision-making process.

METHODOLOGY

The present guideline was prepared by a working group comprised of individuals with expertise in the disciplines of infectious disease, respiratory, intensive care medicine and pharmacy. Members were chosen based on their expertise and upon recommendation by the co-chairs who were members of the Association of Medical Microbiology and Infectious Disease Canada and the Canadian Thoracic Society, and were approved by the respective societies. Each member of the group was assigned a subject for review. For each subject, a literature search was undertaken of English-language peer-reviewed papers and abstracts until December 2006, making use of relevant key words pertinent to that subject. Information was sorted and tabulated. All documents were

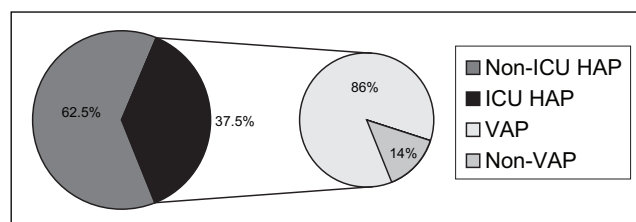


Figure 1 Breakdown of hospital-acquired pneumonia/intensive care unit (HAP/ICU) and HAP/ventilator-associated pneumonia (VAP). Information taken from references 6,12,13,22

merged and a working draft prepared for review by all members. The completed document was reviewed and approved by the aforementioned societies.

The grading system of the evidence used has been previously described and was based on the strength and quality of the evidence according to the Infectious Diseases Society of America (Table 1).

EPIDEMIOLOGY

Incidence and prevalence

HAP is the second most common nosocomial infection with a crude overall rate of 6.1 per 1000 discharges (8). By comparison, the infection rate for nosocomial urinary tract infection, the most common hospital-acquired infection, is 11 per 1000 discharges. The incidence of HAP varies depending on the hospital environment (Figure 1) (9,10).

A Canadian descriptive study (11) of non-ICU HAP in a tertiary care hospital showed a mean (\pm SD) age of 63 ± 17 years of which 55 (65%) were male. The majority of HAP cases (81%) were acquired on surgical wards.

The incidence of HAP is greater among patients in the ICU (Figure 1). Generally, approximately 30% of HAP occurs in critical care settings (12,13).

The incidence of VAP from the National Nosocomial Infections Surveillance (NNIS) data is 7.6 cases per 1000 ventilator-days (14). However, it should be noted that rates vary depending on the method of assessment used (15). The incidence of the first episode of VAP was 22.8 per 1000 patient-days, 29.6 per 1000 patient-days at risk, 35.7 per 1000 ventilator-days, and 44.0 per 1000 ventilator-days at risk. The risk for VAP peaks at day 5 of mechanical ventilation (16). NNIS data showed that the incidence of VAP was highest for trauma ICUs (15.2 per 1000 ventilator-days) (14). The overall prevalence of VAP was 9.3% (17). In a Canadian cohort study of 1014 patients ventilated for 48 h or greater, 177 (17.4%) developed VAP (18). The median duration from ICU admission to the onset of VAP in this study was seven days. Acute respiratory distress syndrome (ARDS) carries an increased risk for VAP (19,20).

Outcomes

HAP has been shown to have the highest mortality rate of all nosocomial infections (4). In one study (10), the crude case-fatality rate was 30%, rising to 33% in cases attributable to an initial episode of HAP. In a Canadian study (11) of non-ICU HAP, overall mortality rate was 20%, with a direct attributable mortality of 14%. The mortality rate from HAP varied from 7% in patients on general wards to as high as 62% in patients in bone marrow transplant units (21).

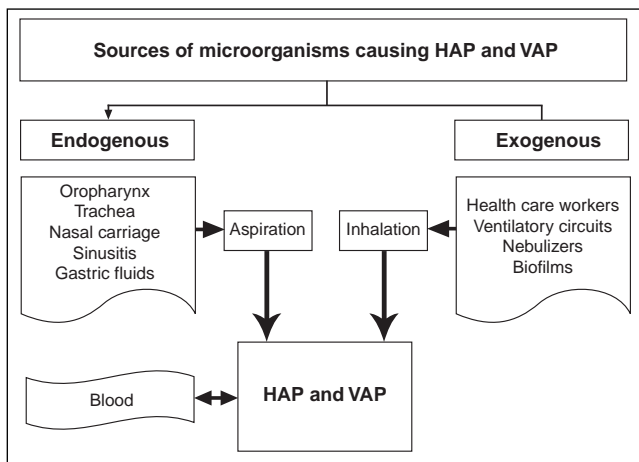


Figure 2) Endogenous and exogenous sources of microorganisms causing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Adapted from references 29,30

Death from bacteremic HAP occurred in 20% of patients within one week of their first positive blood culture, and *Pseudomonas aeruginosa* bacteremia was associated with the highest mortality rate (45%) (22). The mortality rate in this study was similar for both the ICU (22.2%) and non-ICU patients (17.6%) (95% CI 0.4 to 1.5).

The mortality rate for VAP ranges from 24% to 50%, and can reach as high as 76% in specific settings or when lung infection is caused by high-risk pathogens (23). The attributable mortality of VAP in a Canadian study (16) showed an increase in risk of death (absolute risk increase: 5.8%). The attributable mortality was higher for medical patients than for surgical patients (RR increase of 65% versus 27.3%, $P=0.04$). In a French study (20) of patients with ARDS, there was no difference in mortality rates between patients with VAP (28 of 49 [57%]) and without VAP (50 of 85 [59%]) ($P=0.8$).

Economic impact

The costs of HAP are significant because it is associated with longer hospital stays (10). Similarly, VAP is associated with a significant increase in hospital costs. An American study (16) showed that the development of VAP was associated with an increase of \$41,294 in mean hospital charges per patient (\$104,983±\$91,080 versus \$63,689±\$75,030, $P<0.001$).

Major points and recommendations for epidemiology

1. The incidence of HAP and VAP together is between five and 10 cases per 1000 hospital admissions, depending on the case definition used and the study population.
2. Together, HAP and VAP are the second most common cause of hospital-acquired infection and are associated with a higher mortality than any other nosocomial infection.
3. Patients with late-onset HAP or VAP have a similar rate of mortality to those with early-onset disease.
4. Approximately 30% of HAP occurs in the ICU setting where the majority of cases (greater than 85%) occur in patients on mechanical ventilation.

TABLE 3
Microbiological causes of hospital-acquired pneumonia and ventilator-associated pneumonia (level A-2)

Microbiological diagnosis	Frequency of isolation (% of patients)
Gram-negative bacilli	35–80
<i>Escherichia coli</i>	
<i>Klebsiella</i> species	
<i>Enterobacter</i> species	
<i>Proteus</i> species	
<i>Serratia marcescens</i>	
<i>Pseudomonas aeruginosa</i>	
<i>Acinetobacter</i> species	
<i>Stenotrophomonas maltophilia</i>	
Gram-positive cocci	9–46
<i>Streptococcus pneumoniae</i>	
<i>Streptococcus</i> species	
<i>Staphylococcus aureus</i> (MSSA and MRSA)	
Polymicrobial	9–80
Anaerobes	0–54
Blood culture positive	0–40
No growth	2–54

MSSA Methicillin-susceptible *S aureus*, MRSA Methicillin-resistant *S aureus*. Adapted from references 11,44-91

5. The costs of HAP and VAP are substantial and have been attributed to longer stays in hospital and greater hospital expenditures when compared with patients without HAP.

MICROBIAL ETIOLOGY

HAP and VAP occur if a large inoculum of organisms reaches the lower airways and thereby overwhelms host defenses. Alternatively, HAP and VAP can occur if a patient's host defenses are impaired or if they are infected with a highly virulent strain (5,24-38). To establish optimal empirical and pathogen-directed antimicrobial therapy, it is desirable to obtain sensitive, specific and rapid identification of the causative pathogen(s) of HAP and VAP. It is believed that establishing the correct etiological cause of HAP and VAP, followed by directed treatment based on susceptibility testing, will lead to improved outcomes (2,24,39-43). Unfortunately, establishing the etiological agent(s) of HAP and VAP may be difficult because distinguishing between mere colonization of the tracheobronchial tree versus true nosocomial pneumonia is often problematic (24-26). Additional challenges, such as the fact that no organisms or alternatively, several organisms, may be isolated, hamper optimal antimicrobial therapy.

A common classification scheme, which aids in understanding the pathogenesis of HAP and VAP, has been developed. Infections are derived from either an endogenous or exogenous source (Figure 2) (24,29,30). Endogenous infection is the most frequent cause of HAP and VAP, and can occur with either community-acquired or hospital-acquired pathogens that colonize the host. Initial colonization of the respiratory tract occurs most commonly, followed by the microaspiration of oropharyngeal secretions (29,30). In mechanically ventilated patients, leakage of endotracheal secretions around the endotracheal cuff results in aspiration of

TABLE 4
Pathogens causing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (Level A-2)

Disease	Classification	Diagnostic features	Pathogens
HAP	Group 1	No risk factors for resistance [†] AND mild to moderate presentation [‡]	Core pathogens*
	Group 2	Risk factors for resistance [†] AND mild to moderate presentation [‡]	Core pathogens* plus MRSA and <i>Pseudomonas aeruginosa</i>
	Group 3	Severe presentation [§] ± risk factors for resistance [†]	Core pathogens* plus MRSA, <i>P aeruginosa</i> and <i>Legionella</i> species
VAP	Group 4	No risk factors for resistance [†] AND mild to moderate presentation [‡]	Core pathogens*
	Group 5	Risk factors for resistance [†] AND/OR severe presentation [§]	Core pathogens* plus MRSA, <i>P aeruginosa</i> , <i>Legionella</i> species, <i>Acinetobacter</i> species and <i>Stenotrophomonas maltophilia</i>

*Core pathogens include *Streptococcus pneumoniae*, *Streptococcus species*, *Haemophilus influenzae*, *Enterobacter species*, *Escherichia coli*, *Klebsiella species*, *Proteus species*, *Serratia marcescens* and methicillin-susceptible *Staphylococcus aureus*; [†]Risk factors for resistance include antimicrobial therapy in the past 90 days and late-onset during hospitalization (>5 days); [‡]Mild to moderate presentation: no hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end-organ dysfunction; [§]Severe presentation: hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end-organ dysfunction. MRSA Methicillin-resistant *S aureus*. Adapted from references 11,44-91

organisms into the lower airways. Gross aspiration of large volumes of either oropharyngeal or esophageal/gastric contents is not common. Exogenous infection with nosocomial pathogens acquired from the hospital environment is less common and generally occurs late in the ICU admission (Figure 2). Health care workers or medical equipment may harbour pathogenic flora that can prompt colonization of the tracheobronchial tree. Contaminated humidification reservoirs during mechanical ventilation may lead to aerosolization of pathogens and subsequent colonization and infection. Another potential route of infection in HAP and VAP is bacteremia. The hematogenous spread from distant sites of infection, although not a common cause, may also occur in postoperative patients as well as in patients with intravenous or urinary catheters.

Accurate data regarding the etiology of HAP and VAP are limited and may result from the lack of a gold standard for microbiological diagnosis. Microbiological diagnosis of HAP has been defined by samples collected from expectorated sputum, endotracheal suctioning, BAL, or protected specimen brushing (PSB) alone or in combination with blood cultures (11,44-76). In general, the bacteriology of patients with HAP (43,46,55,77) or VAP (24,26,43,59,61,65, 75,78) is similar, although *Stenotrophomonas maltophilia* and *Acinetobacter* species are found predominantly in VAP. Bacteriological

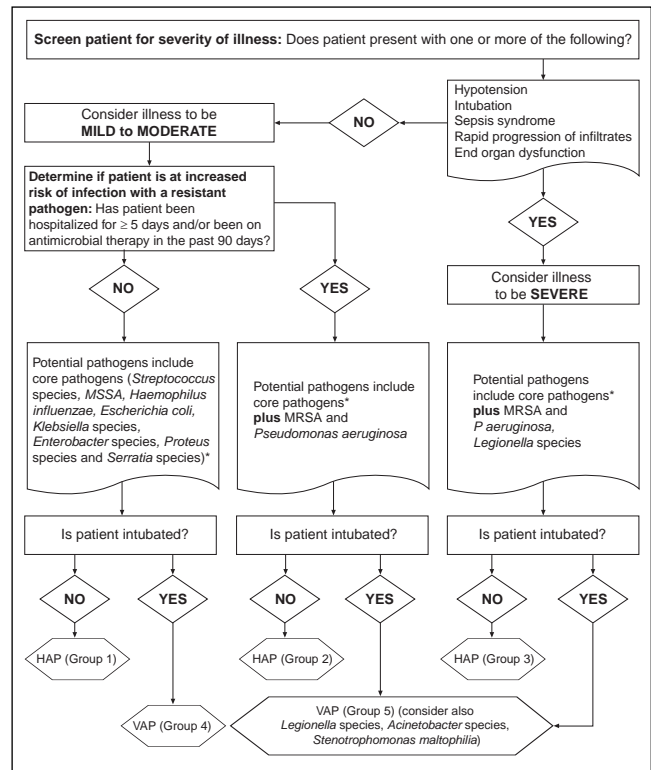


Figure 3) Algorithm for determining the microbiological cause of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) using risk factors for resistance and severity of illness. MRSA Methicillin-resistant *Staphylococcus aureus*; MSSA Methicillin-sensitive *S aureus*. Data are from references 2,11,40,44-91, and represent level A-2 data

analysis in patients with HAP or VAP has revealed that 35% to 80% of individuals are infected with Gram-negative bacilli, 9% to 46% with Gram-positive cocci and 0% to 54% with anaerobes (Table 3) (11,44-91). Studies report that 9% to 80% of patients with HAP or VAP have polymicrobial infection while the inability to isolate a pathogen was found to occur in 2% to 54% of patients (Table 3). Positive blood cultures have been reported in 0% to 40% of patients with HAP or VAP. The microbiology of HAP and VAP is supported by quality clinical studies.

Due to the predominance of certain virulent pathogens in HAP and VAP, the concept of 'core' pathogens was developed (Table 4 and Figure 3) (2,40,42). Core pathogens should be considered as potential causes of HAP or VAP in all patients. Core pathogens include *Streptococcus pneumoniae*, *Streptococcus species*, *Haemophilus influenzae*, *Enterobacteriaceae* such as *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Proteus* species and *Serratia marcescens*, as well as methicillin-susceptible *Staphylococcus aureus* (Table 4) (11,44-101). In addition, severity of presentation of HAP or VAP (mild to moderate versus severe), as well as risk factors for resistant pathogens such as antimicrobial use in the preceding 90 days (for any reason), early-onset (less than five days of hospitalization) versus late-onset (five days or more of hospitalization) and immunosuppression affect the likely causative pathogens. Prior antimicrobial use and late onset are HAP risk factors for methicillin-resistant *S aureus* (MRSA) and *P aeruginosa* (Figure 3) (27,41). Similarly, prior antimicrobial use and late onset are VAP risk factors for

TABLE 5
In vitro antibiotic activity against common Gram-positive aerobes causing hospital-acquired pneumonia and ventilator-associated pneumonia

Bacteria	Susceptibility profiles																					
	Ceftazidime*		Ceftriaxone†		Ciprofloxacin		Clindamycin		Erythromycin‡		Gentamicin§		Levofloxacin¶		Linezolid		Meropenem**		Pip/Tazo††		Vancomycin	
	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀
<i>Staphylococcus aureus</i> (MS)	+	32	++/+++	4	+++	0.5	++++	0.5	+++	2	++	0.5	++++	0.25	++++	2	++++	0.12	++++	1	++++	1
<i>Staphylococcus aureus</i> (MR)	-	256	-	256	-	64	+ / ++	4	- / +	>128	+	128	-	32	++++	2	++	64	- / +	256	++++	1
<i>Staphylococcus epidermidis</i> (MS)	+	32	++/+++	4	+++	1	+++	2	+ / ++	8	+	16	+++	1	++++	2	++++	0.5	++++	1	++++	2
<i>Staphylococcus epidermidis</i> (MR)	-	64	-	64	+	16	+	16	- / +	>128	+	16	+	8	++++	2	++	32	- / +	>32	++++	4
<i>Streptococcus pneumoniae</i>	++	2	++++	0.5	+ / ++	2	++++	0.12	+ / ++	32	- / +	16	++++	1	++++	1	++++	1	++++	0.12	++++	1
<i>Streptococcus pneumoniae</i> (PS)	+++	0.25	++++	0.06	+ / ++	2	++++	0.12	++++	0.06	- / +	16	++++	1	++++	1	++++	0.016	++++	≤0.06	++++	1
<i>Streptococcus pneumoniae</i> (PI)	++	8	++++	1	+ / ++	2	++	1	++	16	- / +	16	++++	1	++++	1	++++	0.5	++++	1	++++	1
<i>Streptococcus pneumoniae</i> (PR)	+	32	+++	2	+ / ++	2	++	1	+	>32	- / +	16	+++	1	++++	1	+++	1	+++	4	++++	1
<i>Enterococcus faecalis</i> (VS)	-	>64	-	>64	+	>32	++	2	+	4	+	>2000	++	4	++++	2	+++	2	++++	1	++++	2
<i>Enterococcus faecalis</i> (VR)	-	>64	-	>64	-	>32	+	8	- / +	16	+	>2000	-	32	++++	2	+	8	+	64	-	>32
<i>Enterococcus faecium</i> (VS)	-	>64	-	>64	+	>32	+	8	+	8	+	>2000	+	32	++++	2	+	64	+	256	++++	2
<i>Enterococcus faecium</i> (VR)	-	>64	-	>64	- / +	>32	- / +	32	-	32	+	>2000	- / +	>32	++++	2	-	64	-	256	-	>32

*Applies to ceftazidime and cefepime; †Applies to ceftriaxone and cefotaxime; ‡Applies to erythromycin and azithromycin; §Applies to gentamicin, netilmicin, tobramycin and amikacin; ¶Applies to levofloxacin, gatifloxacin and moxifloxacin; **Applies to meropenem and imipenem/cilastatin; ††Applies to piperacillin/tazobactam (Pip/Tazo) and ticarcillin/clavulanate. Act Antibiotic activity: - poor activity, + limited activity and/or resistance ≥5%, ++ moderate to good activity and/or resistance 10% to 14%, +++ very good activity and/or resistance 5% to 9%, ++++ excellent activity and/or with resistance ≤4%; MIC₉₀ Minimum inhibitory concentration (µg/mL) of 90% of isolates; MR Methicillin resistant; MS Methicillin susceptible; PI Penicillin intermediate (MIC 0.12 µg/mL to 1 µg/mL); PR Penicillin resistant (penicillin MIC ≥2.0 µg/mL); PS Penicillin susceptible (MIC ≤0.06 µg/mL), VR Vancomycin resistant (MIC ≥8 µg/mL); VS Vancomycin susceptible (MIC ≤4 µg/mL). Antibiotic breakpoints from the Clinical and Laboratory Standards Institute approved breakpoints (368). Data presented in table were adapted from references (11,44-101) and represent level A-2 data

MRSA, *P aeruginosa*, *Acinetobacter* species and *S maltophilia* (Figure 3) (27,41). Unusual pathogens such as *Aspergillus* species, *Candida* species, *Legionella pneumophila*, *Pneumocystis jiroveci* (previously *Pneumocystis carinii*), *Nocardia* species and viruses such as cytomegalovirus are causes of HAP and VAP in patients who are immunosuppressed (2,24,30,31,40,41,43,102-106). A discussion of these and other entities in immunosuppressed patients goes beyond the scope of the present document but have been dealt with in other reports (31,41,107).

Because HAP and VAP may be caused by a variety of aerobic and anaerobic Gram-positive cocci and Gram-negative bacilli, it is important to know the activity of commonly used antimicrobial agents against these pathogens (Tables 5 to 7) (44,45). Third-generation cephalosporins (eg, cefotaxime, ceftriaxone and ceftazidime), broad-spectrum penicillins (eg, piperacillin/tazobactam), fluoroquinolones (eg, ciprofloxacin and levofloxacin), aminoglycosides (eg, gentamicin) and carbapenems (eg, imipenem and meropenem) have very broad-spectrum activity against the common aerobic pathogens causing HAP or VAP (Tables 5 and 6). Other agents such as macrolides (eg, erythromycin and azithromycin) and lincosamides (clindamycin), linezolid and vancomycin have excellent activity against Gram-positive cocci, while demonstrating minimal activity against Gram-negative bacilli

(Tables 5 and 6). The most active antimicrobial against anaerobes include metronidazole, clindamycin, carbapenems and broad-spectrum penicillins combined with beta-lactamase inhibitors. Gatifloxacin and moxifloxacin have good activity against *Bacteroides fragilis* (Table 7) but adverse events associated with gatifloxacin preclude its use.

Impact of antimicrobial resistance

Many patients at risk for HAP or VAP are also at risk for acquiring AROs given that many of these patients have underlying medical conditions. In these patients, colonization by multi-resistant Gram-negative bacilli is often the forerunner of HAP or VAP. Further, inappropriate use of antibiotics in terms of indication, duration or spectrum choices promote the acquisition of AROs (108). Moreover, patients infected by AROs are at increased risk of morbidity and mortality (109-112), not only from the organisms themselves, but also due to complications of the antibiotic therapy.

MRSA is increasingly being recovered in ICUs and on general wards in North American institutions. Data from the NNIS in the United States have confirmed this finding (14). In Canada, the rate of MRSA increased from a mean of 0.95 per 100 *S aureus* isolates in 1995 to 5.97 per 100 isolates in 1999 (94). Moreover, one must be cognizant and wary not only of hospital-acquired MRSA, but also of the potential for

TABLE 6
In vitro antibiotic activity against common Gram-negative aerobes causing hospital-acquired pneumonia and ventilator-associated pneumonia

Bacteria	Susceptibility profiles															
	Ceftazidime*		Ceftriaxone†		Ciprofloxacin		Erythromycin‡		Gentamicin§		Levofloxacin¶		Meropenem**		Pip/Tazo††	
	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀
<i>Acinetobacter</i> species	++	16	+/+	16	+++	1	–	>32	+++	8	+++	1	+++	1	+++	8
<i>Citrobacter freundii</i>	++/+++	32	++/+++	>32	++++	0.25	–	>32	++++	1	++++	0.5	++++	0.12	+++ / ++++	16
<i>Enterobacter aerogenes</i>	++/+++	16	++/+++	>32	++++	0.12	–	>32	++++	1	++++	0.12	++++	0.12	+++ / ++++	16
<i>Enterobacter cloacae</i>	++/+++	16	++/+++	32	++++	0.5	–	>32	++ / +++	8	++++	0.12	++++	0.25	++	64
<i>Escherichia coli</i>	++++	1	++++	0.12	+++	16	–	>32	++++	2	++++	16	++++	0.03	++++	8
<i>Escherichia coli</i> (ESBL)	–	>64	–	>64	++	32	NA	NA	+++	4	++	32	++++	0.06	– / +	>128
<i>Haemophilus influenzae</i>	++++	0.06	++++	0.015	++++	0.008	+/+	16	+++	8	++++	0.03	++++	0.12	++++	0.12
<i>Haemophilus influenzae</i> (BLP)	++++	0.06	++++	0.015	++++	0.008	+/+	16	+++	8	++++	0.015	++++	0.12	++++	0.25
<i>Klebsiella pneumoniae</i>	++++	0.25	++++	0.06	++++	0.5	–	>32	++++	0.5	++++	0.5	++++	0.03	++++	8
<i>Klebsiella pneumoniae</i> (ESBL)	–	>64	–	>64	+++	0.5	NA	NA	++++	0.5	+++	0.5	++++	0.06	– / +	>128
<i>Klebsiella pneumoniae</i> (AmpC)	++	>32	++	>32	++++	0.5	NA	NA	++++	0.5	++++	0.5	++++	0.25	– / +	>128
<i>Klebsiella</i> species	++++	0.25	++++	0.5	++++	0.03	–	>32	++++	4	++++	0.06	++++	0.06	++++	8
<i>Moraxella catarrhalis</i>	++++	0.5	++++	0.5	++++	0.03	++++	0.25	++++	2	++++	0.06	++++	0.008	++++	1
<i>Morganella morganii</i>	++/+++	16	++/+++	8	++++	0.06	–	>32	+++ / ++++	4	++++	0.12	++++	0.25	++++	4
<i>Proteus mirabilis</i>	++++	0.12	++++	0.06	+++ / ++++	0.12	–	>32	++++	4	+++ / ++++	0.12	++++	0.12	++++	1
<i>Proteus vulgaris</i>	++	>32	++	>32	++++	0.03	–	>32	+++ / ++++	4	++++	0.06	++++	1	++++	2
<i>Providencia rettgeri</i>	++/+++	4	+++	2	+++	1	–	>32	+	32	+++	4	++++	2	++++	4
<i>Providencia stuartii</i>	++/+++	4	+++	2	+++	2	–	>32	++	16	+++	1	++++	2	++++	4
<i>Pseudomonas aeruginosa</i>	+++	32	+	128	+++	16	–	>32	+++	64	+++	32	+++	32	+++	64
<i>Serratia marcescens</i>	+++	4	+++	0.5	+++	2	–	>32	++	16	+++	2	++++	0.25	++++	8
<i>Stenotrophomonas maltophilia</i>	– / +	64	–	256	+	16	–	>32	+	32	++ / +++	4	–	256	+	512

*Applies to ceftazidime and cefepime; †Applies to ceftriaxone and cefotaxime; ‡Applies to erythromycin and azithromycin; §Applies to gentamicin, netilmicin, tobramycin and amikacin; ¶Applies to levofloxacin, gatifloxacin and moxifloxacin (gatifloxacin and moxifloxacin have only moderate activity against *P. aeruginosa*); **Applies to meropenem and imipenem/cilastatin; ††Applies to piperacillin/tazobactam (Pip/Tazo) and ticarcillin/clavulanate. Clindamycin, linezolid and vancomycin have not been included in the table because they have limited activity against Gram-negative bacilli. Act Antibiotic activity: – poor activity, + limited activity and/or resistance $\geq 5\%$, ++ moderate to good activity and/or resistance 10% to 14%, +++ very good activity and/or resistance 5% to 9%, ++++ excellent activity and/or with resistance $\leq 4\%$; AmpC Chromosomal AmpC beta-lactamase; BLP Beta-lactamase positive; ESBL Extended spectrum beta-lactamase; MIC₉₀ Minimum inhibitory concentration ($\mu\text{g/mL}$) of 90% of isolates; NA Information not available. Antibiotic breakpoints from the Clinical and Laboratory Standards Institute approved breakpoints (368). Data presented in table were adapted from references 11,44-101 and represent level A-2 data

TABLE 7
In vitro antibiotic activity against common anaerobes causing hospital-acquired pneumonia and ventilator-associated pneumonia

Bacteria	Susceptibility profiles																					
	Ceftazidime		Ceftriaxone*		Ciprofloxacin		Clindamycin		Erythromycin		Gentamicin†		Levofloxacin‡		Linezolid		Meropenem§		Pip/Tazo¶		Metronidazole	
	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀	Act	MIC ₉₀
<i>Bacteroides fragilis</i>	+	64	+	64	+	16	+++	2	– / +	8	–	>16	+	8	++	4	++++	0.5	++++	1	++++	2
<i>Bacteroides fragilis</i> group	– / +	>64	– / +	>64	– / +	32	+++	4	+	4	–	>16	+	16	++	4	++++	0.5	+++	16	++++	1
<i>Fusobacterium</i> species	+++	4	++++	1	+	8	+++	2	– / +	>64	–	>16	+/+	4	++++	0.5	++++	0.5	++++	0.12	++++	2
<i>Peptostreptococcus</i> species	++ / +++	16	+++	8	+/+	4	++++	1	+	>64	–	>16	+++	2	+++	2	++++	0.5	++++	2	+	32

*Applies to ceftriaxone and cefotaxime; †Applies to gentamicin, netilmicin, tobramycin and amikacin; ‡Applies to levofloxacin, gatifloxacin and moxifloxacin (gatifloxacin and moxifloxacin have good activity against *B. fragilis*); §Applies to meropenem and imipenem/cilastatin; ¶Applies to piperacillin/tazobactam (Pip/Tazo) and ticarcillin/clavulanate. MIC₉₀ Minimum inhibitory concentration ($\mu\text{g/mL}$) of 90% of isolates, Act Antibiotic activity: – poor activity, + limited activity and/or resistance $\geq 5\%$, ++ moderate to good activity and/or resistance 10% to 14%, +++ very good activity and/or resistance 5% to 9%, ++++ excellent activity and/or with resistance $\leq 4\%$. Antibiotic breakpoints from the National Committee for Clinical Laboratory Standards approved and tentative breakpoints (369). Data presented in table were adapted from references 11,44-101 and represent level A-2 data

community-associated MRSA with its enhanced transmissibility, to cause HAP and VAP (113).

With respect to Gram-negative bacteria, *S. maltophilia* represents a considerable challenge because of its natural intrinsic

resistance to many commonly used antimicrobial classes (carbapenems, broad-spectrum beta-lactams, fluoroquinolones and aminoglycosides), thus limiting available therapeutic options (114). Patients with severe underlying medical conditions,

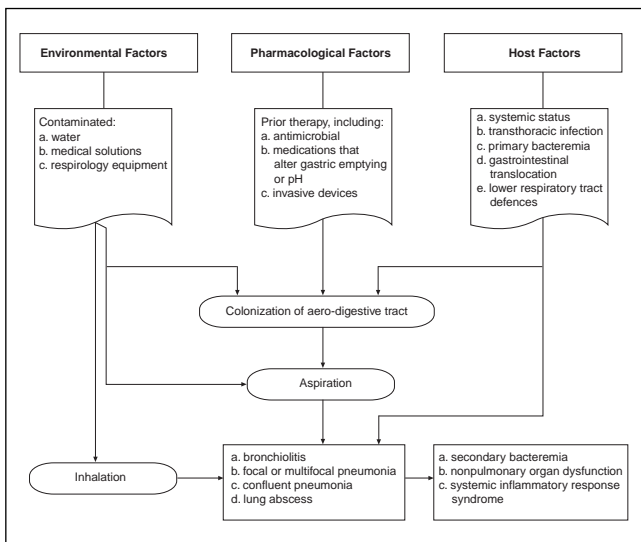


Figure 4) The pathogenesis of hospital-acquired pneumonia and ventilator-associated pneumonia. Adapted from reference 117

particularly those with cancer, are often infected with this organism. Furthermore, risk factors for colonization and infection with *P aeruginosa* and *Acinetobacter* species include being elderly or immunocompromised, respiratory equipment used in ventilated patients and previous antibiotic therapy (115). In the case of *Acinetobacter* species, many outbreaks have occurred in the ICU, thereby putting patients with VAP at particular risk due to the limited antibiotic treatment options available. Extended-spectrum beta-lactamases are mostly present in *Klebsiella* species and *E coli*, and have been associated with increasing resistance to many commonly used antibiotics such as third-generation cephalosporins and trimethoprim-sulfamethoxazole, as well as the fluoroquinolones. This plasmid-mediated resistance can easily be shared and transmitted to other *Enterobacteriaceae* (116).

Major points and recommendations for microbial etiology

Patients with early- or late-onset HAP and VAP and who have recently received antibiotics or had an admission to a health care facility are at risk for colonization and infection with more antibiotic resistant pathogens.

RISK FACTORS

Not only are certain patient groups at greater risk for HAP or VAP, but the presence of specific host, environmental or pharmacological factors enhance the propensity of patients to develop pneumonia (117) (Figure 4). The identification of these risk factors allows the development of strategies for the prevention of HAP and VAP and the design of treatment protocols (23).

Host factors

The major factor predisposing patients to HAP or VAP is the colonization of the upper respiratory and digestive tract with pathogenic microorganisms (118). Factors enhancing airway colonization include previous and continuing antibiotic therapy, endotracheal intubation, smoking, malnutrition, general surgery, dental plaque and therapies that elevate the gastric pH (119-121). Adequate daily oral hygiene in the hospitalized elderly may

reduce the risk of HAP (B-2). Other host-related factors reported in the literature that predispose to oropharyngeal colonization include renal dysfunction, diabetes, coma, shock, advanced age and underlying lung disease (119).

The risk of HAP and VAP increases after surgery (122). The risk of pneumonia is associated with preoperative smoking, longer preoperative admissions, longer surgical procedure times, and thoracic or upper abdominal surgery. Surgical patients admitted to the ICU after cardiothoracic surgery or head trauma were found to be more likely to develop nosocomial pneumonia (16). For ICU patients, the association of VAP and an elevated acute physiological assessment and chronic health evaluation (APACHE) score existed for surgical patients mechanically ventilated for two days and medical patients for more than two days (123).

Intubation and mechanical ventilation increase the risk of pneumonia by six- to 21-fold (1,124-126). The most important independent risk factors were male sex (OR 1.58), ICU admission for trauma (OR 1.75) and intermediate underlying disease severity (OR 1.47 to 1.70) (27). Longer time on ventilation and reintubation are important risk factors in development of VAP (41) (127). Other risk factors include body position during ventilation (OR 6.8), enteral feeding (OR 5.7), mechanical ventilation for more than seven days (OR 10.9) and Glasgow Coma Scale scores of less than 9 (128). Finally, chronic obstructive pulmonary disease, extensive burns, neurosurgical conditions, ARDS, witnessed aspiration and enteral nutrition have also been identified as risk factors for VAP (129).

Reducing the risk of VAP through early tracheostomy remains controversial, with some studies suggesting benefit (130) and others showing none (27). Endotracheal tubes can develop an internal bacterial biofilm and circumvent host defenses causing local trauma and inflammation that may lead to increased aspiration of nosocomial pathogens from the oropharynx in and around the tube (131). High volume, low-pressure cuffs may reduce pooling and aspiration of oral contents (C-3).

Environmental factors

Increased gastroesophageal reflux of stagnant oral secretions caused by indwelling nasogastric tubes has been shown to be an independent risk factor for HAP and VAP (23,132,133). Most experts favour a distal nasogastric tube tip location, although this remains controversial (23).

Tubing associated with mechanical ventilation contains a condensate formed as a result of the temperature difference between inspired gas and ambient air. This condensate can easily be contaminated with patient secretions and high levels of microorganisms. Installing in-line devices with one-way valves can enhance secretion sequestration and decrease the risk of aspiration or inhalation of contaminated condensate. Oral tracheal intubation is associated with a decreased incidence of sinusitis and a lower incidence of VAP in ventilated patients. Concomitant sinusitis was predicted to increase the risk of VAP by a factor of 3.8 (134,135).

Closed suctioning versus open suctioning and frequency of ventilator changes have not been shown to alter the risk of VAP in ventilated patients (129,136).

Lastly, the movement of ICU patients for diagnostic and surgical procedures out of the ICU is an independent risk factor for VAP (OR 3.8) (137).

Pharmacological factors

Various studies have produced contradictory outcomes with regard to antibiotic use as a risk for HAP and VAP (16,138,139). Some experts suggest that prophylactic antibiotics in the ICU encourage the risk of superinfection by multiresistant bacteria but delay the onset of nosocomial infection (23).

Gastric bacterial colonization, which leads to contamination of tubing in mechanically ventilated patients, correlates with nonacidic gastric pH and consequently, drugs affecting the latter can have an impact on the risk of VAP (20,140-145). If stress ulcer prophylaxis is indicated, the risks and benefits of acid-suppression versus sucralfate should be weighed before prescribing (A-1). Administration of a paralytic agent to mechanically ventilated patients has also been documented as a risk factor for VAP (76).

Major points and recommendations for risk factors

1. Colonization of the oropharynx with pathogenic organisms is an important risk factor leading to subsequent HAP/VAP.
2. Host factors such as supine positioning, extensive burns, mechanical ventilation, cardiothoracic surgery, ARDS and head trauma are predisposing factors for VAP.
3. Nasogastric tubes and condensate in ventilator tubing are environmental factors that enhance the risk of developing VAP and should be avoided (A-2).
4. Acid-suppressing medications (eg, antacids and H₂ blockers) that are employed to prevent stress ulcer bleeding in ventilated patients can increase the risk of developing VAP and careful consideration should be given to their use (A-1).

CLINICAL MANIFESTATIONS

The clinical manifestations of HAP and VAP are nonspecific and there are no pathognomonic signs or symptoms that are unique to these conditions (146). The symptom constellation of fever, shortness of breath, chest pain, cough, sputum production, hypoxia and leukocytosis that comprise the clinical manifestations of HAP and VAP may be mimicked by other clinical entities such as pulmonary embolism, congestive heart failure and ARDS. The performance of a chest radiograph to confirm the presence of a pulmonary infiltrate may not provide definitive confirmation for HAP and VAP. Signs of pulmonary consolidation on a chest radiograph can be duplicated in congestive heart failure, pulmonary emboli, pulmonary hemorrhage and ARDS. Furthermore, there is no specific pulmonary radiographic pattern that is unique to a particular microorganism.

Similarly, laboratory investigations are not predictive of specific symptoms associated with HAP and VAP. Numerous clinical conditions produce leukocytosis and hypoxia. Although the presence of microorganisms with pus cells in respiratory secretions combined with the aforementioned symptoms should portend the presence of HAP or VAP, this is not the case. The presence of microorganisms in a respiratory sample without a pulmonary infiltrate on a chest radiograph has low specificity for the diagnosis of VAP (147,148). This may merely represent colonization or tracheobronchitis and not pulmonary infection. On the other hand, overt symptoms as listed above and the presence of microorganisms in respiratory

secretions with a pulmonary infiltrate are certainly not always specific for HAP or VAP.

HAP and VAP clinical manifestations run the gamut from asymptomatic disease to the sepsis syndrome with multiple organ dysfunction. Asymptomatic disease manifestations are indolent, and HAP and VAP may only become obvious after viewing a chest radiograph. However, asymptomatic disease is an uncommon clinical presentation of HAP and VAP. In contrast, the manifestations of hypotension, electrolyte derangement, lactic acidosis, and renal and hepatic dysfunction that comprise the cardinal signs and symptoms of the sepsis syndrome may also be produced by HAP and VAP. Both Gram-positive and Gram-negative organisms can precipitate the sepsis syndrome, resulting in these clinical manifestations.

There is a paucity of evidence-based data on the presence of various symptoms in HAP and VAP. Shah and Stille (149), in reporting their randomized trial comparing cefotaxime versus ceftriaxone for the treatment of nosocomial pneumonia, actually described the frequency of symptoms at study entry. Fever was present in 82% of their patients, and chest pain was present in 46%, cough with or without sputum present in 85%, dyspnea in 72%, pulmonary consolidation in 64%, rales in 85% and a pleural friction rub in approximately 5%. Other investigators have also described septic shock in less than 10% of their patients with HAP and VAP (150,151).

Finally, the clinical presentation of patients with HAP and VAP varies from an illness of abrupt onset to one that is insidious and gradual in onset. An abrupt onset may be the harbinger of the sepsis syndrome, with rapid progression of pulmonary infiltrates and multiple organ dysfunction. On the other hand, a more insidious onset without hypotension, multiple organ dysfunction, sepsis syndrome, or rapid progression of infiltrates and the need for ventilation may also occur. These presentations are discussed in more depth in a later section describing the treatment of HAP and VAP.

Thus, the presentation and clinical manifestations of HAP and VAP may be nonspecific and mimicked by other clinical entities. Presentations may be gradual in onset or more abrupt, portending the development of the sepsis syndrome. Early recognition of HAP and VAP is imperative to ensure the initiation of appropriate antimicrobial therapy.

Major points and recommendations for clinical manifestations

The presentation and clinical manifestations of HAP and VAP are nonspecific and resemble other clinical entities.

DIAGNOSTIC APPROACHES

HAP and VAP present diagnostic challenges, and the precise role of diagnostic testing, especially when using invasive techniques, is controversial (7). Generally, a presumptive diagnosis of HAP or VAP is made on clinical grounds when a patient develops a clinical syndrome that includes fever, leukocytosis, purulent tracheobronchial secretions, and a new or changing pulmonary infiltrate. Unfortunately, this strategy has led to the overestimation of HAP and VAP because tracheobronchial colonization can lead to purulent tracheobronchial secretions. Moreover, there are other conditions that can result in fever and changing lung infiltrates. In addition, with increasing antimicrobial resistance, clinicians are more motivated to examine techniques that properly identify infected patients, thereby making attempts to minimize the indiscriminate use of

TABLE 8
Clinical pulmonary infection score (CPIS) chart

Diagnostic feature	CPIS points		
	0	1	2
Tracheal secretions	Rare	Abundant	Abundant and purulent
Chest x-ray infiltrate	None	Diffuse	Localized
Temperature (°C)	≥36.5 and ≤38.4	≥38.5 and ≤38.9	≥39 or ≤36
White blood cells (×10 ⁹ /L)	≥4.0 and ≤11.0	<4.0 or >11.0	<4.0 or >11.0 plus band forms ≥0.5
PaO ₂ /FiO ₂ mmHg	>240 or ARDS		≤240 and no ARDS
Microbiology	Negative	Positive*	Positive plus positive Gram stain†

*Microbiology not relevant in the case of the modified clinical pulmonary infection score as described by Fartoukh et al (157); †Determination is only 'positive' for the purpose of the modified clinical pulmonary infection score as described by Fartoukh et al (157). ARDS Acute respiratory distress syndrome; FiO₂ Fraction of inspired oxygen; PaO₂ Partial pressure of oxygen in arterial blood

antibiotics, especially in the ICU. Confronted with a patient's changing clinical picture or radiographic parameters demanding specific therapy, clinicians have considered using an invasive testing strategy to supplement clinical judgment. Invasive techniques include PSB, BAL and blinded versions of these techniques.

Clinical diagnosis

The initial diagnosis of HAP or VAP is based on clinical suspicion and the presence of new or progressive radiographic infiltrates. The standard diagnostic clinical criteria for HAP and VAP, along with abnormal findings from chest radiographic studies, are comprised of at least two of the following three findings: fever, leukocytosis and purulent tracheal secretions. When these conditions occur, the likelihood of VAP is high (147). The presence of a radiographic infiltrate in a patient with fever, leukocytosis or purulent tracheobronchial secretions has high diagnostic sensitivity but low specificity. When all four criteria are present, specificity improves but sensitivity drops to below 50% (152). The only study examining interobserver diagnostic reliability found no major differences between individual physicians or those grouped by level of training (147).

The diagnosis of HAP or VAP based on the presence of alveolar infiltrates as determined by chest radiography has a sensitivity of 58% to 83% when using air bronchogram signs, and is 50% to 78% for new or worsening infiltrates when compared with invasive techniques or histological studies (153,154). Unfortunately, the specificity is unknown because reports do not state the appropriate denominator (the number of ventilator-assisted patients without pneumonia and with normal findings on a chest radiograph). Chest radiographs are not a reliable diagnostic tool because there is only marginal reproducibility of the findings obtained from two readers for patients with HAP in the ICU (155). The presence of any one radiographic sign does not significantly increase the likelihood of VAP, because other potential causes of radiographic abnormalities occur in ventilated patients (154). The sensitivity and specificity of interpretation of chest radiographs have not been extensively evaluated, nor have the detrimental clinical and economic impacts of misinterpreting chest radiographs. Moreover, the incidence of pneumonia is unknown among immunocompetent patients with a normal chest radiograph and compatible clinical presentation using more advanced computed tomography imaging or invasive microbiological techniques (as seen in patients with *P. jiroveci* pneumonia).

The presence of abnormal clinical manifestations combined with abnormal radiographic findings can be used for initial screening for VAP. However, the lack of specificity with this method suggests that additional procedures are needed, such as cultures of lower respiratory tract secretions. In 1991, Pugin et al (156) combined body temperature, white blood cell count, volume and appearance of tracheobronchial secretions, oxygenation, chest radiograph findings and tracheal aspirate cultures into a clinical pulmonary infection score (CPIS) for VAP (156). A total score greater than six out of a maximum of 12 correlated with high bacterial counts isolated from the lower respiratory tract and a sensitivity and specificity of 93% and 100%, respectively, were demonstrated for this approach. More recently, Fartoukh et al (157) found that clinical prediction alone was inaccurate but a modified CPIS score, incorporating a Gram stain of respiratory tract secretions, improved diagnostic accuracy (Table 8) (157). The diagnostic accuracy was enhanced and the likelihood ratio for pneumonia based on a score greater than 6 increased from a baseline of 1.46 (using the CPIS) to 1.67 if a Gram stain of blind protected samples was obtained and to 1.77 if a Gram stain of a directed sample was obtained. Nonetheless, the authors cautioned that further refinement of the clinical scoring approach was necessary to improve the diagnostic accuracy in patients suspected of having VAP. Blot et al (158) reported that a positive Gram stain from a plugged telescoping catheter, with its high specificity, should prompt starting empirical therapy immediately. Conversely, a negative Gram stain of an endotracheal aspirate (that is highly sensitive) should lead to withholding of antibiotics (158).

Microbiological diagnosis

Qualitative cultures of endotracheal secretions are often used in lieu of invasive diagnostic testing, because health care workers can perform the aspiration procedure at the bedside with minimal training. Typically, qualitative cultures identify pathogenic organisms found by invasive tests and thereby suggest high sensitivity. Incidentally, such tests frequently identify nonpathogenic organisms as well, thereby reducing the positive predictive value of this procedure. If the culture results are negative for pathogens, VAP is very unlikely to be present, unless the patient has been treated with antibiotics (159).

The use of invasive diagnostic strategies for diagnosing HAP and VAP remains controversial. Procedures to quantitatively identify likely pathogens include endobronchial aspirates, non-bronchoscopic techniques (quantitative endotracheal aspiration,

blinded bronchial sampling [BBS], mini-BAL, blinded PSB [BPSB] and bronchoscopic techniques (BAL, PSB, protected BAL). Because these tests have a similar sensitivity, specificity, positive predictive value and likelihood ratio, the choice depends on local expertise, experience, availability and cost factors.

Growth above a certain threshold indicates the presence of HAP or VAP, whereas growth below this threshold suggests colonization or contamination. The results of quantitative cultures on specimens obtained by endotracheal aspiration vary depending on the bacterial load, the duration of mechanical ventilation and the prior administration of antibiotics. Sensitivity and specificity of the culture results obtained by these methods can range from 38% to 100% and 14% to 100%, respectively (160,161). Gram stain and culture of endotracheal secretions obtained by aspiration may be useful in diagnosing VAP. Neither bacterial antibody coating nor the presence of elastin fibres are diagnostically sensitive or specific for VAP (162-164), and they are not recommended for clinical diagnostic use (B-2).

Bronchoscopic BAL has been used diagnostically in VAP since 1988, but bronchoscopic and bacteriological methods have not been standardized. The sensitivity of quantitative BAL fluid cultures ranges from 42% to 93%, with a mean of 73%. The variability reflects the characteristics of the study population, prior administration of antibiotics (which reduces sensitivity) and the reference test used (165,166). For quantitative cultures of BAL samples, most studies cite 10^4 cfu/mL as a positive result; however, a finding of 10^3 cfu/mL to 10^5 cfu/mL is also considered positive. Sensitivity varies inversely with the cutoff point. Specificity ranges from 45% to 100%, with a mean of 82% in most studies (167,168). Detection of intracellular organisms by BAL is highly specific (89% to 100%) and has a high positive predictive value. However, such a test is not highly sensitive (37% to 100%) (164,169), thus indicating problems in sampling or laboratory techniques.

The PSB sampling technique was developed in 1987 by Wimberly et al (170), but the technique has not been standardized. As a result, few definitive, evidence-based recommendations have been reached. Reasons for this include concerns about diagnostic accuracy, reliability of findings, reproducibility of results, diagnostic thresholds, nonstandardized methodology, safety concerns and lack of data on clinical outcome (171,172).

Most studies do not report the quality of the samples nor do they state whether secretions were cleared by using a separate bronchoscope before the test (173). The accuracy of PSB sampling has been determined and, in 25% of cases, a single bronchial brush determination led to a false-positive or false-negative result (174). Specimens taken from an affected lobe have a much higher concentration of organisms than those taken from an unaffected lobe (173). Sensitivity for PSB tests ranges from 33% to 100% (175,176), with a median of 67%. Specificity ranges from 50% to 100%, with a median of 95%. PSB sampling appears to be somewhat more specific than sensitive in diagnosing VAP.

Blinded invasive procedures have also been used to obtain lower respiratory tract samples. In BBS, a catheter is blindly wedged into a distal bronchus, and secretions are aspirated without instillation of fluid. In mini-BAL, a sterile, single-sheathed, 50 cm, plugging, telescoping catheter is used and 20 mL to 150 mL of lavage fluid is instilled. In some instances,

an unprotected catheter can be used instead. In BPSB, a sterile brush that is protected from contamination is used. Incidentally, none of these techniques have been standardized. The sensitivities of these tests is as follows: BBS, 74% to 97% (165,177,178); mini-BAL, 63% to 100% (156,165,179); and BPSB, 58% to 86% (180-183). The specificities are: BBS, 74% to 100%; mini-BAL, 66% to 96%; and BPSB, 71% to 100%. These specificity ranges are similar to those reported for BAL and PSB. Risks from blinded techniques are minimal and would appear to be no greater than those with fibre optic bronchoscopy.

In nonventilated patients, the use of invasive techniques appears to be too aggressive and costly and, therefore, a clinical approach is preferred. There is insufficient robust evidence to indicate that quantitative testing produces better clinical outcomes than empirical treatment. While invasive tests may avoid the use of antibiotics for clinically insignificant organisms in ventilated patients, no direct evidence or consensus indicates the superiority of one invasive test over another. Withholding antibiotic therapy when invasive tests do not confirm a clinical suspicion of VAP has not been found to be associated with recurrence of VAP or with increased mortality rates (184). Issues to consider in choosing a diagnostic test include sensitivity and specificity, ability to improve patient outcome, potential adverse effects, availability of the test, local expertise in performing the test and cost.

Recommended diagnostic algorithms

Based on the data from the clinical and invasive strategies reviewed above and their applicability to the Canadian environment, the following diagnostic algorithms are suggested when HAP or VAP is suspected (Figure 5). Specifically, an associated pneumonia should be suspected in patients whether ventilated or not, if two or more of the following clinical features are present: temperature greater than 38°C or less than 36°C, leukopenia or leukocytosis, purulent tracheal secretions and decreased PaO₂. In the absence of such findings, no further investigations are required and observation will suffice (Figure 5) (B-3).

The presence of two or more of the aforementioned clinical abnormalities and the absence of an alternative infective focus mandates that a chest radiograph be performed. If the findings are normal, other causes of the abnormal clinical features should be investigated. If the radiograph shows alveolar infiltrates or an air bronchogram sign, or if the findings have worsened, it is recommended that the CPIS be calculated regardless of whether the patient is in the ICU or mechanically ventilated. If the CPIS is less than 6, infection is unlikely and the decision to treat with antibiotics should be carefully considered. Patients should have their CPIS recalculated daily and if it remains persistently below 6, the decision to stop antibiotics or not start them in the first instance was correct (Figure 5) (A-1). In the case of ventilated patients, if the CPIS is between 4 and 6, pneumonia should be considered if no alternative diagnosis for the findings can be obtained (Figure 5) because of the mortality associated with this disease (C-3). Therapy should be considered taking into account the Gram stain of tracheobronchial secretions. Again, the CPIS should be recalculated daily and cessation of antibiotic therapy should be considered if the CPIS remains below 6 by the third day (C-3). Although the only evidence that supports this approach is the study by Singh et al (185),

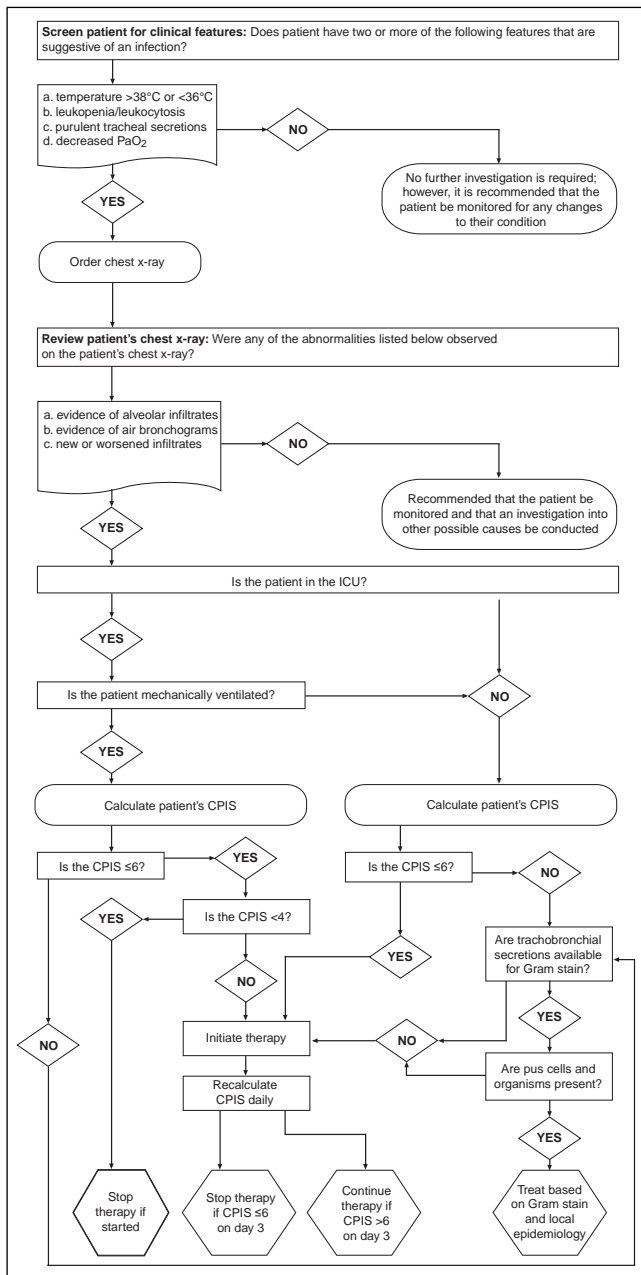


Figure 5) Diagnostic algorithm for hospital-acquired pneumonia and ventilator-associated pneumonia. Please note that there is no definitive scientific evidence or expert consensus that quantitative testing produces better clinical outcomes than empirical treatment. Scientific evidence of improved specificity, supplemented by expert opinion, supports the performance of invasive tests to avoid the use of antibiotics for clinically insignificant organisms, but there is no direct evidence or consensus regarding the superiority of one invasive test over another. Factors to consider in choosing an appropriate test include sensitivity and specificity, ability to improve patient outcome, potential adverse effects, test availability and cost. CPIS Clinical pulmonary infection score; ICU Intensive care unit; PaO₂ Partial pressure of oxygen in arterial blood

it is a reasonable compromise given that the CPIS score on day 1 is not sufficiently accurate to drive all clinical decisions.

If the CPIS is greater than 6, a Gram stain of tracheo-bronchial secretions should be obtained and cultures of the secretions undertaken. Treatment should be started based on the findings of the Gram stain and consideration of local epidemiology. If the Gram stain does not reveal pus cells or organisms, antibiotic therapy should be considered at least initially. Thereafter, the CPIS score should be recalculated on a daily basis and antibiotics discontinued on the third day if the score is consistently less than 6 (C-3).

Treatment should be based on the results of diagnostic testing. Decisions about empirical therapy should be determined by the patient's clinical stability, risk factors for resistant pathogens and the local epidemiology, together with the results of preliminary tests. Many patients receive antimicrobial agents before testing is performed, thus making it difficult or even impossible to interpret test results. After the initiation of antibiotic treatment for suspected VAP, the diagnostic thresholds for numbers of organisms in the culture must be decreased to maintain accuracy. By contrast, ongoing antibiotic therapy for a pre-existing infectious disease does not affect the diagnostic accuracy of PSB or BAL (186). In addition, five randomized prospective clinical trials (187-191) comparing invasive techniques and noninvasive quantitative techniques in patients with VAP have been performed. In the first, invasive techniques led to more frequent changes in antibiotic therapy but did not change the mortality rate. In the second, invasive techniques reduced early (but not late) mortality, produced less multiorgan damage and led to less antibiotic use. Finally, the other three trials did not support the use of invasive techniques. Singh et al (185) demonstrated in a randomized trial that pneumonia could be reasonably excluded and empirical therapy stopped when the CPIS fell below 6 at baseline and again at three days. Overall, a substantial reduction in antibiotic use with no adverse outcomes was observed.

These investigations indicate that an approach to reduce antibiotic use is possible without using an invasive strategy. Because the costs of an invasive strategy are significant and not all institutions are adequately resourced to perform these procedures continuously, an alternative approach using clinical criteria supplemented by noninvasive microbiological investigations is feasible and welcomed (C-3).

Major points and recommendations for diagnosis

1. The clinical diagnosis for HAP and VAP is not sensitive or specific.
2. The CPIS score should be calculated to improve sensitivity and specificity for the diagnosis of HAP and VAP (B-2).
3. Invasive diagnostic testing has not been demonstrated to improve clinical outcomes and therefore is not recommended unless dealing with immunocompromised hosts (A-1).
4. It is recommended that for most patients a clinical approach supplemented by noninvasive quantitative cultures of respiratory tract samples is sufficient to guide appropriate antibiotic choices (C-3).
5. A low CPIS score may allow careful observation of the patient without antibiotics.

6. By the third day of calculating the CPIS, a score below a threshold of 6 may allow early discontinuation of antibiotics.

ANTIMICROBIAL THERAPY OF HAP AND VAP

PHARMACOKINETIC AND PHARMACODYNAMIC ISSUES

Clinical outcome in HAP is dependent on an interplay of factors relating to the host (eg, immune status, comorbid conditions and severity of clinical presentation), the pathogen (eg, inoculum, virulence factors), as well as antimicrobial properties including the concentration at the site of the infection, pharmacodynamic properties and the intrinsic activity of the antibiotic against the offending pathogen(s). Only the choice and dosing of the antimicrobial regimen are modifiable by clinicians.

There are no data suggesting that the postantibiotic effect or the pharmacodynamic properties of an antibiotic, such as concentration or time-dependent killing, have an impact on outcomes in HAP. An important issue for consideration, however, is whether the infection is intracellular (eg, *Legionella* species) or extracellular (eg, typical Gram-negative and Gram-positive bacteria). For intracellular pathogens, it is the concentration of drug within the alveolar macrophage that is believed to be most relevant. Because the majority of pathogens encountered in nosocomial pneumonia are extracellular, concentrations in the epithelial lining fluid (ELF) are thought to be more important (192). Drugs achieving concentrations in ELF greater than or equal to those in the serum include the fluoroquinolones (193-195), macrolides and linezolid (196-198), followed by the beta-lactams (194,199-201) and carbapenems (202,203). The aminoglycosides and vancomycin achieve lower levels (204,205). It is not clear whether these differences relate to clinical outcomes in patients with HAP, although Wunderink et al (206) have implied that superior levels of linezolid in the ELF may contribute to enhanced efficacy.

Plasma concentrations have been evaluated as predictors of microbiological and clinical outcome in patients with both community-acquired pneumonia and HAP. In patients with HAP, Forrest et al (207) found that for ciprofloxacin, an area under the curve/minimum inhibitory concentration (AUC/MIC) greater than 125 was associated with an increased probability of clinical success and more rapid eradication of gram negative bacteria (207), while for levofloxacin an AUC/MIC from 87 to 100 was associated with pathogen eradication (208). Pharmacokinetic modeling suggests that AUC/MIC may also predict outcomes with beta-lactams, and aminoglycosides in lower respiratory tract infection (209). For agents with relatively poor penetration into ELF such as aminoglycosides (210,211) and vancomycin, there is also evidence supporting the concept that plasma concentrations may predict both clinical and microbiological success. With vancomycin, the currently accepted therapeutic range for peak and trough levels may be inadequate and more aggressive dosing strategies may enhance outcomes in patients with MRSA HAP (212).

De-escalation and streamlining

De-escalation or streamlining is one strategy that has been developed that allows for the initiation of appropriate broad-spectrum

antibiotic therapy while limiting the risks for resistance and adverse effects associated with continuing unnecessary agents (213-218). Following this strategy, empirical broad-spectrum antibiotic therapy is initiated based on patient risk factors and clinical presentation. Patients are then re-evaluated at 24 h to 48 h of therapy based on clinical response and results from microbiological evaluations. Therapy can be tailored to the offending pathogen, ie, streamlining therapy to ensure appropriate coverage without antibiotic over-use. If cultures are negative for organisms, antibiotics may be discontinued (219).

Institutional guidelines

A number of publications have demonstrated the positive impact of institution-specific guidelines on the management of HAP patients (220-226). Demonstrated benefits include improved empirical therapy (222,225,226), reductions in duration of therapy (220,222,224), inappropriate antibiotic use with discontinuation of some initial antibiotic therapy (221-223,226), adverse drug reactions, exposure to medications to which patients were reported allergic (221), as well as reduced antibiotic costs (220,221).

Duration of therapy

There are currently limited data concerning the optimal duration of therapy for patients with HAP and VAP. Traditionally, the majority of patients have received antibiotics for 10 to 14 days while those infected with non-lactose-fermenting organisms such as *P aeruginosa* have been treated for 14 to 21 days. Recent evidence indicates that patients infected with susceptible pathogens experience rapid microbiological eradication and significant improvement in signs and symptoms of pneumonia within six days of receiving appropriate therapy (214). Luna et al (227) also demonstrated that signs and symptoms of pneumonia steadily improved according to the CPIS during the first seven days in patients responding to antibiotic therapy for VAP. These studies support the concept that patients treated with effective antibiotic therapy will respond within the first week of treatment.

Chastre et al (228) reported the results of a randomized double-blind trial of eight versus 15 days of antibiotics for patients with VAP. Patients randomly assigned to eight days of therapy achieved significantly more antibiotic-free days. No statistically significant differences were seen with respect to all-cause mortality or infection recurrence. Higher rates of pulmonary infection recurrence occurred in the eight-day arm for patients infected with non-lactose-fermenting bacteria, suggesting that infections with *P aeruginosa* or *Acinetobacter* species may require longer courses of therapy. These results support the observations of Micek et al (224) and Ibrahim et al (222), who demonstrated that patients experienced resolution of their signs and symptoms of infection, with mean durations of therapy of 6.0 and 8.6 days, respectively, compared with patients treated for longer durations.

Novel treatment of resistant nosocomial respiratory pathogens

Colistin: Colistin, or polymyxin E, is an antibiotic originally isolated from *Bacillus colistinus* in 1950 (229), with activity against many Gram-negative bacteria including *E coli*, *Klebsiella pneumoniae*, *P aeruginosa*, *Enterobacter* species and *Acinetobacter* species. There has been renewed interest in

colistin despite concerns about its nephrotoxicity and neurotoxicity in light of the increasing numbers of infections caused by multi-drug-resistant (MDR) pathogens, particularly *P aeruginosa* and *Acinetobacter baumannii*.

Currently, there are no randomized, controlled trials with colistin in the management of HAP or VAP, but case series with inhaled or intravenous colistin for the management of acute and chronic infections in patients with cystic fibrosis who developed nosocomial infections caused by MDR *A baumannii* and *P aeruginosa* (230,231), as well as other serious nosocomial infections (232-237), have been published. In patients with HAP or VAP, colistin at doses of 2.5 mg/kg/day to 5 mg/kg/day has been associated with positive outcomes of 25% to 73% (233,235-237). Although resistance to colistin has not been identified, superinfections due to *S maltophilia* and *S marcescens* have been noted (236).

Local and inhalation therapy

Direct local instillation or nebulization of antibiotics has been used to increase concentrations of antibiotics in the lower respiratory tract. The majority of experience and research in this area has involved the use of aminoglycosides or colistin for the management of chronic or recurrent infections in patients with bronchiectasis with or without cystic fibrosis (238-241). Data in patients with HAP and VAP are limited to small, randomized, controlled trials (242,243) and case series (234). In a double-blind, randomized, controlled trial, adjunctive endotracheal instillation of tobramycin was shown to increase pathogen eradication compared with intravenous antibiotics alone (56% versus 25%, $P < 0.005$); however, no significant differences in clinical outcomes were seen (242). Adjunctive once-daily, nebulized tobramycin was also associated with a nonsignificant trend toward extubation at day 10 compared with controls (35% versus 18.5%, $P = 0.18$) (243).

Major points and recommendations for pharmacokinetic and pharmacodynamic issues in antimicrobial therapy of HAP and VAP

1. Institutions should develop their own guidelines for the management of HAP and VAP that incorporate local resistance patterns. These guidelines should provide recommendations for empirical therapy as well as for de-escalation and duration of therapy (B-1).
2. It is recommended that for patients treated initially with appropriate antibiotics, seven to eight days of therapy for VAP should be considered appropriate except in those patients infected with non-lactose-fermenting bacteria (A-1).
3. Based on the available evidence, intravenous colistin at a dose of 2.5 mg/kg/day to 5 mg/kg/day divided in two to three doses is a reasonable option for the management of HAP and VAP caused by *P aeruginosa* or *A baumannii* where no alternative antibiotics are appropriate.
4. Additional research including randomized, controlled trials involving larger numbers of patients is needed to delineate the role of inhaled antibiotics in the management of HAP and VAP. In the interim, it is recommended that they may be used as adjunctive

therapy in selected cases of MDR Gram-negative pneumonia or in patients unresponsive to parenteral therapy (C-2).

ANTIMICROBIAL SELECTION

Antibiotic treatment of HAP and VAP is predicated on five overarching principles: early initiation of therapy, correlation of the severity of infection with the clinical presentation, reduction in mortality rates with appropriate therapy, association of late onset HAP and VAP with resistant pathogens and prudent use of combination therapy for certain resistant pathogens. The first of these principles suggests that treatment of HAP and VAP must be initiated as soon as the diagnosis is entertained. Iregui et al (244) demonstrated that the commencement of appropriate antibiotic therapy within 24 h of diagnosing VAP enhanced survival compared with waiting at least 24 h for therapy to begin. Hospital mortality was 28.4% (21 of 74) for early initiation versus 69.7% (23 of 33) for delayed initiation of therapy (244).

The second principle is that a more severe clinical presentation manifested by hypotension, organ dysfunction, electrolyte derangement (particularly hypophosphatemia) and hypoxia associated with the need for mechanical ventilation (low $\text{PaO}_2/\text{fraction of inspired oxygen ratios}$) implies a more severe nosocomial pneumonia often due to *P aeruginosa* (227,245-247). VAP mortality rates have been predicted by the number of organ dysfunctions on the day of diagnosis (245,246), hypophosphatemia (247), and reduced $\text{PaO}_2/\text{fraction of inspired oxygen ratios}$ (227). A more severe clinical presentation should dictate broader spectrum antibiotic therapy.

The third premise of importance is the concept that appropriate initial antimicrobial therapy providing adequate coverage for the potential pathogens will result in lower mortality rates in VAP compared with inappropriate therapy (248-252). Inadequate initial antibiotic therapy consistently conferred a statistically significant survival disadvantage. A corollary of this issue is that one must not only ensure appropriate selection of antibiotics to reduce the risk of inadvertently neglecting potentially resistant pathogens, but also appropriate dosing.

A natural segue to the aforementioned principle is the fourth concept. This concept dictates that resistant pathogens that may have greater potential to cause late onset HAP (MRSA, *P aeruginosa*) and VAP (*P aeruginosa*, MRSA and *Acinetobacter* species) should be adequately covered in the antimicrobial regimen employed (245,253).

Finally, the issue of combination therapy compared with monotherapy for HAP and VAP must be addressed. Combination therapy with two or more antibiotics may appear advantageous from a clinical perspective because it provides security by reducing the risk of inadvertently neglecting potentially resistant pathogens. Although retrospective data on initial therapy using piperacillin-tazobactam for the treatment of VAP achieved lower in-hospital mortality compared with not including piperacillin-tazobactam in the therapeutic regimen (HR 0.41, $P = 0.009$) (254), combination therapy employing piperacillin-tazobactam with vancomycin, an aminoglycoside or ciprofloxacin resulted in no difference in mortality or length of hospital stay compared with monotherapy. Although these data did not focus on

TABLE 9
Randomized clinical trials (RCTs) for hospital-acquired pneumonia (HAP)

Reference	Regimen	Population	Disease severity	Setting	Response	Comments
370	Aztreonam (AZ) 1–2 g q6–12 h IV versus tobramycin (T) IV; peaks 4–10 mg/mL, trough <2 mg/mL; + Gram-positive coverage	>50 years old; confirmed Gram-negative infection	Mild-moderate	NA (AZ) n=26 (T) n=14	Clinical cure (AZ) 93% (T) 50%, P=0.05	Open label RCT; 2:1 randomization
259	Cefoperazone (CPZ) 2 g q12 h IV versus cefazolin 1–2 g q6 h IV or clindamycin 600 mg q8 h IV + gentamicin 1–2 mg/kg q8 h IV (COMB)	MV 27% (CPZ) MV 25% (COMB)	NA	Ward-ICU (CPZ) n=46 (COMB) n=61	Clinical response (CPZ) 89% (COMB) 72%, P=0.052	Open label RCT
260	Cefotaxime (CFT) 2 g q8 h IV versus antibiotic combination (AC)	NA	Mild-moderate	Ward	Cure (CFT) 79% (AC) 71%, P=0.03	Open label RCT
149	CFT 2 g q12 h IV versus ceftriaxone (CRX) 4 g qd IV or 2 g q12 h IV	>18 years old	Mild-moderate	Ward (CFT) n=56 (CRX) n=62	Clinical response at end of treatment (CFT) 80% (CRX) 82%	Open label RCT
264	Piperacillin/tazobactam (P/T) 3.375 g q4 h IV or ceftazidime (CTZ) 2 g q8 h IV with tobramycin (T) 5 mg/kg/d IV	>16 years old HAP 87% (P/T) HAP 72% (CTZ+T)	Moderate	Ward (P/T+T) n=70 (CTZ+T) n=42	Clinical response at follow-up in patients with pathogen (P/T+T) 73% (CTZ+T) 52%, P=0.046	Open label RCT
371	P/T 4.5 g q8 h IV versus imipenem (I) 500 mg q6 h IV	>16 years old MV 47% (P/T) MV 51% (I)	Moderate	Ward-ICU (P/T) n=75 (I) n=79	Resolution of signs and symptoms (P/T) 83% (I) 71%, P=0.09	Open label RCT
372	Cefepime (CPM) 2 g q12 h IV versus CTZ 2 g q8 h IV	>18 years old	Mild-moderate	Ward (CPM) n=64 (CTZ) n=65	Clinical response at end of therapy (CPM) 78% (CTZ) 82%	Open label RCT
373	Moxifloxacin (MOX) 400 mg qd IV/po versus ceftriaxone (CRX) 2 g qd IV → cefuroxime 500 mg BID po	>18 years old MV 35% (MOX) MV 38% (CRX)	Mild-moderate (APACHE <20)	Ward-ICU (MOX) n=72 (CRX) n=73	Clinical response 7–10 d post-therapy (MOX) 86% (CRX) 84%	Pooled analysis of two RCTs: one double-blind, one open label

Mechanical ventilation (MV) >75% = ventilator-associated pneumonia (VAP); MV 50% to 75% = HAP/VAP; MV <50% = HAP. APACHE acute physiological assessment and chronic health evaluation; BID Twice daily; d Day; ICU Intensive care unit; IV Intravenous; NA Not available; po By mouth; q Every

P. aeruginosa, nor substantiate the merit of combination therapy, a well-accepted practice has remained to treat *P. aeruginosa* with combination therapy. Bodey et al (255) previously demonstrated that combination therapy with an antipseudomonal beta-lactam and an aminoglycoside attained superior outcomes in *P. aeruginosa* bacteremia in cancer patients (255). Yet, clinical evidence and the in vitro synergy of such combination therapy were not parlayed into improved outcomes by Hilf et al (256), although mortality was reduced in the *P. aeruginosa* pneumonia and bacteremia subgroup treated with combination therapy. Combination therapy did not produce better outcomes in the *P. aeruginosa* VAP cases studied by Crouch Brewer et al (245). Moreover, a meta-analysis has evaluated all prospective randomized trials of beta-lactam/aminoglycoside combination regimens, including a group of patients who had HAP or VAP (257). No advantage for combination therapy compared with beta-lactam monotherapy for *P. aeruginosa* infections was realized. In addition, another meta-analysis assessing the effect of beta-lactam and aminoglycoside combinations compared with beta-lactam monotherapy on the emergence of antimicrobial resistance failed to show a beneficial effect for the

combination (258). Thus, although beta-lactam-aminoglycoside combinations have been employed most commonly in *P. aeruginosa* infections, a clear benefit has not been documented. Other combinations, eg, beta-lactam-fluoroquinolone and double beta-lactam combinations, need to be explored for the treatment of *P. aeruginosa* HAP and VAP, before one totally rejects the potential benefit of combination regimens.

It should be acknowledged that not all of the aforementioned treatment principles have been validated in both HAP and VAP. Evidence exists validating the applicability of early initiation of therapy (244), the clinical severity at onset (227,245,246) and the advantage of appropriate initial therapy (248–252) for VAP; however, inclusion of HAP under the umbrella of these principles has not been verified. One must be cognizant that the principle of severity of presentation with organ dysfunction may also imply the presence of more resistant, harder to eradicate pathogens, and this issue is applicable to both HAP (247) and VAP and is associated with a poorer prognosis. Also, one can accept that combination therapy with appropriate initial agents may be preferred to attain a better outcome in *P. aeruginosa* HAP and VAP.

TABLE 10
Randomized clinical trials (RCTs) for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)

Reference	Regimen	Population	Disease severity	Setting	Response	Comments
261	Ceftazidime (CTZ) 2 g q8h IV versus ticarcillin (TIC) 3 g q4h IV + tobramycin (T) IV with peak levels of 5–7 mg/mL and troughs of 1.5–2.0 mg/mL	>18 years old, neurosurgical patients MV NA	Moderate	ICU (CTZ) n=17 (TIC + T) n=18	Clinical cure (CTZ) 88% (TIC + T) 83%	Open label RCT
374	Cefotaxime (CFT) 2 g q6h IV with aztreonam (AZ) 1 g q8h IV or amikacin (AM) 500 mg q12h IV	Adults (>20 years old), MV NA	Moderate-severe	ICU (CFT+AZ) n=13, (CFT+AM) n=16	Clinical cure (CFT+AZ) 77%, (CFT+AM) 75%	Open label RCT
375	Ciprofloxacin (CIP) 300 mg q12h IV versus CTZ 2 g q8h IV	>18 years old MV 59% (CIP) MV 73% (CTZ)	Moderate	Ward-ICU (CIP) n=17 (CTZ) n=15	Clinical response (CIP) 88.2% (CTZ) 86.2%	Double-blind RCT
262	Imipenem (I) 500 mg q6h IV or I 500 mg q6h IV + netilmicin (N) 50 mg q12h IV	>16 years old MV 52.7% (I) MV 56.9% (I+N)	Moderate	Ward-ICU (I) n=91 (I+N) n=86	Success (I) 82.4% (I+N) 83.7%	Open label RCT
263	CTZ 2 g q12h IV versus ceftriaxone (CRX) 2 g IV qd + T 3–5 mg/kg/d IV	Adults ICU 43%, MV 65%	Moderate-severe	Ward-ICU (CTZ) n=159 (CRX+T) n=138	Clinical response (CTZ) 73% (CRX+T) 65%, P=0.09	Open label RCT
376	CIP 300 mg q12h IV → 750 mg q12h po after 72 h versus CTZ 2 g q8h IV	>18 years old MV 52.8% (CIP), MV 50.7% (CTZ)	Moderate-severe	Ward-ICU (CIP) n=56 (CTZ) n=68	Clinical response at 96 h (CIP) 87.1% (CTZ) 87.3%	Open label RCT
91	Cefepime (CPM) 2 g q8h IV versus I 500 mg q6h IV	>16 years old MV 66% (CPM), MV 66% (I)	Severe	ICU (CPM) n=108 (I) n=101	Clinical response (CPM) 70% (I) 74%	Open label RCT
270	Quinupristin/dalfopristin (Q/D) 7.5 mg/kg q8h IV +/- aztreonam 2 g q8h IV versus vancomycin (V) 1 g q12h IV ± aztreonam 2 g q8h IV	>18 years old, MV 74% (Q/D) MV 68.9% (V)	Moderate-severe	Ward-ICU (Q/D) n=87 (V) n=84	Clinical response 7–13 d post therapy in bacteriologically evaluable patients, (Q/D) 56.3% (V) 58.3%	Open label RCT
268	Linezolid (L) 600 mg q12h IV or V 1 g q12h IV with aztreonam 1–2 g q8h IV	>18 years old, MV 50.5% (L) MV 50.7% (V)	Moderate-severe	Ward-ICU (L) n=169 (V) n=176	Clinical response 15–21 d post-therapy (L) 67.9% (V) 64.9%	Double-blind RCT
269	L 600 mg q12h IV or V 1 g q12h IV plus aztreonam 1–2 g q8h IV	>18 years old MV 58.2% (L) MV 56.4 (V)	Moderate-severe	Ward-ICU (L) n=107 (V) n=91	Clinical response in evaluable patients with 12–28 d follow-up (L) 66.4% (V) 68.1 %	Double-blind RCT
206	L 600 mg q12h IV or V 1 g q12h IV +/- aztreonam 1–2 g q8h IV	>18 years old MV 70.2% (L) MV 66.7% (V)	Moderate-severe	Ward-ICU <i>S aureus</i> (L) n=136 (V) n=136 MRSA (L) n=61 (V) n=62	Clinical cure at end of therapy <i>S aureus</i> (L) 51.5% (V) 43.4% MRSA (L) 59.0% (V) 35.5%, P<0.001	Double-blind RCTs with (L) versus (V) combined
88	Levofloxacin (LEV) 750 mg q24h IV then po versus I 500–1000 mg q6–8h IV then CIP 750 mg BID po	>18 years old MV 71.4% (LEV) MV 70.6% (I)	Moderate-severe	Ward-ICU (LEV) n=93 (I) n=94	Clinical response in microbiological efficacy patients at 7–15 d post-therapy (LEV) 58.1% (I) 60.1%	Open label RCT
377	CPM 2 g q12h IV versus CFT 2 g q8h IV	>18 years old MV 54% (CPM) MV 62% (CFT)	Moderate-severe	Ward-ICU (CPM) n=18 (CFT) n=5	Clinical response at follow-up (CPM) 83% (CFT) 40%	Open label RCT; 2:1 randomization

Continued on next page

TABLE 10 – CONTINUED
Randomized clinical trials (RCTs) for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)

Reference	Regimen	Population	Disease severity	Setting	Response	Comments
150	Meropenem (M) 1 g q8h IV versus I 1 g q8h IV	>16 years old, % MV NA	Moderate-severe	Ward-ICU (M) n=36 (I) n=44	Clinical response at end of therapy (M) 75% (I) 75%	Open label RCT
82	M 1 g q8h IV versus CTZ 2 g q8h IV ± T 1 mg/kg q8h IV	> 17 years old MV 73% (M) MV 67% (CTZ+T)	Moderate-severe	Ward-ICU (M) n=63 (CTZ+T) n=58	Clinical response at end of therapy (M) 89% (CTZ+T) 72%, P=0.04	Open label RCT
378	M 1 g q8h IV versus I 1 g q8h IV	>16 years old MV 73% (M) MV 72% (I)	Moderate-severe	Ward-ICU	Clinical response at end of therapy (M) 91% (I) 78%	Open label RCT

Mechanical ventilation (MV) >75% = VAP; MV 50% to 75% = HAP/VAP; MV <50% = HAP. BID Twice daily; d Day; ICU Intensive care unit; IV Intravenous; NA Not available; po By mouth; q Every; MRSA Methicillin-resistant *Staphylococcus aureus* (S aureus)

Randomized clinical trials for HAP and VAP

The randomized clinical trials undertaken for the treatment of HAP and VAP are presented in Tables 9-11. These tables outline the antibiotic regimens, (monotherapy or combination therapy), the characteristics of the patient populations studied (percentage of patients receiving mechanical ventilation), the disease severity (mild, moderate or severe) as described in the clinical trial, the clinical setting (ward or ICU), the response rates for the respective regimens and pertinent comments about the trials.

A number of observations may be gleaned from these listings. First, the trials were often performed in heterogeneous patient populations containing both mechanically ventilated and nonventilated patients. This presents difficulties in determining the efficacy of a particular regimen for HAP compared with VAP. Therefore, in an effort to standardize the presentation of the data, populations in which the percentage of mechanical ventilation was less than 50% were considered to have HAP. Patient populations in which 50% to 75% of the patients were mechanically ventilated are presented as an amalgamation of HAP and VAP, while the patient population characterized by greater than 75% mechanical ventilation was considered to be VAP.

Second, the randomized clinical trials do not substantiate any advantage whatsoever for combination therapy compared with monotherapy (47,259-263). In fact, in two studies (for HAP [82,260] and VAP [82], respectively), the combination regimen was inferior to the monotherapy regimen.

Third, it would appear that the relatively small size of the prospective clinical trials in general precludes any statement demonstrating the superiority of one agent over another. There are, however, some exceptions. In a study of HAP comparing piperacillin-tazobactam to ceftazidime, each combined with tobramycin, the piperacillin-tazobactam arm achieved superior response rates (73% versus 52%, P=0.046) (264). Similarly, meropenem produced greater success in HAP and VAP compared with ceftazidime plus tobramycin (89% versus 72%, P=0.04) (82). Cefotaxime was superior to ceftriaxone in a small trial treating VAP (265). Moreover, in two studies, one in HAP and one in VAP, combined results from the two randomized clinical trials showed that linezolid produced higher response rates for MRSA (191,266). Thus, one can only state that, in general, the comparative regimens listed in the tables

were considered to be equivalent in efficacy for both HAP and VAP. The use of combination therapy for *P aeruginosa* still remains theoretical at this time and is based on retrospective data and expert opinion (255,267) (C-3). Individual clinical trials have not demonstrated the superiority of combination therapy using a beta-lactam and an aminoglycoside. However, double beta-lactam or beta-lactam-fluoroquinolone combinations have not been studied adequately. Such combinations may have additive antimicrobial properties but their use is contingent on local susceptibility patterns.

Although individual trials have not found a distinct superiority of linezolid over vancomycin for MRSA HAP and VAP (268,269), superior efficacy of linezolid was demonstrated when the data from the two prospective randomized clinical trials were combined (206,266). Noteworthy are the response rates for vancomycin found by Wunderink et al (206) and Kollef et al (266) that appear to be consistent with the vancomycin response rate reported by Fagon et al (270). Additional studies are warranted to advise clinicians of the optimal agents and dosages for treating *P aeruginosa* and MRSA HAP and VAP.

Risk stratification of patients with HAP and VAP

Risk stratification schemata have evolved as important concepts in the treatment of patients with infectious diseases in the past 15 years. A risk stratification paradigm has been readily applied to the management of febrile neutropenic episodes in cancer patients, separating febrile episodes into low-risk febrile episodes in patients with short duration of neutropenia and no significant comorbid features versus higher risk febrile neutropenic episodes in those individuals who may have prolonged neutropenia associated with comorbid conditions (271,272). Similarly, a risk stratification schema using clinical presentation as the paradigm may be applied to the management of HAP and VAP. Clearly, those individuals diagnosed with HAP who are hospitalized on wards or the ICU yet do not present with hypotension, multiple organ dysfunction, sepsis syndrome, rapid progression of infiltrates or the need for ventilation are far different from those individuals who require life-supporting ancillary therapies such as mechanical ventilation, aggressive fluid management and vasopressors. As clinicians, it would also seem reasonable to adopt narrower spectrum therapy for the management of such patients provided resistant

TABLE 11
Randomized clinical trials (RCTs) for treatment of ventilator-associated pneumonia (VAP)

Reference	Regimen	Population	Disease severity	Setting	Response	Comments
265	Cefotaxime (CFT) 2 g q8h IV versus ceftriaxone (CRX) 2 g q24h IV	>18 years old MV 90%	Moderate-severe	ICU (CFT) n=26 (CRX) n=25	Clinical response at end of therapy (CFT) 73% (CRX) 48%, P=0.04	Open label RCT
379	Ceftazidime (CTZ1) 1 g q8h IV versus ceftazidime (CTZ2) 2 g q8h IV	Adults MV 72% (CTZ1) MV 92% (CTZ2)	Moderate-severe	ICU (CTZ1) n=25 (CTZ2) n=25	Clinical response at end of therapy (CTZ1) 80% (CTZ2) 92%	Single-blind RCT
60	Imipenem (I) 1 g q8h IV versus ciprofloxacin (CIP) 400 mg q8h IV	>18 years old 78% (I)-HAP 78% (CIP)-HAP MV 80.6% (CIP) MV 76.9% (I)	Moderate-severe	ICU (I) n=76 (CIP) n=83	Primary end point bacteriological response 3-7 d post Rx (I) 58% (CIP) 69%	Double-blind RCT
151	Piperacillin/tazobactam (P/T) 4.5 g QID IV or CTZ 1 g QID IV with amikacin 7.5 mg/kg BID IV	Adults MV 100% (P/T) MV 100% (CTZ)	Moderate-severe	ICU (P/T) n=51 (CTZ) n=64	Clinical response 6-8 d post-therapy (P/T) 51% (CTZ) 36%	Open label RCT
85	CIP 800-1200 mg IV/d versus I 2-4 g IV/d	>18 years old MV 100% (CIP) MV 100% (I)	Moderate-severe	ICU (CIP) n=41 (I) n=34	Clinical response (CIP) 71% (I) 79% <i>P aeruginosa</i> (CIP) 71% (I) 67%	Open label RCT
47	P/T 4.5 g q6h IV or CTZ 2 g q8h IV with amikacin (A) 7.5 mg/kg q12h IV	>18 years old MV 100% (P/T) MV 100% (CTZ+A)	Moderate-severe	ICU (P/T) n=83 (CTZ+A) n=26	Clinical response at end of treatment (P/T) 63.9% (CTZ+A) 61.5%	Open label RCT
380	CTZ-CI (continuous infusion) 3 g/d or CTZ-II 2 g q8h IV plus tobramycin (T) 7 mg/kg QD IV	>18 years old MV 89% (CTZ-CI) MV 94% (CTZ-II)	Moderate-severe	ICU (CTZ-II) n=17 (CTZ-II) n=18	Clinical response 14-21 days post-therapy (CTZ-CI) 83% (CTZ-II) 94%	Open label RCT
266	Linezolid (L) 600 mg q12h IV or vancomycin (V) 1 g q12h IV with aztreonam 1-2 g q8h IV	>18 years old MV 100% (L) MV 100% (V)	Severe	ICU (L) n=282 (V) n=262 <i>S aureus</i> (L) n=88 (V) n=91 MRSA (L) n=37 (V) n=33	ITT population clinical cure 12-28 d post-therapy <i>S aureus</i> (L) 48.9% (V) 35.2%, P=0.06 MRSA (L) 62.2% (V) 21.2%, P=0.001	2 double-blind RCTs (L) versus (V) combined
381	Levofloxacin (LFX) 750 mg q24h IV versus I 500-1000 mg q6-8h IV	Adults MV 100% (LFX) MV 100% (I)	Moderate-severe	ICU (LFX) n=111 (I) n=111	Response in clinically evaluable (LFX) 56.1% (I) 58.1%	Open label RCT

Mechanical ventilation (MV) >75% = VAP; MV 50% to 75% = hospital-acquired pneumonia (HAP)/VAP; MV <50% = HAP. BID Twice daily; d Day; ICU Intensive care unit; ITT Intention to treat; IV Intravenous; MRSA Methicillin-resistant *Staphylococcus aureus*; NA Not Available; *P aeruginosa* *Pseudomonas aeruginosa*; q Every; QD Daily; QID Four times daily; Rx Treatment

microorganisms are not present. In fact, at times, oral rather than parenteral therapy may be sufficient for this group. On the other hand, the clinical presentation of HAP with multiple organ dysfunction, sepsis syndrome, rapid progression of infiltrates, need for mechanical ventilation and/or known colonization with resistant organisms should prompt more aggressive antibiotic management in concert with the use of life support measures. With these thoughts in mind, one may attempt to risk stratify patients with HAP into those patients who may be managed on the ward as opposed to those who should be managed in the ICU with or without mechanical ventilation and other life support measures. The former

group may present with mild to moderate symptoms and clinical manifestations. In such patients, the infection may be early (four days or less after admission to the hospital) (group 1) or late (five or more days postadmission) in onset (group 2) (Figure 6). Finally, there is a group of patients with HAP initially hospitalized on the ward who must be transferred to the ICU due to the need for mechanical ventilation and other life supporting measures because of the severity of their clinical presentation with HAP. These individuals require more aggressive initial antibiotic therapy for fear of potential resistant pathogens that produce a more severe clinical presentation (group 3) (C-3).

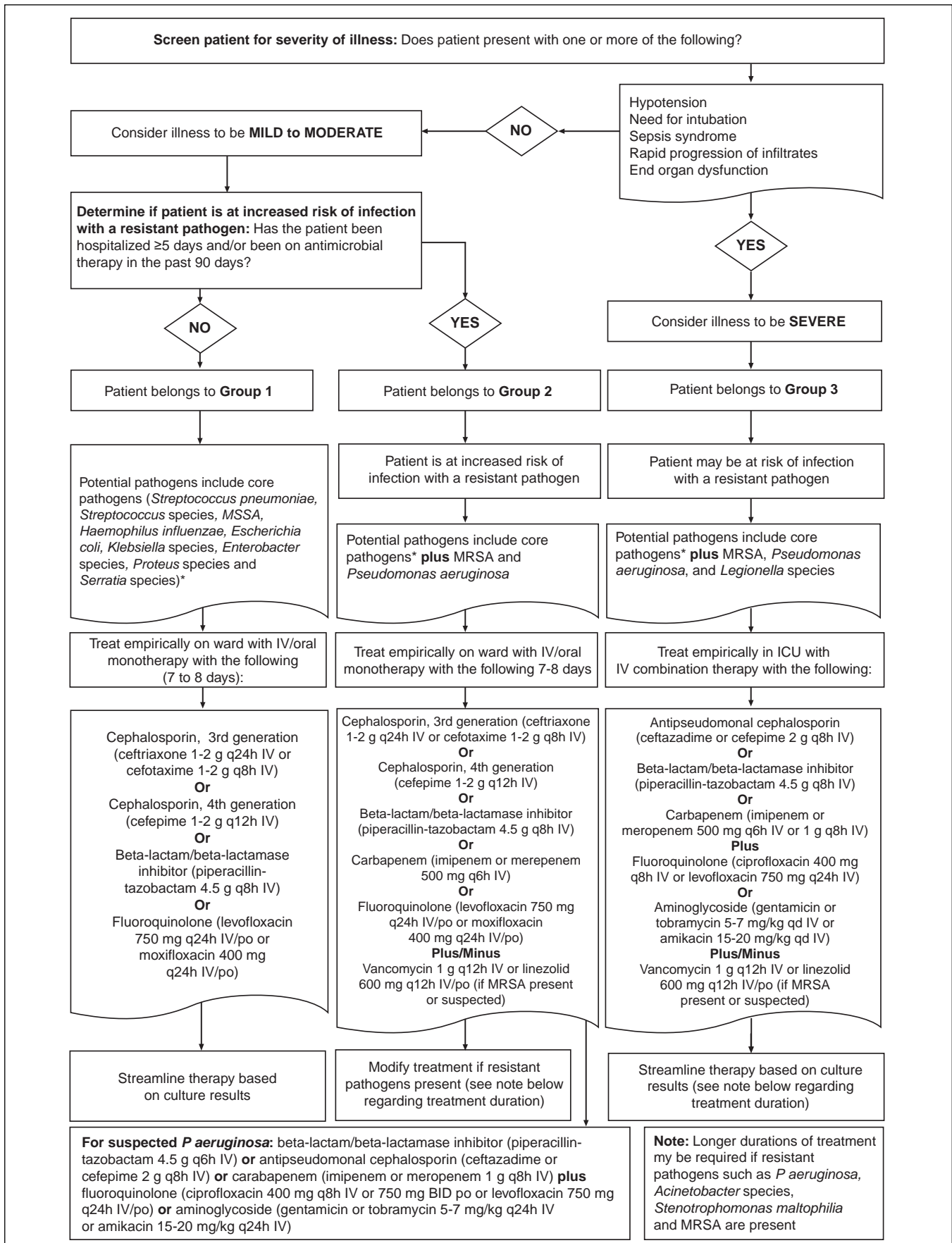


Figure 6) Treatment algorithm for hospital-acquired pneumonia. BID Twice daily; ICU Intensive care unit; IV Intravenous; MRSA Methicillin-resistant Staphylococcus aureus; MSSA Methicillin-susceptible S aureus; q Every; po By mouth

Other considerations in the risk stratification schemata for HAP and VAP are the time of onset after admission to the hospital and the predilection for the presence of resistant pathogens due to antecedent antibiotic exposure. Early-onset HAP (less than five days after the patient's admission to the hospital), without prior antibiotic exposure, is usually caused by susceptible organisms. The late-onset time frame of HAP (five or more days after admission) often associated with prior exposure to antimicrobial agents in the preceding 90 days are risk factors that predispose patients to the acquisition of more antibiotic-resistant microorganisms (5,43). Therefore, HAP of early-onset with no risk factors for resistant organisms and a mild to moderate presentation (group 1) may be treated with a third-generation (ceftriaxone or cefotaxime) or a fourth-generation cephalosporin (cefepime), a beta-lactam/beta lactamase inhibitor combination (piperacillin-tazobactam) or a fluoroquinolone (levofloxacin or moxifloxacin) on the ward as outlined in Figure 6. Thereafter, HAP therapy may be streamlined according to available pathogen susceptibilities. However, although the presentation may be mild to moderate, the presence of risk factors for resistance, ie, previous antibiotic therapy and/or onset five or more days after admission to the hospital (group 2) should prompt more potent therapy for potentially resistant pathogens, ie, a beta-lactam/beta-lactamase inhibitor combination (piperacillin-tazobactam), a carbapenem (imipenem or meropenem), a fluoroquinolone (ciprofloxacin, levofloxacin or moxifloxacin) or a third- or fourth-generation cephalosporin with either vancomycin or linezolid if MRSA is suspected as an etiologic agent (Figure 6). Moreover, if there is concern about *P aeruginosa*, a beta-lactam/beta-lactamase inhibitor combination, antipseudomonal cephalosporin (ceftazidime or cefepime), or a carbapenem with an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside are warranted as therapy. Furthermore, a severe presentation with hypotension, need for intubation, rapid progression of infiltrates, sepsis or multiple organ dysfunction (group 3) mandates aggressive combination therapy with an antipseudomonal cephalosporin, beta-lactam/beta-lactamase inhibitor combination, or carbapenem plus a fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside with either linezolid or vancomycin if MRSA is a potential pathogen (Figure 6). Once more, the regimen may be streamlined with the availability of organism identification and susceptibility.

Similar risk stratification schemata may also be applied to VAP (Figure 7). In individuals who are in the ICU for less than five days within five days of admission to the hospital, with no risk factors for resistant pathogens (ie, no antibiotics in preceding 90 days leading to colonization of the respiratory tract with resistant pathogens) and develop VAP with a mild to moderate clinical presentation (group 4), therapy is consistent with that of group 1. Therefore, a third- or fourth-generation cephalosporin, a beta-lactam/beta-lactamase inhibitor, a carbapenem or a fluoroquinolone (levofloxacin, moxifloxacin or ciprofloxacin) monotherapy are all appropriate therapy (Figure 7). One must recognize, however, that resistance in *S aureus* can emerge more readily with ciprofloxacin (273). The local epidemiology of microorganism susceptibilities must be taken into account with a willingness to adopt the use of other antimicrobial agents based on resistance patterns.

The final cohort of patients with VAP (group 5) may present with a severe clinical presentation of VAP and/or risk factors for

resistant organisms due to the late onset of VAP and/or prior antibiotic exposure. This group should be treated with an antipseudomonal cephalosporin, a beta-lactam/beta-lactamase inhibitor, or a carbapenem plus a fluoroquinolone with antipseudomonas activity or an aminoglycoside with or without vancomycin or linezolid if the presence of MRSA is present or suspected (Figure 7).

Adjustments to these initial antibiotic regimens for HAP and VAP should be undertaken based on the diagnostic approach as outlined above, using the CPIS to re-evaluate the need for antibiotics. Antibiotics may be discontinued based on a low clinical probability of HAP or VAP. All initial regimens may be streamlined following the availability of microbiological data. The duration should also be dictated by the aforementioned recommendations. In addition, failure of a patient to respond to a seemingly appropriate regimen should prompt concerns about resistant organisms, poor host response due to the presence of complications such as a lung abscess or empyema or, potentially, a diagnosis other than HAP or VAP to account for the patient's clinical problems.

Major points and recommendations for antimicrobial treatment

1. It is recommended that antibiotic therapy for HAP (C-3) and VAP (B-2) should commence within 24 h (or earlier) of diagnosis.
2. Patient risk stratification schemata based on clinical presentation (B-2), time of onset (B-2) and potential for resistant pathogens based on antibiotic exposure (B-2) should be applied to individuals with HAP and VAP.
3. Initiation of appropriate therapy and dosing in VAP will produce improved clinical outcomes.
4. A more severe clinical presentation implies infection with more resistant pathogens.
5. Randomized clinical trials do not show a benefit of any regimen over another with the exception of poorer outcomes with ceftazidime.
6. Combination therapy was not found to be superior to monotherapy.
7. A short course of therapy of seven to eight days should suffice for most cases of HAP and VAP (C-3 and A-1).
8. It is recommended that combination therapy be used for the treatment of *P aeruginosa* HAP and VAP for more prolonged periods of time (14 days) (C-3).
9. Combination therapy should be prescribed for a severe presentation of HAP and VAP and streamlined based on culture results (C-3).

NONANTIMICROBIAL APPROACH TO MANAGEMENT

Although antimicrobial agents are the mainstay of the management of HAP and VAP, nonantimicrobial therapeutic interventions can also alter outcome. These interventions include hemodynamic management, ventilation strategies, immunological treatments, fluid and nutritional management, and administrative issues.

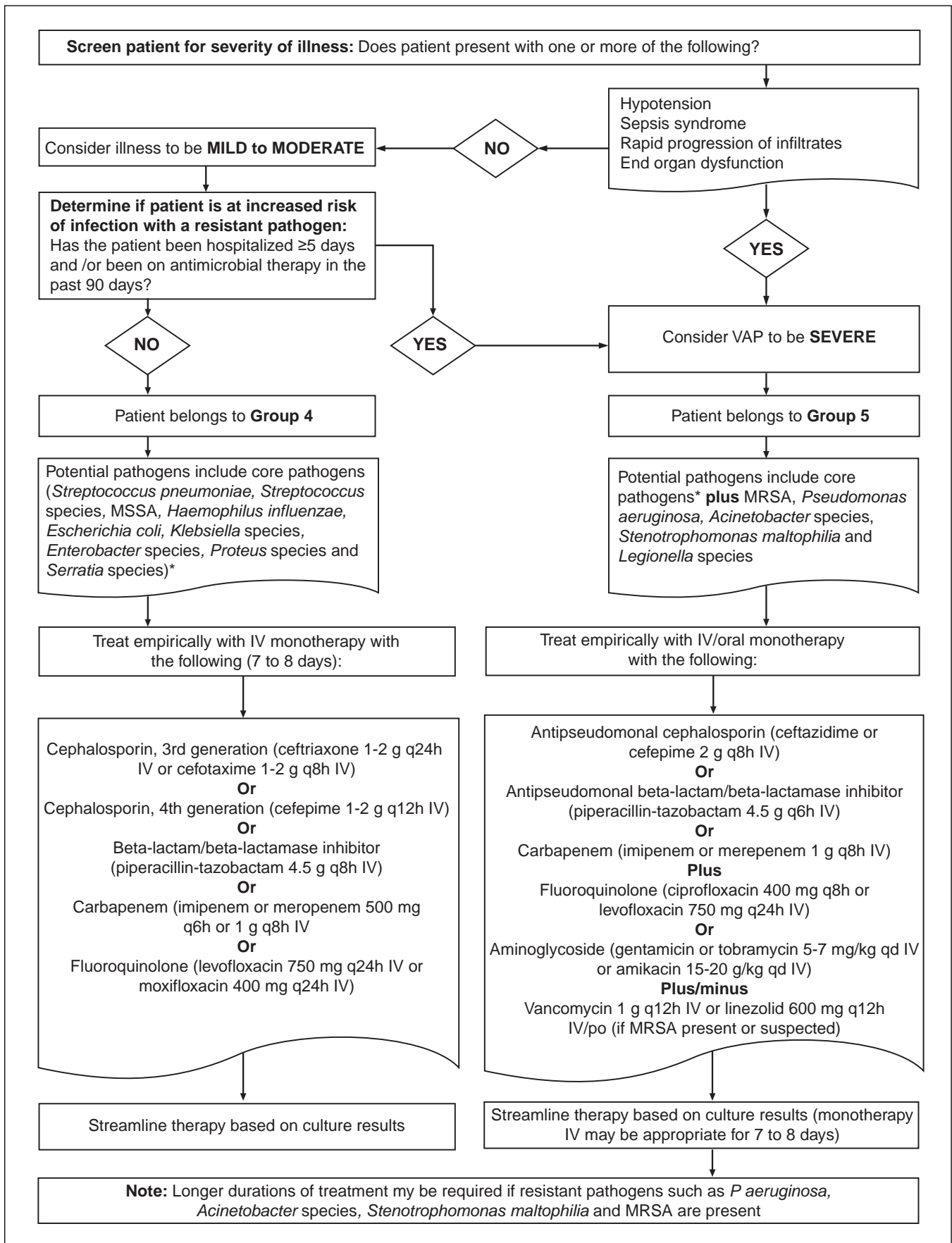


Figure 7) Treatment algorithm for ventilator-associated pneumonia (VAP). d Day; IV Intravenous; MRSA Methicillin-resistant Staphylococcus aureus; MSSA Methicillin-sensitive S aureus; q Every

Hemodynamic support

Although no data in humans indicate that hemodynamic support alters outcome in patients with HAP and VAP, improved survival has been demonstrated in patients with severe sepsis presenting to the emergency department and managed with early goal-directed hemodynamic support (274). These data support the importance of early aggressive resuscitative measures directed at maintaining an appropriate hemodynamic response for all patients with sepsis, including those with HAP or VAP. Sepsis management should include the placement of a central venous catheter, noninvasive or invasive measurement of cardiac output, measurement of oxygen extraction as assessed by central or mixed venous oxygen saturation, and transfer to the ICU.

Ventilator support

Ventilator use in the management of HAP is relevant (119); however, it is not apparent which mechanical ventilation strategy is superior, nor under what circumstances should such strategy be employed. The management of HAP patients with noninvasive ventilation has been associated with a lower incidence of complications and shorter stays in the ICU (275), but no such association was reported in another study (276). Nonetheless, the use of early, noninvasive ventilation to circumvent the need for intubation has been effective in immunocompromised patients. Patients who received such support had less serious complications (277).

Ventilation with reduced lung volumes has improved survival (278). This approach, while suitable for patients with bilateral diffuse lung disease, has not been proven for patients with localized lung disease.

Immune modulation

Attempts at improving the clinical outcome of septic patients by immune modulation have been unsuccessful using anti-endotoxin antibodies (279,280), tumour necrosis factor- α (281), interleukin-1 (282,283), high-dose corticosteroids (284,285) and nonsteroidal anti-inflammatory agents (286). Cheng et al (287) also reported that boosting the leukocyte response with granulocyte colony stimulating factor as an adjunct to antibiotics did not improve outcome. Interestingly, Bernard et al (286) showed that treatment of septic patients with intravenous ibuprofen decreased fever but was not associated with a clinical benefit. In contrast, treatment with activated protein-C (drotrecogin- α) reduced the absolute mortality of patients with sepsis by 6.1% compared with patients treated with placebo; unfortunately, such treatment was also associated with an increased risk of bleeding (288). Although Laterre et al (289) showed that treatment with drotrecogin- α improved the survival of patients with severe sepsis caused by community-acquired pneumonia, a less impressive benefit was observed in patients with sepsis caused by HAP (289). It is recommended that treatment with drotrecogin- α be confined to those HAP patients with concomitant severe sepsis (B-1).

Fluids

There are limited data on the effect of the amount of volume infused on lung function. Increased capillary leak caused by inflammatory processes, when combined with excessive fluid administration, leads to greater increases in pulmonary lung water and thereby poorer gas exchange. Greater fluid intake

was found to produce progression of radiographic pneumonia (290). Furthermore, in patients with acute lung injury, high tidal volume and positive fluid balance are associated with a worse outcome (291). More recently, a large randomized trial by the ARDS network showed that conservative use of fluid in patients with acute lung injury decreases the time to extubation and time in the ICU (292). Excess fluid volume replacement should be avoided in the management of patients with pneumonia (B-2).

Nutritional issues

A number of investigations have examined the role of nutritional support on the outcome of critically ill patients with pneumonia, but none have specifically addressed this issue in HAP and VAP. Evidence indicates that there is no advantage of total parental nutrition over enteral nutrition. When safety, cost and feasibility are considered, the latter is favoured (293), as is the early introduction of feeding (B-2). By contrast, peptide-based formulas compared with intact proteins do not improve outcomes. There is no evidence to suggest that supplementation with arginine, fish oil or glutamine improves outcome.

Administrative issues

Though the administrative structure of the ICU is fundamental to the management of severely ill patients, there are no data on the issue as it relates to the management of patients with HAP and VAP. However, clinical outcomes of patients treated in a 'closed' ICU with dedicated physicians are improved compared with those of patients treated in an 'open' setting (294,295). In addition, the surveillance of microorganisms in an ICU, including susceptibility testing to assess resistance trends, can enhance outcome by promoting the selection of more appropriate empiric regimens (1,296,297). The calculation of infection rates per 100 ICU days or per 1000 ventilatory days may also verify the success of prevention strategies. Finally, computer-assisted antimicrobial management may reduce overall antibiotic usage (221). The collection of routine cultures is not recommended, because these cultures are not predictive of subsequent invasive organisms (reviewed in [23]).

Major points and recommendations for nonantimicrobial issues related to the management of HAP and VAP

1. Attention to judicious use of fluids and nutritional support, and careful management of mechanical ventilator support, can contribute to improved outcomes in patients with HAP and VAP.
2. Computerized antibiotic management systems and systems for monitoring the incidence and susceptibility of local hospital microbial flora are useful.
3. Establishing a closed ICU staffed by dedicated intensivists may improve outcomes.
4. Optimizing hemodynamic management with judicious use of fluids, inotropic and vasopressor agents should be instituted early in patients who develop sepsis in association with VAP and HAP (B-2).
5. Patients who develop HAP and sepsis outside of the ICU should be transferred to the ICU for optimal management (A-2).

6. The use of drotrecogin-alpha in patients with severe sepsis and HAP can improve survival although the data in VAP is less clear.

PREVENTION AND RISK REDUCTION

Risk factors for the development of HAP can be differentiated into modifiable and nonmodifiable conditions (43,298). Nonmodifiable risk factors may be patient-related, such as male sex, pre-existing pulmonary disease or multiple organ system failure. However, although patient-related risk factors are nonmodifiable, long-term primary prevention or general health maintenance, such as exercise, weight reduction, and use of influenza and pneumococcal vaccines, are modifiable and recommended in patients at risk (299,300). Smoking cessation should also be encouraged in all patients, particularly those who have had HAP or VAP.

Modifiable risk factors for HAP and VAP are crucial targets for prevention that can reduce patient mortality and morbidity, and also promote the cost-effective use of health care resources. Effective prevention strategies include the use of strict infection control, hand hygiene, microbiological surveillance with availability of data on local drug resistant pathogens, monitoring and early removal of invasive devices, and programs to reduce or alter antibiotic prescribing practices (1,117,125,221,244,299,301-303).

Excellent, detailed, evidence-based guidelines for the prevention of HAP and VAP have been published by the Centers for Disease Control and Prevention and the Hospital Infection Control Practices Advisory Committee (1), as well as the Nosocomial and Occupational Infections Section of the Public Health Agency of Canada (304). Prevention strategies are also discussed in a number of more concise review articles (23,124,298,305).

Infection control

Effective targeted surveillance for high-risk patients coupled with staff education and use of proper infection control practices is the cornerstone for prevention of nosocomial pneumonia (117,125,298,306). Cross infection is an important source of AROs, and hands or gloves of hospital personnel are potential reservoirs for spread (307). No single infection control measure is efficient in reducing the threat of AROs. It is rather a combination of interventions coupled with the judicious use of antibiotics that will ultimately have a clinical impact. A comprehensive hand hygiene program has been shown to decrease the overall incidence of MRSA, extended-spectrum beta-lactamase-producing *Klebsiella* species and vancomycin-resistant enterococci (308,309). The lack of easily reachable appropriate physical facilities (sinks, bathrooms) has led many institutions to turn to alcohol-based gels, and clinical data have indicated that rates of all nosocomial infection may be significantly reduced by the use of alcohol-based hand disinfection (125,303,306).

Contact precautions, including gowns and gloves, patient cohorting and staff cohorting, have been recommended as methods of limiting the transmission of AROs (108). Infection control measures have so far been the best weapon to curb rates of spread of AROs.

Intubation and invasive devices

The use of endotracheal tubes bypasses the natural defense mechanisms of the upper respiratory tract and impairs the

host's capability to fend off infection (129). Endotracheal tubes also favour the development of bacterial biofilms that may contribute to the occurrence of VAP. Noninvasive positive pressure ventilation (NIV) using a face mask is an alternative to intubation (277,310-315). The use of NIV has been shown to decrease the incidence of VAP and even mortality; however, most of these studies were small, not blinded and included selected patients (129,312,314,316,317). Strategies to reduce the duration of mechanical ventilation are also recommended, such as improved methods of sedation and the use of protocols to facilitate and accelerate weaning (318-322). Reintubation should be avoided because it increases the risk of VAP (126). NIV to avoid reintubation after initial extubation can be attempted (310).

The major drawback of NIV is the inability to easily obtain patients' secretions, thus hindering the clinical diagnosis of VAP. When using mechanical ventilation, oral endotracheal and orogastric tubes reduce the frequency of nosocomial sinusitis and possibly HAP (135,323). Oral intubation has been associated with a lower incidence of VAP (129,316,324).

Efforts to reduce the likelihood of aspiration of oropharyngeal bacteria around the endotracheal tube cuff and into the lower respiratory tract include maintaining endotracheal cuff pressure at greater than 20 cmH₂O, and limiting the use of sedative and paralytic agents that depress cough and other host protective mechanisms (325,326). Continuous aspiration of subglottic secretions, through the use of a specially designed endotracheal tube, has been shown to significantly reduce the incidence of early-onset VAP in several studies, but may be a less effective strategy for prevention of late onset disease that carries a greater risk of infection with AROs, and higher mortality and morbidity (107,327-331).

Pulmonary aspiration, body position and enteral feeding

Supine patient positioning facilitates aspiration; semirecumbent positioning decreases it (332-334). Infection in patients in the supine position was associated with the simultaneous administration of enteral nutrition and an increased risk of aspiration of gastric contents (1,335). Gastroesophageal reflux occurs less frequently in the semirecumbent position. Thus, it is recommended that intubated patients should be managed in a semirecumbent position, particularly during feeding (A-2).

Kinetic beds

Kinetic beds or continuous lateral rotational therapy is a technique using a continuous movement of the bed along its longitudinal axis within a certain range (-40° to +40°) (129,316). This movement improves secretion drainage, and thus may decrease the risk of VAP. Two small studies showed some benefits in terms of decreasing VAP rates, and a meta-analysis concluded a significant reduction in the risk of VAP, but no reduction in mortality or duration of mechanical ventilation (129,316,336).

Circuit changes, humidifiers and ventilator equipment

Bacterial colonization of condensates in ventilatory circuits plays a role in the pathogenesis of VAP (328). Vigilance is needed to prevent inadvertently flushing the condensate into the lower airway or into in-line medication nebulizers when the patient turns or the bedrail is raised (16,328,337-339). Frequent changes of ventilator circuits should theoretically lower the risk of initial bacterial colonization. However, a

study by Craven et al (340) and at least three other well-designed studies showed no advantage to change circuits less than once a week (337-339). In fact changing circuits more often was only associated with a higher cost (339,341).

A heat and moisture exchanger (HME) recycles heat and moisture exhaled by the patient, and with a bacterial filter acts as an additional protection for the airways (342). HMEs seem to be associated with a decreased incidence of VAP (343).

Chest physiotherapy

No data exist to support the use of chest physiotherapy as a standard therapy for intubated patients.

Suctioning catheters

There are two types of suctioning catheters: open single-use and closed multiuse. Only a handful of studies with a limited number of patients have compared these two options. There is no significant difference in the incidence of VAP. A closed suction catheter changed between each patient is more advantageous in terms of cost and maintenance (129,316,324).

Antimicrobial modulation of host bacterial colonization

Oropharyngeal colonization, either present on admission or acquired during the ICU stay, is an independent risk factor for the development of ICU-acquired HAP caused by enteric Gram-negative bacteria and *P aeruginosa* (344). In a randomized trial, DeRiso et al (345) demonstrated that the use of the oral antiseptic, chlorhexidine, significantly reduced rates of nosocomial infection in patients undergoing coronary artery bypass surgery.

Modulation of oropharyngeal colonization, by combinations of oral antibiotics, with or without systemic therapy or selective decontamination of the digestive tract (SDD) is also effective in reducing the frequency of HAP, although the methodological study quality appeared to be inversely related to the magnitude of the preventive effects (141,302,346-351).

Higher ICU survival has been noted among patients receiving SDD (352,353). In the former study (352), patients had a lower ICU mortality, although ICU mortality rates of all patients included did not differ significantly. In the largest study performed so far, SDD administered to 466 patients in one unit was associated with relative risk for ICU mortality of 0.65 and of hospital mortality of 0.78, when compared with 472 patients admitted in a control ward (353). In addition, infections due to AROs occurred more frequently in the control ward. Importantly, levels of AROs were low in both wards, with complete absence of MRSA. The preventive effects of SDD for HAP have also been lower in ICUs with high endemic levels of antibiotic resistance. However, SDD may increase the selective pressure for antibiotic-resistant microorganisms (354-360) and should be discouraged.

Major points and recommendations for prevention and risk reduction of HAP and VAP

1. To control the spread of AROs, an effective infection control program must be implemented in all institutions (A-1).
2. Oral intubation should be the preferred way for invasive mechanical ventilation (B-2).

3. Patients should be nursed in a semirecumbent position (30° to 45° angle) (A-2).
4. Kinetic beds may be useful in some carefully selected groups of patients.
5. Circuit changes should be performed not more than once a week, except if visibly soiled (A-1).
6. If not contraindicated, HME should be used and changed on a weekly basis (B-2).
7. The regular use of subglottic secretion drainage should be encouraged in intubated patients (A-2).
8. A closed suction catheter should be used for each new patient (B-2).
9. Routine prophylaxis of HAP with oral antibiotics (SDD), with or without systemic antibiotics, reduces the incidence of ICU-acquired VAP, has helped contain outbreaks of MDR bacteria, but is not recommended for routine use, especially in patients who may be colonized with MDR pathogens (B-3).
10. Modulation of oropharyngeal colonization by the use of oral chlorhexidine can prevent ICU-acquired HAP in selected patient populations (345).

FUTURE DIRECTIONS

The guidelines for HAP and VAP have helped to highlight deficiencies in our knowledge and by doing so have served to point the way for future studies and investigations. There are issues in diagnosis, treatment and prevention that still require more data and definitive answers.

Diagnosis

Historically, the detection of pathogens has relied on the staining and growth of microorganisms. Molecular diagnostics offer the opportunity for the rapid and accurate identification of specific etiological agents. The most widely employed of the molecular tests involves detection of nucleic acid molecules and nucleic acid amplification. Other advances such as matrix-assisted laser desorption ionization – time of flight (MALDI-TOF) mass spectrometry and Raman and Fourier transformed infrared spectroscopy are also being developed (361,362). The former has been used for the identification of proteins and separation of DNA fragments and the latter two for the rapid identification of pathogens in blood cultures. The further development of genomics, proteomics, glycomics and metabolomics should allow the development of inventories of bacterial genes and their proteins to help in the identification and virulence profiling of potential pathogens (363).

Treatment

One of the main issues in treatment is how to best deal with *P aeruginosa* and MRSA. The two main questions in the treatment of pseudomonal HAP and VAP are whether one should use mono- or combination therapy, particularly in nonbacteremic cases; and how long to treat. Appropriately designed randomized controlled trials with sufficient sample sizes are needed to answer the former question.

How long to treat pseudomonal HAP or VAP is also an unknown. Physicians have often treated for up to two weeks

and sometimes longer, but there are data suggesting that this may be too long. In a study of VAP patients, it was found that by day 6, the specified criteria indicating clinical response had been satisfied (214). Administration of antibiotics for a second week not only did not improve clinical response, but was associated with colonization by other pathogens. However, *P aeruginosa* VAP was associated with higher relapse rates when treated for only eight days (228). While eight days of treatment may be too short for *P aeruginosa*, it is not clear for how long to extend therapy. Similar issues are applicable to HAP and VAP caused by MRSA.

Aerosolized antibiotics for VAP

Not all antibiotics achieve reasonable levels in the lung. Aerosolization of antibiotics allows greater access to the lower respiratory tract with higher levels being achieved in the ELF. Pseudomonas unresponsive to systemically administered agents subsequently responded to aerosolized aminoglycosides or polymyxin, and aerosolized aminoglycosides have been used in cystic fibrosis patients for some time (234). Unfortunately, very few antibiotics have formulations developed specifically for administration by this route and often an intravenous formulation of a drug is used. Adverse effects such as bronchospasm may result when such an approach is tried. A nebulizer that delivers the appropriate particle size (1 µm to 5 µm) is also required. The use of aerosolized vancomycin may be worth exploring for treatment of MRSA HAP and VAP.

Prevention

Recent appreciation of the concept of quorum sensing has shown that this same mechanism may be involved in the production of biofilms (364). Two different approaches have been

tried to minimize or prevent this process and thus have an impact on the development of VAP. Altered surface characteristics of the endotracheal tube through the use of silver-coated or hexetidine-impregnated tubes, or oxygen-plasma treatment of the polyvinyl chloride interfere with the ability of bacteria to adhere to the tubes. Another approach is to use nebulized antibiotics such as gentamicin (365). Clinical studies are needed to show whether they actually have an impact on the development of VAP.

Also, nebulized ceftazidime for prevention has been shown to produce fewer VAP cases at day 14 and cytokine levels such as tumour necrosis factor-alpha, interleukin-1 beta and interleukin-8 were lower in the ceftazidime group than in the placebo group (366). Such preventive approaches are worth pursuing with appropriately designed trials.

Through expansion of our knowledge of the epidemiology, risk factors, diagnosis, treatment and prevention of HAP and VAP, reductions in the morbidity and mortality of these significant infections will hopefully be realized.

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