RECOMMENDATIONS OF THE LATIN AMERICAN THORACIC SOCIETY (ALAT)

Clinical Guidelines for the Treatment of Nosocomial Pneumonia in Latin America: an Interdisciplinary Consensus Document

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Introduction

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection overall and the most common in intensive care units (ICUs). It causes morbidity and mortality and increases both length of stay in hospital and cost of treatment. Medical progress gave rise to a special environment (the hospital) occupied by a specific population (seriously ill patients), and this has given rise to the emergence of new germs (nosocomial pathogens). HAP poses an ongoing challenge owing to continuous changes in nosocomial epidemiology and growing resistance to antibiotics; we are far from a solution, and new problems requiring new strategies are arising continuously. In this context, consensus documents incorporating clinical guidelines are an effective weapon. Although the problem of nosocomial infection transcends national borders and exists on a worldwide scale, HAP in Latin America has certain peculiarities that mandate a specific analysis of its epidemiology and treatment from a regional rather than a global standpoint.

The present document is the result of the work of an ad hoc committee set up by the Asociación Argentina de Medicina Respiratoria (Argentinian Respiratory Medicine Society, AAMR), the Sociedad Argentina de Infectología (Infectious Diseases Society of Argentina, SADI), and the Sociedad Argentina de Terapia Intensiva (Argentinian Society of Intensive Care Medicine, SATI) to compile a consensus document on respiratory infections. Members of these 3 organizations joined forces with colleagues from the Sociedad Argentina de Bacteriología (Argentinian Society of Bacteriology, SADEBAC) and the Sociedad Argentina de Medicina (Argentinian Medical Society) to draw up these guidelines. After the proposed draft had been revised by members of the assemblies on infectious diseases and critical care of the Latin American Thorax Society (ALAT) and by other Latin American colleagues, the resulting consensus document was officially adopted by ALAT.

*A list of the members of GALANN is included at the end of the article.

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Methods

The members of the participating organizations worked together on the 6 main topics covered by this consensus document: definition, epidemiology, and etiology; risk factors and mortality associated with HAP; diagnosis; antibiotic treatment; duration of treatment, assessment of response, and non-antibiotic treatment measures; and prevention. Conclusions drawn up at a plenary meeting were discussed and submitted to internal and external review. The present document summarizes the conclusions reached by consensus after incorporating the comments and corrections of the members of the infectious diseases and critical care assemblies of ALAT and other Latin American colleagues.

Guidelines published by medical associations in other countries and important studies published during the last 20 years, and particularly the last 5, were used as a basis for the present document. A systematic search for relevant literature was carried out on MEDLINE. In exceptional cases, owing to the scarcity of pertinent information in the indexed literature, data gleaned from unpublished abstracts and papers were used to provide information on local etiology and antibiotic resistance patterns. The scientific evidence supporting the conclusions was classified into the following 4 levels depending on its source: level A evidence, randomized controlled trials; level B evidence, controlled trials without randomization; level C evidence, case series; and level D evidence, expert opinion.

Definition, Epidemiology, Etiology

Definition

HAP is pneumonia that occurs more than 48 hours after the patient is admitted to the hospital (in order to distinguish clearly between HAP and community-acquired pneumonia). Ventilator-associated pneumonia (VAP), which is HAP that appears in patients on mechanical ventilation, should appear after ventilation

is commenced, but the most important criterion is the presence of an artificial airway in a patient with HAP.[1] Two subgroups of HAP are recognized:

– Early onset—when HAP appears within a few days of hospital admission or start of ventilation. The threshold between early and late HAP varies; some experts put it at fewer than 4 days while others set this threshold as high as 7 days. Early-onset HAP is caused by the bacteria found outside the hospital environment that are the usual colonizers of the oropharynx (*Streptococcus pneumoniae, Haemophilus influenzae,* methicillin-sensitive *Staphylococcus aureus*, etc).

– Late onset—when HAP develops after the established threshold. Late-onset HAP is caused by nosocomial pathogens that colonize the oropharynx after admission.

The lack of a gold standard diagnostic test has provided the impetus for standardizing the criteria used to diagnose HAP (level A evidence).[2,3] The following levels of diagnostic certainty are recognized:

– Definite pneumonia: persistent (>24 hours) and progressive new pulmonary infiltrates and purulent tracheal secretions found in conjunction with one of the following[4]: *a)* radiographic cavitation—preferably detected by computed tomography—indicative of an abscess and confirmed by culture of needle aspirate; or *b)* histological evidence of pneumonia (biopsy or autopsy) showing abscess formation or areas of consolidation with intense leucocyte infiltration, and positive culture of the parenchyma revealing $\geq 10^4$ colony forming units per gram (cfu/g) of tissue.

– Probable pneumonia: persistent (>24 hours) and progressive new pulmonary infiltrates and purulent tracheal secretions found in conjunction with one of the following: *a)* quantitative culture of a specimen of pulmonary secretions obtained using a protected brush ($>10^3$ cfu/mL) or by bronchoalveolar lavage (BAL, $>10^4$ cfu/mL); *b)* isolation of microorganisms in a blood culture (without any other probable focus of infection) 48 hours before or after taking a simple respiratory sample (tracheal aspiration or sputum). The pathogens found in both the blood culture and the secretions must be microbiologically identical and have the same pattern of antibiotic sensitivity; *c)* isolation of pathogens in pleural fluid (without prior instrumentation) that are microbiologically identical and have the same pattern of antibiotic sensitivity as those isolated in a simple respiratory sample; or *d)* histologic evidence of pneumonia (biopsy or autopsy) revealing abscesses or areas of consolidation with intense leucocyte infiltration with negative culture of the lung parenchyma ($<10^4$ cfu/g of tissue).

Incidence and Prevalence

The incidence of HAP is 5 to 10 cases per 1000 hospital admissions, and is 6- to 20-fold higher in mechanically ventilated patients (level C evidence).[5,6] A 15% prevalence and an average of 3 days on invasive ventilation before onset was reported in a multicenter study of 2897 patients.[7] Since the level of risk varies greatly between hospitalized patients and those on mechanical ventilation, the equation should be expressed in terms of cases per 1000 patient days (HAP) and cases per 1000 days of mechanical ventilation (VAP).[8,9] The incidence per day of ventilation has been estimated as 1% to 3% (level B).[10,11]

An extensive study of infections in European ICUs reported a prevalence of infection of 45%, and half of the cases were pneumonia.[12]

Etiology and Pathogenesis

The development of pneumonia is preceded by colonization with normal flora (*Streptococcus, Staphylococcus,* or *Haemophilus* species) or nosocomial pathogens (gram-negative rods or methicillin-resistant *S aureus* [MRSA]). Pathogens present in the oropharynx and contiguous structures colonize bronchial secretions after endotracheal intubation. Aspiration of contaminated secretions is the chief mechanism by which the pathogens reach the lung parenchyma. Other mechanisms are inhalation of aerosolized material, hematogenous spread, and dissemination from contiguous structures.

The etiology of HAP coincides temporally with the colonization pattern described, and pathogens may cause anything from colonization of the oropharynx or contiguous structures (paranasal sinuses and dental plaque) to VAP (level B).[9,13-17] The importance of the gastrointestinal tract in this process is more controversial (level C).[18,19]

Aerosol inhalation may play a role in HAP caused by respiratory viruses, such as *Legionella* species and *Mycobacterium tuberculosis.* Pathogens vary depending on the population studied, the underlying disease, the duration of exposure to risk, and the site of care (level B).[19-27] Etiologies vary according to country, city, hospital, and even different areas within the same hospital.[20]

Causative pathogens can be identified by cultures of blood, pleural fluid, or respiratory samples obtained using a protected specimen brush or BAL. However, prior antibiotic therapy reduces the sensitivity of such methods depending on the duration of treatment and the sensitivity of the microorganisms to the antibiotic used.[4,13, 22,28-30] Even the value of culturing lung tissue has been questioned. In patients with HAP, the relationship between histology and quantitative cultures of tissue and respiratory samples is very complex.[2,3,30]

Pseudomonas aeruginosa and *S aureus* are the most common pathogens in adults with HAP in ICUs.[31] The frequency of other pathogens is shown in Tables 1 and 2. It is difficult to interpret the development of commensal oropharyngeal flora in quantitative cultures of distal specimens. These agents are called nonpotentially pathogenic microorganisms.[32] They may, however, give rise to infection in both immunocompetent and immunodeficient individuals[33-36] and be responsible for up to 9% of VAP episodes, and associated with deterioration

of organic function. They should, therefore, be treated with antibiotics.[37,38]

The presence of viruses and *Legionella pneumophila* is rarely investigated. The role of *Candida* species as a pathogen is still controversial.[39] Anaerobic bacteria have generally been isolated together with aerobic bacteria and are associated with early-onset pneumonia.[40]

Polymicrobial etiology is common. It is found in around 40% of HAP cases in reports of case series[11,41,42] and is more common in patients with acute respiratory distress syndrome (ARDS).[43]

Tracheobronchitis (nonpneumonic inflammation of the lower respiratory tract) has been little studied.[12] The pathogens most often found in the few cases studied were the same as those identified in cases of HAP.[44-46]

According to the literature, the pathogens that most often cause VAP are *P aeruginosa* and *S aureus,* followed by *Acinetobacter* species and various Enterobacteriaceae genera (Table 1). Argentina has a higher incidence of *Acinetobacter* species and a lower incidence of *P aeruginosa* and *H influenzae* than the United States and Europe (Table 2).

TABLE 1
Etiology in 4305 Episodes of Nosocomial Pneumonia Documented Using Bronchoscopic Techniques or Blood Cultures Representing a Total of 5604 Pathogens (1.3 Microorganisms Per Episode)[2,20,21,29,37,42,43,46,57,66,76,81,83,87,94,104-107,112,131,133,135,204,205]

Pathogen	Number, %
Gram negative bacilli	
Pseudomonas aeruginosa	1205 (21.4)
Acinetobacter species	479 (8.5)
Stenotrophomonas maltophilia	120 (2.1)
Enterobacteriaceae*	1010 (17.9)
Haemophilus species	350 (6.2)
Moraxella catarrhalis	29 (0.5)
Legionella species	9 (0.2)
Other gram-negative bacilli	150 (2.7)
Gram positive bacilli	
Staphylococcus aureus†	1226 (21.7)
Coagulase-negative Staphylococcus	89 (1.6)
Streptococcus pneumoniae	185 (3.3)
Other *Streptococcus* species	340 (6.0)
Enterococcus species	38 (0.7)
Upper airway flora‡	144 (2.5)
Anaerobic organisms	30 (0.5)
Fungi§	119 (2.1)
Virus	22 (0.4)
Other pathogens‖	157 (2.8)

*Distribution by genus: unspecified, 4.0%; *Klebsiella* species, 3.8%; *Enterobacter* species, 3.0%; *Escherichia coli,* 3.0%; *Proteus* species, 2.0%; Serratia *species, 1.4%;* and other Enterobacteriaceae, 0.7%.
†Distribution by methicillin sensitivity: unspecified, 7.5%; resistant *S aureus*, 8.9%; and sensitive *S aureus*, 5.2%.
‡Unspecified upper airway flora as reported by different studies.
§*Candida* species, 1.3%; *Aspergillus* species, 0.3%, *Pneumocystis jiroveci*, 0.2%.
‖Other unspecified pathogens reported by different studies.

Risk Factors for HAP and Death

Risk Factors for HAP

The main risk factors for HAP are endotracheal intubation and invasive ventilation.[8,27,47-52] Overall, risk factors are grouped according to whether or not they can be modified and whether or not they are associated with intubation and mechanical ventilation.

Modifiable risk factors include bronchial aspiration, compromised consciousness, the use of antacids or H_2 blockers, and the presence of a nasogastric tube. Nonmodifiable risk factors include age over 60, chronic obstructive pulmonary disease (COPD), upper respiratory tract abnormality, disease severity—as measured by the Acute Physiology Score and Chronic Health Evaluation (APACHE II)—, neurological disease, trauma, and surgery (level B).[8,21,27,47-64]

In the case of patients on ventilation, the specific modifiable risk factors are as follows: not elevating the head of the bed, frequent changes of the ventilation circuit, use of muscle relaxants, continuous sedation, reintubation, and transport outside of the ICU. The unavoidable risk factors in these patients are as follows: ventilation for more than 24 hours, ARDS, heart disease, burns, altered consciousness, need for monitoring of intracranial pressure, and emergency endotracheal intubation (level B).[10,50,51,55,56,65-73]

Risk Factors for HAP Caused by Multiresistant Microorganisms

Multivariate analysis has shown that the most important risk factors for VAP caused by multiresistant

TABLE 2
Etiology of Episodes of Nosocomial Pneumonia Documented by Bronchoscopic Techniques or Blood Cultures. Relative Frequency in Different Parts of the World

Pathogen	United States, Number, %[2,46,66,83,87,94,135]	Europe, Number, %[21,37,43,57,76,81,104-107,131,133,205]	Latin America, Number, %[20,29,42,112,204]
Gram negative bacilli			
Pseudomonas aeruginosa	345 (18.7)	595 (22.61)	66 (11.1)
Acinetobacter species	44 (2.4)	184 (7.0)	149 (25.0)
Stenotrophomonas maltophilia	60 (3.3)	45 (1.7)	10 (1.7)
Enterobacteriaceae*	339 (18.4)	446 (16.9)	92 (5.4)
Haemophilus species	88 (4.8)	216 (8.2)	7 (1.2)
Gram positive bacilli			
Staphylococcus aureus	405 (22.0)	566 (21.5)	143 (24.2)
Methicillin-resistant *S aureus*	41.2%	71.9%	47.6%
Streptococcus pneumoniae	62 (3.4)	85 (3.2)	20 (3.3)

**Klebsiella* species, *Enterobacter* species, *Escherichia coli, Proteus* species, *Serratia* species, and other Enterobacteriaceae.

pathogens are prolonged mechanical ventilation (>4-7 days) and prior use of antibiotics (level B).[21,73,74] The other risk factors identified were neurosurgery and ARDS for *Acinetobacter baumannii*[56]; COPD and use of metronidazole for *P aeruginosa*[23]; and head injury and corticosteroid treatment for MRSA.[75] In general, it is not possible to draw any definitive conclusions from the studies that identified risk factors for acquiring VAP caused by specific agents because they included only small numbers of patients or were limited by other methodological defects (level B).

HAP in ARDS

VAP is present in 30% to 70% of ARDS cases.[43,76,77] In a Latin American case series, the incidence of VAP was 65% in patients with ARDS lasting more than 1 week.[78] In patients with ARDS, the phagocytosis of alveolar macrophages and neutrophils is abnormal and they display decreased activity when stimulated by *ex vivo* bacteria.[79,80] Early-onset HAP seems to be more common in patients without ARDS, probably because patients with ARDS more often receive antibiotics prior to developing HAP (level B).[43,76,81] The diagnosis of VAP in patients with ARDS is complex. The classic criteria (fever, leukocytosis, increase in pulmonary infiltrates, purulent secretions) are insufficient, since all of these signs may occur in the absence of infection.[77,82] VAP does not increase mortality in patients with ARDS, and the course of the episode tends to be more closely linked to the underlying disease than to ARDS.[43,81,83,84] However, pneumonia does increase morbidity in patients with ARDS because it prolongs the duration of mechanical ventilation.[81,85]

Mortality

The risk of death is 2 to 10 times higher in patients with VAP than in patients who do not develop this disease.[86] The attributable mortality expresses the proportion of the crude mortality due to HAP or VAP; it is also the proportion reported as the increase in relative risk of mortality.[87] Crude mortality rates for HAP range from 24% to 76%.[11,58,87-97] This broad range reflects the disparity in diagnostic criteria and differences between populations in disease severity. Four studies found significant mortality attributable to VAP of between 14% and 49%,[91-93,96] while others observed no differences between patients with and without VAP.[94,95] VAP appears to be associated with higher mortality, although this relationship is less obvious in severely ill patients (such as those with ARDS) and in those in whom the risk of death associated with their underlying disease is lower (young trauma patients for example) (level B).[94.98]

Prognostic Factors for Death

The following risk factors for death have been described: advanced age, poor prior quality of life, presence of rapidly fatal or ultimately fatal disease (3 and 2 respectively on the McCabe scale), diseases associated with immunodeficiency (cancer, transplants, AIDS), admission to surgical ICUs, need for oxygen at concentrations greater than 35%, need for positive end-expiratory pressure, reintubation, nonpulmonary organ dysfunction (particularly when more than 3 organs are affected), shock, severe sepsis, septic shock, bilateral involvement, and high serum concentrations of interleukin 6 and 8 (level B).[8,11,29,47,51,54,65,83,87,88,99-102] Inappropriate antibiotic treatment has been associated repeatedly with a higher mortality rate in VAP (level B).[42,87,97,103-106] Mortality associated with late-onset pneumonia and pneumonia caused by high risk pathogens (nonfermenting gram-negative bacilli and MRSA) is higher. High risk pathogens are more often found in patients requiring prolonged ventilation (level B).[75,92,96,107]

Diagnosis

Clinical Diagnosis

Clinical diagnosis of HAP should be considered in patients hospitalized for longer than 48 hours who present a new radiographic infiltrate or progression in existing infiltrates in conjunction with any of the following findings: fever or hypothermia, leukocytosis, leukopenia, or any increase in the quantity and/or purulence of secretions.[16,77] One study confirmed that only 42% of patients who present such nonspecific signs and symptoms actually have HAP.[108] When a new infiltrate is found in conjunction with at least 2 or 3 clinical criteria, sensitivity and specificity may improve.[109] It is generally considered that the clinical diagnosis of VAP is associated with a 30% to 35% false negative rate and a 20% to 25% false positive rate.

Pugin et al devised a Clinical Pulmonary Infection Score (CPIS), which combines the criteria listed above with the qualitative culture of secretions and the ratio of PaO_2 to fraction of inspired oxygen as an indicator of oxygenation. The CPIS is useful both as a diagnostic tool and an indicator of disease severity, and can be used to monitor the course of HAP over time. In the original study, the CPIS had a sensitivity of 93% for a score of 6 or higher and was considered to be a better diagnostic tool than the clinical signs mentioned earlier.[110] Other authors have used the original CPIS or a modified version to diagnose VAP, but the sensitivity reported has been lower. The CPIS has also been used as a prognostic indicator of treatment efficacy and clinical improvement.[111-115]

Radiographic Diagnosis

Chest radiography plays a crucial role in the initial assessment of patients with suspected HAP, despite the fact that the radiographic signs of HAP and VAP are of limited sensitivity and specificity. In the ICU, chest

radiographs are usually taken using simple portable equipment in less than ideal conditions. In general, the only projection possible is anteroposterior, and in ventilated patients it is difficult to obtain an image at deep inspiration. In patients with abnormalities in an earlier chest radiograph (mainly those with ARDS), diffuse and/or asymmetric abnormalities may conceal the presence of new or progressive infiltrates. The specific radiographic criteria for HAP have been compared with histologic findings and cultures of lower airway material.[77,108,110,113,116-118]

It has been reported that alveolar infiltrates, aerial bronchogram, and new or progressive infiltrates are the most sensitive signs of pneumonia (from 50% to 100%) in patients with VAP. The specificity of these signs is unknown since the number of patients without pneumonia having a normal chest radiograph cannot be determined. Since ventilated patients have other potential causes of radiographic infiltrates, no single specific radiographic sign increases the likelihood of VAP (level B).[77,118-120] Comparison with prior chest radiographs and/or basic clinical information does not improve interpretation.[116] In critically ill patients, radiographic signs may be secondary to ARDS, atelectasis, pulmonary embolism, alveolar hemorrhage, drug toxicity, aspiration, cardiogenic pulmonary edema, pleural effusion, bronchiolitis obliterans, radiogenic pneumonitis, or other causes.[121]

Chest computed tomography can improve diagnostic certainty. In a study of patients not intubated after abdominal surgery, 26% of the alveolar opacities detected by computed tomography in the lower lung fields were not visible on chest radiographs.[122] The diagnostic accuracy of computed tomography for HAP in patients with ARDS was 69% when compared to cultures obtained by bronchoscopy, but no single sign, alone or in combination, helped to establish an exact diagnosis.[123] Routine chest radiographs should be obtained when pneumonia is suspected. Computed tomography should probably be limited to the diagnosis of confusing clinical presentations or cases in which the pneumonia does not resolve or progresses in spite of appropriate antibiotic therapy.

Etiologic Diagnosis

Identification of the causative microorganisms allows the physician to confirm the diagnosis and select an appropriate antibiotic regimen. Quantitative microbiological study of respiratory specimens facilitates differentiation between colonization and infection, and the yield of this test depends on the procedure used to obtain sample material from the lower respiratory tract.[124,125] Both invasive and noninvasive methods can be used to obtain lower airway specimens for quantitative culture.

Noninvasive procedures include blood culture, tracheal aspiration, blind BAL or mini-BAL, and blind protected brushing. Two blood culture samples should be taken.[125] The sensitivity of blood cultures for diagnosing HAP is under 20%, and the positive predictive value is around 80%.[29]

The noninvasive method most often used is tracheal aspiration, which also affords sputum smears for direct microscopic examination. The presence of squamous epithelial cells in a sample is indicative of upper airway contamination. A lower airway specimen should contain more than 25 polymorphonuclear cells and fewer than 10 squamous epithelial cells per 100 power field.[86,124] A diagnosis of bacterial pneumonia is less likely if too few polymorphonuclear cells are observed on direct examination. Similarly, if microorganisms are not detected with Gram stain it is unlikely that they will be found in cultures.[86,126] Quantitative study of tracheal aspirate has an average sensitivity of 81% and a specificity of 65%.[127] The recommended threshold of positivity is $\geq 10^5$ to $\geq 10^6$ cfu/mL for each microbiologically significant microorganism.[120,128,129] In mini-BAL, the catheter is placed blindly in a distal bronchus. Then 20 mL of sterile saline solution is injected into the lung, and about 10% of the return volume is sampled and processed in the same way as for BAL. A culture with $\geq 10^3$ to $\geq 10^4$ cfu/mL is considered positive.[125] The threshold of positivity for blind protected brush specimens is $\geq 10^3$ cfu/mL. The sensitivity and specificity of these procedures are very similar to those of bronchoscopic techniques. The advantage of non-bronchoscopic techniques is that they are more often available, less invasive, less expensive, and can be performed with endotracheal tubes of small diameter. The greatest disadvantage of these techniques is the potential for error in the sampling location because the procedure is blind.

Invasive procedures were developed to obtain secretions directly from the affected lower airway while minimizing contamination of the sample with upper airway microorganisms. Protected brush specimens have a sensitivity ranging from 33% to 100%, and a specificity of 60% to 100%.[130] The recommended threshold for positivity is $\geq 10^3$. This technique is not, however, useful for obtaining specimens of anaerobic microorganisms. BAL is performed by instilling 100 to 150 mL of sterile saline solution in 20 mL aliquots. The threshold for considering a microorganism to be significant is $\leq 10^4$ cfu/mL. BAL fluid with less than 50% neutrophils has a 100% negative predictive value for pneumonia.

When no bacteria are detected on direct examination of BAL fluid, the positive predictive value of the specimen for absence of infection is 91%.[2] In several studies, the sensitivity of BAL has been as high as 100%, and its specificity has been estimated to be between 88% and 100%. The presence of 5% of leukocytes with intracellular bacteria is highly indicative of pneumonia (sensitivity of 91% and specificity of 89%).[86,125] The minimum sample volume required for a complete bacteriologic study of BAL performed using fiberoptic bronchoscopy is 10 mL. When bronchoscopic samples are obtained with both the protected brush and BAL, the protected brush

specimen should be obtained first to minimize false positive results. Specimens should always be processed within 30 minutes of sampling.

Bronchoscopy may cause a decrease in PaO_2, fever, infiltrates, pneumothorax, hemoptysis, and exacerbation of respiratory insufficiency. It is contraindicated in patients with refractory hypoxemia, significant airway obstruction, hemodynamic instability, or a platelet count under 20 000/μL.

Negative cultures may indicate that the patient does not have pneumonia, but are also found in patients with HAP who have received or are receiving antibiotic treatment, or can be caused by a technical fault in the procedure. Invasive techniques identify the pathogen more reliably, and this increases the confidence of the medical team in the treatment and tends to minimize the unnecessary use of antibiotics. Moreover, such techniques provide more accurate information concerning local epidemiology. However, the use of invasive methods in patients who have received prior antibiotic treatment is debatable since such procedures may place the patient at risk (arrhythmias, hypoxia, hemorrhage, etc) and increase costs. Although studies have been carried out to assess the impact of invasive diagnostic techniques on outcomes in patients with VAP, their use remains controversial.[104,105,131-133]

The diagnosis of HAP is multifactorial, and cultures should be obtained before antibiotic therapy is started or before any changes are made in the treatment regimen. Quantitative culture of tracheal aspirate is as sensitive but less specific than bronchoscopic methods; both techniques help to differentiate between colonization and infection. Routine qualitative tracheal aspirate culture is not recommended. The use of this method is only justified when other diagnostic techniques are impossible (level A).

Treatment

Principles of Antimicrobial Treatment

Treatment is usually started empirically guided by clinical data, severity, prior use of antibiotics, interval between admission and diagnosis, duration of mechanical ventilation, risk factors for specific pathogens, prevalence of pathogens, and patterns of resistance, both general and those specific to the ICU or hospital.

Once the decision has been taken to start treatment, 2 basic principles should be kept in mind: *a)* the aim is to ensure appropriate and timely initial treatment; and *b)* antibiotics should be used prudently in order to prevent the development of bacterial resistance.

Appropriate initial treatment. Appropriate treatment is a regimen that includes antibiotics with proven in vitro activity against the pathogens causing the infection. Delay in starting treatment increases the risk of death (level C).[134] Treatment should be started as soon as microbiological samples have been obtained. Subsequent modification of treatment on the basis of culture results has not been shown to reduce mortality, but does serve to contain bacterial resistance, reduce costs, and provide a better understanding of epidemiology (level B).[42,135] Antibiotics should be given at full doses, and the duration of treatment should be consistent with the resolution of the infection.[136]

Antibiotic resistance. The activity of all beta-lactam antibiotics is impaired by resistance when disease is caused by MRSA. Most strains of *S aureus* found in Latin American ICUs are multidrug resistant.[137,138] Until recently, glycopeptides were the only treatment option in such cases. Intermediate sensitivity to vancomycin has been reported (minimum inhibitory concentration, 8-16 μg/mL).[139-141] Linezolid and quinupristin/dalfopristin are 2 of the new antibiotics effective against MRSA.[142] *Klebsiella* and *Enterobacter* species are sensitive to carbapenem and cefepime, and to a varying degree sensitive to the fluoroquinolones, co-trimoxazole, and the aminoglycosides. These species are naturally resistant to the aminopenicillins and may acquire resistance to third- and fourth-generation cephalosporins. *Enterobacter* species is naturally resistant to first-generation cephalosporins and cefoxitin owing to a constitutive AmpC beta-lactamase (a class C noninducible beta-lactamase). The resistance of *Klebsiella pneumoniae, Escherichia coli,* and *Proteus mirabilis* to third-generation cephalosporins may be mediated by extended-spectrum beta-lactamase (ESBL), while in the *Enterobacter* species, *Citrobacter freundii,* and *P aeruginosa* such resistance is generally due to highly resistant beta-lactamase. In the *Acinetobacter* species, multidrug resistance is due to various beta-lactamases (AmpC and ESBL), efflux, and impermeability. *P aeruginosa* has a great capacity to adapt and survive. While certain penicillins, cephalosporins, carbapenem, monobactams, aminoglycosides, fluoroquinolones, and polymyxins may be active, their effect can be hindered by mutational resistance mediated by various mechanisms.[143-148] The selection of resistant mutants depends on the type of antibiotic administered, the dose, and the site of infection. Multidrug therapy prevents this selection from occurring.[149-151] Almost all nosocomial strains of *Acinetobacter* species are resistant to penicillins and cephalosporins, basically because of beta-lactamases. Carbapenem is the treatment of choice, but resistance to this agent is emerging and has reached epidemic proportions in Latin America; in such cases, sulbactam and minocycline may be active, but polymyxins are still the antibiotics of last resort.[152,153] The importance of the multiresistant pathogen *Stenotrophomonas maltophilia* is growing, particularly in Europe.[154] This microorganism is intrinsically resistant to carbapenems and extended-spectrum cephalosporins. The activity of co-trimoxazole and the new fluoroquinolones is better.[155]

Surveillance systems monitor secular resistance trends. In general, pathogens are more drug resistant in Latin America. MRSA is very common in Hong Kong and Japan.[138] The resistance patterns of *Acinetobacter*

TABLE 3
Antibiotic Resistance of Staphylococcus aureus and Certain Gram-Negative Bacilli Observed in a Study in Argentina*[162]

Pathogens	IMI	MERO	CAZ	PIP/TZ	COLIS	TMS	AMIKA	CIPRO
Nonfermenting								
Acinetobacter species	25.3%	29.6%	90%	90%	0%	–	–	–
Pseudomonas aeruginosa	32.4%	38.8%	29.8%	42.8%	0%†	–	–	46.7%
Klebsiella pneumoniae	0%	0%	51.6%	32%	–	41.1%	36.3%	26.4%

Pathogens	OXA	TMS	RFP	MINO	VANCO	TEICOP
Fermenting						
Staphylococcus aureus	72%	40.6%	38.2%	16.4%	0%	2%

*IMI indicates imipenem; MERO, meropenem; CAZ, ceftazidime; PIP/TZ, piperacillin/tazobactam; COLIS, colistin; TMS, trimetoprim/sulfamethoxazole; AMIKA, amikacin; CIPRO, ciprofloxacin; OXA, oxacillin; RFP, rifampicin; MINO, minocycline; VANCO, vancomycin; TEICOP, teicoplanin.
†Three strains presented intermediate resistance to colistin.

vary by region. Sensitivity in North America as compared to Latin America is as follows: ceftazidime, 67.0% versus 25.9%; piperacillin/tazobactam, 68.5% versus 25.0%; ciprofloxacin, 69% versus 29.7%; amikacin, 87.5% versus 32.2%; and carbapenems, 96% versus 88.6%. Some 90% of the carbapenem-resistant strains are highly sensitive to low doses of polymyxin B and colistin (≤2 µg/mL).[154] The sensitivity of multiresistant *P aeruginosa* is 8.2% in Latin America and only 0.9% in Canada. ESBL-producing *K pneumoniae, P mirabilis,* and *E coli* are more common in Latin America than elsewhere.[156,157]

The prudent use of antibiotics. Abuse of antibiotics induces colonization by resistant bacteria. There is a direct relationship between the use of antibiotics and increases in the resistance of ESBL-producing enterobacteria, multiresistant *P aeruginosa* and *A baumannii*, vancomycin-resistant enterococci, MRSA, and *S aureus* with reduced sensitivity to vancomycin.[42,158-160] The indiscriminate use of antibiotics in ICUs can contribute to the emergence of multiresistant microorganisms, not only in the patients being treated but also in other patients in the same ICU and those in other parts of the hospital.[161]

Information on resistance surveillance. There are various computerized systems in place that monitor drug resistance in Latin America, such as the program coordinated by SADEBAC's antimicrobial subcommittee (Subcomisión de Antimicrobianos).[162] Between 1996 and 2001, this program studied 394 microorganisms isolated from BAL samples taken from adults more than 72 hours after hospital admission in Argentina and evaluated their resistance profile. The levels of resistance found confirm the need to improve measures for controlling nosocomial infection and to ensure appropriate use of antibiotics (Table 3).

The bioavailability and pharmacokinetics of antibiotics in critically ill patients. Since distribution volume may be increased by mechanical ventilation or overhydration and this in turn can lead to a reduction in serum concentrations of the drug, it may be appropriate in ventilated patients to use higher doses or a loading dose for all antibiotics and continuous perfusion if the activity of the agent is greater when serum concentrations remain above the minimum inhibitory concentration over time (time-dependent antibiotics).[163,164] Concentrations of antibiotics that are eliminated by glomerular filtration (the aminoglycosides, quinolones, and vancomycin) increase during shock and decrease during the hyperdynamic phase of sepsis. Hypoalbuminemia increases the free drug concentration of antimicrobials with a high affinity for proteins, such as the beta-lactam antibiotics. Aminoglycosides and fluoroquinolones are concentration-dependent antibiotics, so their capacity to eliminate bacteria depends on serum concentrations. The optimal bactericidal activity of such agents is achieved when the peak concentration is approximately 10 times the minimum inhibitory concentration; they also have a postantibiotic effect. While aminoglycosides are more active than beta-lactam antibiotics against certain resistant gram-negative bacteria, the two are used in combination against such bacteria because the therapeutic action of the aminoglycosides in serum and penetration of infected pulmonary tissue is low.[165,166] In contrast, the efficacy of beta-lactam antibiotics and vancomycin is time dependent, and these agents have no postantibiotic effect. While vancomycin has poor penetration in pulmonary tissue, it is used frequently because until recently it was the only treatment option for MRSA.[167] Fluoroquinolones, on the other hand, achieve higher concentrations in pulmonary epithelial fluid and in macrophages than in serum. The pulmonary penetration of beta-lactams is good, especially in the presence of inflammation.[168]

Initial Empiric Treatment

The aim of initial empiric treatment is to cover 90% of potential pathogens. Information on the epidemiological situation provided by a nosocomial infection control program administered by a multidisciplinary committee is essential. Such information will serve to guide empiric treatment and should be used in conjunction with the recommendations contained in the present guidelines, which are based on the international and regional literature.

Treatment regimens. Initial empiric antibiotic treatment should be based on the general recommendations shown

TABLE 4
Recommended Initial Empiric Treatment for Nosocomial Pneumonia*

Group	Characteristics	Target Pathogens	Recommended Treatment
Group 1 (low risk of infection with resistant pathogens)	<4 days in ICU or <7 days in hospital No antibiotic treatment during the preceding 15 days No other risk factors for chronic oropharyngeal colonization by multiresistant pathogens	*Streptococcus pneumoniae, Haemophilus influenzae,* MSSA, sensitive enterobacteria, bacteria of the upper airway saprophytic flora (*Corynebacterium* species, viridans group *Streptococcus,* coagulase-negative *Staphylococcus*, *Neisseria* species, etc)	Ampicillin + sulbactam or ceftriaxone or cefotaxime or a new fluoroquinolone (levofloxacin, gatifloxacin, or moxifloxacin)
Group 2 (high risk for infection with multiresistant pathogens)	>4 days in the ICU or >7 days in hospital Prior antibiotic treatment during the preceding 15 days Other risk factors for chronic oropharyngeal colonization by multiresistant pathogens (neurosurgery, ARDS, COPD, head injury, corticosteroid therapy, or prolonged mechanical ventilation)	*Pseudomonas aeruginosa, Acinetobacter* species, *Stenotrophomonas maltophilia,* multiresistant enterobacteria, and MRSA	Cover for gram-negative bacilli (taking into account local resistance patterns) Carbapenems (imipenem, meropenem) or cefepime or ceftazidime or piperacillin/tazobactam or fluoroquinolones (ciprofloxacin and the new fluoroquinolones) + combined treatment with an aminoglycoside or ciprofloxacin ± (depending on the local incidence of MRSA) glycopeptides (vancomycin, teicoplanin) or linezolid or quinupristin/dalfopristin

*ICU indicates intensive care units; MSSA, methicillin sensitive *Staphylococcus aureus*; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; and MRSA, methicillin-resistant *S aureus.*

TABLE 5
Treatment According to the Etiology of the Nosocomial Pneumonia*

Pathogen	Antibiotic	Evidence Level
Methicillin-sensitive *Staphylococcus aureus*	First-generation cephalosporins	No evidence
Methicillin-resistant *S aureus*	Glycopeptides (vancomycin or teicoplanin)	B
	Linezolid	B
	Quinupristin/dalfopristin	B
Penicillin-sensitive *Streptococcus pneumoniae*	Penicillin, aminopenicillins	B
Penicillin-resistant *S pneumoniae*	Penicillin, aminopenicillins, ceftriaxone	B
Acinetobacter baumannii	Carbapenems	B
	Third- and fourth- general cephalosporins	B
	Ampicillin-sulbactam	B
Enterobacteriaceae (*Escherichia coli, Proteus, Klebsiella*)	Aminopenicillins	B
	Third- and fourth-generation cephalosporins	B
	Fluoroquinolones	B
	Piperacillin/tazobactam	B
	Carbapenems	B
Enterobacteriaceae *(Enterobacter, Serratia, Morganella morganii)*	Quinolones	B
	Third- and fourth-generation cephalosporins	B
	Piperacillin/tazobactam	B
	Carbapenems	B
Stenotrophomonas maltophilia	Trimethoprim-sulfamethoxazole	C
	Doxycycline	C
	Ceftazidime	C
Enterococcus faecalis	Ampicillin	No evidence
	Vancomycin	No evidence
Enterococcus faecium	Ampicillin	No evidence
	Vancomycin	No evidence
	Linezolid	C
	Quinupristin/dalfopristin	C
Pseudomonas aeruginosa	Ceftazidime, cefoperazone, cefepime	B
	Piperacillin/tazobactam	B
	Ciprofloxacin	B
	Carbapenems	B
	Colistin	D

*Chosen because of its greater bactericidal action, narrower spectrum, lesser tendency to promote resistance, and lower cost. Antibiotics available in Latin America.

in Table 4 and tailored to meet the requirements of local microbiology. When the causative pathogen is identified, the regimen should be modified accordingly. Table 5 lists the recommended treatments by etiology. The final choice of antibiotic should be guided by the results of antibiograms, the availability of different antibiotics, cost,

and the restrictions imposed by each institution. In the choice of treatment special attention should be paid to multiresistant microorganisms.

– Group 1 (patients at low risk for infection with resistant pathogens). This group includes patients who fulfill the following conditions: a stay of fewer than 4 days in the ICU or 7 days in hospital; no prior antibiotic treatment lasting more than 24 hours during the preceding 15 days (level B)*;* no other risk factors for oropharyngeal colonization with multiresistant pathogens. In such patients, the following pathogens should be targeted: *S pneumoniae, H influenzae,* methicillin-sensitive *S aureus*, sensitive enterobacteria, bacteria of the upper airway saprophyte flora (*Corynebacterium* species, viridans group *Streptococcus*, coagulase-negative *Staphylococcus*, *Neisseria* species, etc).

The recommended treatment for patients in this group is as follows: ampicillin-sulbactam, ceftriaxone, or cefotaxime (which should all be used with caution in institutions where the incidence of ESBL-producing microorganisms is increasing), or one of the new fluoroquinolones (levofloxacin, gatifloxacin, or moxifloxacin).

– Group 2 (patients at high risk for infection with multiresistant pathogens). This group includes patients who fulfill any of the following conditions: a stay of more than 4 days in the ICU or more than 7 days in hospital; prior antibiotic treatment for more than 24 hours in the preceding 15 days (level B)[21,73,74]*;* other risk factors for chronic oropharyngeal colonization with multiresistant pathogens, such as neurosurgery and ARDS for *A baumannii,*[56] COPD for *P aeruginosa,*[23] head injury and corticosteroids for MRSA,[75] and prolonged mechanical ventilation. In such patients, antibiotic treatment should target the following pathogens: *P aeruginosa, Acinetobacter* species, *S maltophilia,* multiresistant enterobacteria, and MRSA.

The treatment proposed for this group is as follows: carbapenems (imipenem, meropenem), cefepime, ceftazidime, piperacillin/tazobactam, fluoroquinolones (ciprofloxacin and the new fluoroquinolones) for gram-negative bacilli (taking local resistance patterns into consideration) and glycopeptides (vancomycin, teicoplanin), linezolid, and quinupristin/dalfopristin for MRSA.

Single-drug therapy versus combined therapy. Combined therapy is recommended in cases of VAP caused by *P aeruginosa.* The importance of synergistic activity against *P aeruginosa* has been demonstrated in vitro only for patients with neutropenia or bacteremia, situations that are not common in HAP.[149,150,169] Another argument for combined therapy is that it broadens the spectrum of initial empiric treatment, thereby lowering the risk of multiresistant pathogens.[149,170,171] The prevalence of MRSA in many ICUs justifies the addition of vancomycin or linezolid (or quinupristin/dalfopristin)[17] in patients receiving intensive care. Single-drug therapy used when HAP is not caused by multiresistant bacteria reduces costs and unnecessary exposure to antibiotics.[111,149,150,169,172-174] Better clinical studies will be needed before single-drug therapy can be reliably recommended for the treatment of HAP[92] (level C) in cases where infection by *P aeruginosa* or other multiresistant bacteria, such as *Klebsiella, Enterobacter, Citrobacter, Serratia,* and *Acinetobacter* species*,* has been ruled out.[25,149,174-178]

Considerations Regarding the Route of Antibiotic Administration

– *Vancomycin.* Intermittent administration of vancomycin produces high peak concentrations alternating with troughs at subtherapeutic levels.[179,180] Continuous perfusion (a loading dose of 15 mg/kg in 1 hour followed by 30 mg/kg over 24 hours adjusting the dose to achieve a plateau of 20-30 µg/mL) produces concentrations 4 to 5 times the minimum inhibitory concentration for the pathogen and may be ideal in HAP caused by MRSA, although experience with this regimen is scant.[179-181]

– *De-escalating therapy.* De-escalation strategies are based on the initial empiric use of high doses of broad spectrum antibiotics and subsequent modification of the regimen to take into account the sensitivity of the pathogen identified in order to reduce, where possible, the antimicrobial spectrum of the treatment. This strategy is particularly recommended in patients at risk for infection with resistant microorganisms and at high risk for death since it ensures appropriate early treatment and reduces selective pressure through the use of broad spectrum antibiotics.[21,31,182-184]

– *Nebulized antibiotics.* Inhaled antibiotics are available for dealing with the problems of multiresistance, toxicity, and low pulmonary concentrations associated with certain antimicrobials (the aminoglycosides and polymyxins). Endotracheal instillation results in poor distribution in the lung parenchyma[185] and may interfere with gas exchange.[186,187] Controlled trials with aerosolized antibiotics have not demonstrated any clinical benefit, particularly when concomitant therapy comprising beta-lactams and aminoglycosides was administered systemically.[185,188] The use of aerosolized antibiotics may be acceptable in patients with pulmonary infections caused by multiresistant microorganisms (level B).[189]

Duration of Treatment and Response

Clinical improvement criteria include reduction of fever, leukocytosis and sputum purulence, and increased oxygenation. Infiltrates take more time to resolve, especially in elderly or severely ill patients.[190] Since improvement may not be apparent until 72 hours after start of treatment, the antibiotic regimen should not be changed during this period unless clear deterioration is observed.[17] Follow-up cultures are only necessary when the patient does not respond to initial treatment.[191]

Quantitative bronchoscopic cultures may remain positive for the first 72 hours of appropriate treatment,[192] and secretions may still be colonized even after 15 days of treatment.[115]

Very little data is available on the optimum duration of treatment. The average of the durations reported in several studies was 14 days.[111,112] Selective pressure on bacterial ecology, potential toxicity, and cost constitute solid arguments in favor of shortening the duration of treatment. The American Thoracic Society recommends treatment lasting from 7 to 21 days depending on severity, the causative pathogen, and timing of response, and recommends a longer course of treatment for *P aeruginosa, Acinetobacter* species, and necrotizing pneumonia caused by gram-negative bacilli. Recent findings indicate that treatment may be shortened to around 8 days without any increase in morbidity or mortality when supported by a guideline or protocol.[136,193] Treatment should be continued in all patients for at least 72 hours after a clinical response has been observed.[194] The few investigations undertaken to study discontinuation of treatment when cultures were negative have shown good results.[130,195]

Switching to oral administration. Intravenous administration is the most reliable and fastest way of initiating treatment.[196,197] Identifying the ideal moment for switching from intravenous to oral treatment is crucial,[198] but no clear guidelines are available on this subject.[199,200] A minimum of 2 to 3 days of intravenous treatment has been recommended, followed by oral treatment.[199] There is evidence that supports the use of switch therapy (level B).[196,197] The oral antibiotics should have good absorption characteristics and should cover the same spectrum and have a similar pharmacokinetic and pharmacodynamic profile as the intravenous treatment.[197,201,202] Clinical response should be good and the patient's gastrointestinal function normal before a switch is made from intravenous to oral treatment.[91,203]

Treatment failure. Treatment failure is defined as deterioration or lack of improvement 72 hours after start of treatment.[204] In such cases, the following infectious causes should be considered: HAP caused by resistant pathogens; superinfection; atypical pathogens (*M tuberculosis,* fungi, *Pneumocystis jiroveci,* cytomegalovirus); pulmonary abscess; and nonpulmonary infections (empyema, sinusitis, catheter-related infections, urinary infection). Noninfectious causes include the following: heart failure; atelectasis; ARDS; pulmonary embolism; chemical pneumonitis; hemorrhage; postobstructive pneumonia; and lung contusion. Without interrupting treatment, a bronchoscopic examination can be performed to detect the presence of abnormalities and to obtain secretions for culture.[114,115,204,205] Tracheal aspiration, a technique with a high negative predictive value in such cases, can also be performed to rule out lung infection as the cause of treatment failure.[176]

Nonantibiotic Treatment

– *Kinesitherapy.* The utility of kinesitherapy and multimodal chest physiotherapy as coadjuvant treatments for pneumonia has not been demonstrated (level A).[206-211] In patients with unilateral lung disease, a transitory increase in oxygenation has been observed when the patient is placed in the opposite lateral decubitus position.[177,212-214] Certain physiological parameters may also improve in patients with a high sputum production (level B).[207-209]

– *Immunomodulation and colony stimulating factors.* The inflammatory response depends on the expression of cytokines. Recombinant cytokines can modulate this response and are used as a coadjuvant strategy in cases of severe infection.[215,216] The intensity of the local inflammatory response should be regulated to prevent excessive tissue damage.[217] Routine administration of granulocytic colony stimulating factor is only indicated in HAP patients who are neutropenic, and there is no evidence to support the use of interferon gamma or antitumor necrosis factor treatment in HAP.[216,217]

– *Activated protein C.* Recombinant activated protein C modulates the systemic inflammatory response and reduces mortality in patients with severe sepsis and/or septic shock and APACHE II scores of 25 or higher.[218] Although such treatment may be beneficial in patients with more than 2 organic dysfunctions and those with a Sepsis-Related Organ Failure Assessment score of 10 or higher, its use is limited in many cases by the high cost, especially in Latin America.

Prevention

Prevention strategies can be classified as pharmacological or nonpharmacological.

Nonpharmacological Strategies

General Measures:

– *Education.* Education should form part of all infection control programs with a view to educating staff about epidemiology and the procedures that have been shown to reduce the incidence of HAP (level B).[219-221]

– *Epidemiological surveillance.* In the event of a HAP outbreak, particularly in an ICU, causative pathogens and resistance patterns should be identified in clinically representative samples so that appropriate prevention strategies can be developed (level A).[222-224] Systematic surveillance cultures of equipment used in respiratory procedures, lung function testing, and inhaled anesthesia are not useful (level B).[89]

– *Nursing and kinesitherapy personnel.* An increase in the number of professional nurses per patient and higher level of academic qualification are factors associated with a reduction in the incidence of pneumonia and reintubations (level B).[225-227] A structure involving multidisciplinary teams favors a reduction in the incidence of HAP.[228] As part of the preventative

strategy and given the composition of health-care teams in Latin America, the inclusion on the ICU team of a kinesiologist trained in critical care and mechanical ventilation is recommended in order to ensure better control and management of ventilation (level D).

– *Strategies for preventing or reducing the duration of endotracheal intubation and conventional mechanical ventilation.* Avoiding intubation in patients who can be treated with noninvasive mechanical ventilation eliminates one of the principal risk factors for HAP.[229] Noninvasive mechanical ventilation makes it possible to curtail the use of intubation in COPD exacerbations[230,231] and other situations,[232,233] and reduces the incidence of VAP and mortality in certain selected subgroups. Moreover, because it facilitates weaning, noninvasive ventilation tends to shorten the duration of invasive ventilation,[234-236] although its application in the treatment of extubation failure is still controversial.[237,241] Noninvasive ventilation is recommended in selected cases where there are no contraindications (level B).[242]

– *Weaning.* Shortening the duration of intubation reduces the principal risk factor of HAP. The implementation of weaning protocols (routine assessment aimed at identifying patients capable of breathing spontaneously, discontinuation of sedation, and use of other techniques)[243] reduces the duration of invasive ventilation (level A).[244]

– *Prevention of person-to-person contagion. Handwashing.* The role played by the hands of health care workers in the transmission of pathogenic bacteria to patients has been demonstrated. Handwashing reduces such transmission (level A).[245-247] The quality of handwashing is important; hands should be washed with soap and water or a waterless antiseptic before and after touching patients, their secretions, or respiratory equipment, whether or not gloves are used (level B).[248,249]

– *Use of gloves and gown.* The use of gloves and gown reduces the rate of nosocomial infection.[250-252] This practice is more effective when directed against certain antibiotic-resistant agents (MRSA and vancomycin-resistant enterococci).[250]

– *Preventing the aspiration of contaminated secretions. Patient position.* Elevating the head of the bed at an angle of 30º to 45º is a simple cost-free measure that reduces the incidence of VAP (level B).[253-254] This technique should be used in patients receiving enteral feeding even when they are not on ventilation (level B).[255]

– *Avoid large gastric volumes.* Avoiding overdistension of the stomach caused by enteral feeding can reduce the incidence of VAP. Various ways of achieving this have been described in the literature (level B).[256]

It is not clear whether enteral feeding should be continuous or intermittent, nor is there a clear recommendation on where the feeding tube should be placed (jejunum or stomach).

– *Enteral feeding.* While enteral feeding is a risk factor for VAP, this route is still preferable because of the complications associated with parenteral feeding and its negative impact on survival. Even though formulas enriched with glutamine, arginine, or immunomodulators would reduce the incidence of nosocomial infections, the systematic use of such formulas is not recommended since this reduction is not associated with any decrease in mortality (level B).[257] Many studies have shown that both VAP and bacteremia are associated with contamination of enteral formulas (level B).[258-260] When enteral formulas must be prepared in the hospital, extreme precautions should be taken, and routine bacteriologic controls performed.

– *Prevention of contamination/aspiration of the secretions in ventilator circuits and interfaces.* When endotracheal intubation is used, air filtering, heating, and humidifying functions disappear, while the gas provided by the ventilator should be warmed and humidified to avoid contributing to the pathogenesis of VAP (cold, dry air favors impaction of secretions and the development of lesions in the bronchial mucosa).

– *External circuits.* A decrease in the incidence of VAP has been observed when ventilator circuits are changed less frequently or only when mechanical ventilation has been withdrawn unless the quantity of secretions, blood, or water in the tubing is excessive (level A).[261,262] The reusable components and circuits of respiratory support systems should be completely and carefully cleaned, sterilized or high level disinfected before being used for another patient. Condensation water should be eliminated regularly from the tubing to ensure that condensate does not flow towards the patient (level A).[261-263]

– *Fluids used in the humidifier.* Only sterile or pasteurized water should be used in bubble humidifiers.

– *Active humidifiers versus heat and moisture exchangers.* Studies have demonstrated that the use of passive humidifiers (heat and moisture exchangers) as opposed to active humidifiers is associated with a significant reduction in the incidence of VAP. Active humidifiers increase the resistive dead space load making the administration of aerosolized drugs more difficult. Since these humidifiers can also increase the risk of airway obstruction, patients must be monitored more often when they are used. Heat and moisture exchangers should only be changed when they are no longer functioning properly or are visibly soiled (level B).[264,265]

– *Aspiration of respiratory secretions.* Two systems are used to aspirate secretions: open systems, in which all of the suctioned material is disposed of after each procedure; and closed systems, in which the equipment can be reused many times before emptying. There is no evidence that the closed system reduces the incidence of VAP (level B).[266] The closed system does not depressurize the airway, maintains oxygenation, and facilitates the clearance of secretions. The apparatus should be changed when it no longer works properly or is visibly soiled. There are no recommendations regarding the use of sterile gloves in preference to clean gloves, nor in favor of continuous aspiration systems rather than conventional systems.[267,268] Only pasteurized or sterile

water should be used to flush secretions out of aspiration catheters if they are going to be reused (level B).

– *Small volume nebulizers for drug administration.* This equipment should be disinfected, rinsed with sterile water, and air dried between treatments of the same patient (level A).[269] Drugs supplied in multidose vials should be handled, dispensed, and stored in accordance with the manufacturer's instructions.[270]

– *Other materials used in respiratory procedures.* When used with different patients the following materials should be sterilized or high level disinfected: portable spirometers and ventilometers, oxygen sensors, reusable reanimation equipment, and any other devices used by more than one patient.

– *Lung function testing apparatus.* Single-use mouthpieces should be used or else the mouthpiece should be sterilized, chemically high level disinfected, or pasteurized (level C).

– *Ambient air humidifiers.* High-volume ambient air humidifiers that generate aerosols should not be used unless they can be sterilized or chemically high level disinfected at least daily. Only sterilized water should be used in such equipment.

Artificial airway:

– *Endotracheal tube and VAP.* Certain characteristics of the artificial airway are associated with respiratory infections. High volume, low pressure cuffs have longitudinal folds that allow silent aspiration. Continuous subglottic aspiration systems reduce the incidence of early onset VAP.[267,268] The role of the bacterial biofilm on the internal walls of the endotracheal tube in the genesis of VAP remains unclear.[271] Orotracheal intubation is recommended over nasotracheal intubation. The use of tubes for the continuous aspiration of subglottic secretions and the aspiration of secretions from the supraglottal area before manipulation or extraction of the endotracheal tube should be considered (level B).[267]

– *Tracheostomy.* An aseptic technique should be used when a tracheostomy tube is changed. The following questions have not been fully resolved: the daily application of topical antibiotics in the area around the tracheostomy; the definition of a window of opportunity when tracheostomy should be performed; and the most appropriate technique for performing a tracheostomy (percutaneous or surgical).[272]

Pharmacological Strategies

Prevention of hemorrhages caused by stress ulcers. The results of administering prophylactic sucralfate, H_2 blockers, and/or antacids for stress ulcers are similar (level B). A study of several meta-analyses reveals the advisability of choosing sucralfate in patients at low or moderate risk for hemorrhage (level B).[273] The advisability of routine acidification of the gastric tract remains unclear.

Use of antiseptic and antibiotic agents. It may be useful to administer a chlorhexidine gluconate mouthwash as a preventative measure in severely ill patients at risk for HAP.

Selective decontamination of the digestive tract. This regimen has generated great interest. Many studies have demonstrated that a regimen of topical antibiotics and antifungal agents in the mouth reduces the incidence of HAP and in some cases (when such treatment is combined with parenteral antibiotics over a short period) can also produce a decline in mortality.[10,59,273-278] However, because of the potential risk of inducing bacterial resistance and the laboriousness of the procedure, some experts are still opposed to this strategy. Consequently, the usefulness of routine selective decontamination as a way to prevent HAP is still an unresolved issue.

Prophylactic systemic antibiotics. Prophylactic systemic antibiotics should not be administered as a routine measure in critically ill or other patients to prevent HAP (level B).[279]

Vaccination. The vaccinations against influenza and the pneumococcus that should be administered to the population at risk play a secondary role in the prevention of HAP.

Immunomodulators/gamma globulin. The routine use of colony stimulating factors or intravenous gamma globulin as prophylactics for HAP is not recommended.

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