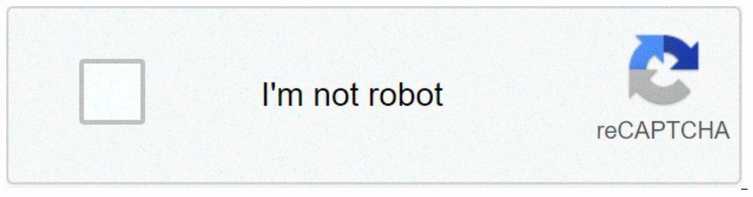

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Idsa hospital acquired pneumonia treatment guidelines

SummaryIntroductionMethodology used to provide the GuidelineEpidemiologyIncidenceEtiologyMajor Epidemiologic PointsPathogenesisMajor Points for PathogenesisModifiable Risk FactorsIntubation and Mechanical Ventilation Aspiration, Body Position, and Enteral FeedingModulation of Colonization: Oral Antiseptics and Antibiotic Stress Bleeding Prophylaxis, Transfusion, and Glucose ControlMajor Points and Recommendations for Adjustable Risk Diagnostic TestingLarge Points and Recommendations for DiagnosisDiagnostic Strategies and ApproachesClinical StrategyBacteriological StrategyIncuratory Diagnostic StrategyFormer Points and Recommendations for Comparing Diagnostic StrategiesAntibiotic Treatment of Hospital-Acquired PneumoniaGeneral ApproachInitial Empiric Antibiotic TherapyAppropriate Antibiotic Selection and Adequate DosingLocalLocal Instillation and Aerosolized AntibioticsCombination vs. MonotherapyDuration of TherapyMajor Points and Recommendations for Optimal Antibiotic TherapySpecific Antibiotic RegimensAntibiotic Heterogenity and Antibiotic Cycling Response to TherapyModification of Empiric Antibiotic RegimensDefining the Normal Pattern of ResolutionReas Ours for Deterioration or Non-ResolutionEvaluation of the non-responding PatientMajor Points and Recommendations for Assessing Response to TherapySuggested Performance IndicatorsInce the first American Thoracic Society (ATS) Directive of 1996 on nosocomial pneumonia , a number of new developments have appeared, mandating a new evidence-based guideline for hospital-acquired pneumonia (HAP), including health care-associated pneumonia (HCAP) and respiratory-associated pneumonia (VAP). This document, prepared by a joint committee of the ATS and Infectious Diseases Society of America (IDSA), focuses on the epidemiology and pathogenesis of bacterial pneumonia in adults, and emphasizes modipherable risk factors for infection. In addition, hap microbiology is being reviewed, with an emphasis on multidrug-resistant (MDR) bacterial pathogens, such as Pseudomonas aeruginosa, Acinetobacter species and methicillin-resistant Staphylococcus aureus. Controversies over diagnosis are discussed, focusing on the initial examination of lower respiratory tract samples for bacteria, and the rationale for both clinical and bacteriological approaches, using either semi-quantifying or quantitative microbiological methods that help direct selection of appropriate antibiotic therapy. We also provide recommendations for additional diagnostic and therapeutic evaluations in patients with non-soluble pneumonia. This is an evidence-based document that highlights VAP's problems because there is much less data available on HAP in non-deintated patients and on HCAP. Extrapolation should manage patients who are not intubated and mechanically ventilated patients with VAP, using the same approach to identify risk factors for infection with specific pathogens. The main objectives of this evidence-based directive the management of HAP, VAP and HCAP emphasize early, appropriate antibiotics in adequate doses, while over-antibiotics are avoided by de-escalation of initial antibiotic therapy, based on microbiological cultures and patient clinical response, and shortening the duration of therapy to the minimum effective period. The Directive recognises the variability of bacteriology from one hospital to another and from one period to another and recommends that local microbiological data be taken into account when adapting treatment recommendations to a specific clinical environment. The first empirical antibiotic therapy algorithm includes two groups of patients: one without a need for broad spectrum therapy, because these patients have bite, VAP or HCAP with an early onset and no risk factors for MDR pathogens, and a second group that requires broad spectrum therapy, due to late pneumonia or other risk factors for infection with MDR pathogens. Some of the key recommendations and principles in this new, evidence-based guideline are as follows: HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy for MDR pathogens. A lower respiratory tract culture should be collected from all patients before antibiotic therapy, but the collection of cultures should not delay the initiation of therapy in seriously ill patients. Either semi-quantitative or quantitative culture data can be used to treat patients with HAP. Lower respiratory cultures can be obtained bronchoscopic or nonbronchoscopic, and can be grown quantitatively or semiquantifyingly. Quantitative cultures increase the specificity of the diagnosis of HAP without harmful consequences, and the specific quantitative technique should be chosen based on local expertise and experience. Negative lower respiratory cultures can be used to stop antibiotic therapy in a patient who has had cultures obtained in the absence of an antibiotic change in the past 72 hours. Early, appropriate, broad spectrum, antibiotic therapy should be prescribed with sufficient doses to optimize antimicrobial efficacy. An empirical therapy regimen should contain substances from a different class of antibiotics than the patient has recently received.Combination therapy for a specific pathogen should be used judiciously in hap therapy, and short-term aminoglycoside therapy (5 days) should be taken into account when used in combination with a β lactam to treat P. aeruginosa pneumonia. Linezolid is an alternative to vancomycin, and unconfirmed, preliminary data suggest that it may have an advantage for proven VAP due to methicillin-resistant S. aureus. should be considered therapy for patients with VAP due to carbapenem-resistant Acinetobacter species. Aerosolized antibiotics may have value as complementary therapy in patients with VAP due to some MDR pathogens. De-escalation of antibiotics should be considered as soon as data are available on the results of respiratory organs and the patient's clinical response. A shorter duration of antibiotic therapy (7 to 8 days) is recommended for patients with uncomplicated HAP, VAP or HCAP who initially received the appropriate therapy and have had a good clinical response, with no evidence of infection with non-fermenting gram negative germs. As with all guidelines, these new recommendations, although the evidence has been reviewed, should be validated for their impact on the outcome of patients with HAP, VAP and HCAP. Moreover, this Directive points to areas of incomplete knowledge, which can be used to set an agenda for future research. Hospital-acquired pneumonia (HAP), respiratory-associated pneumonia (VAP), and health care-associated pneumonia (HCAP) continue to be major causes of morbidity and mortality, despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide range of preventive measures (1-5). HAP is defined as pneumonia that occurs 48 hours or more after recording, which was not incubated at the time of recording (1, 3). HAP can be managed in a hospital ward or in the intensive care unit (ICU) when the disease is more severe. VAP refers to pneumonia that develops more than 48-72 hours after endotracheal intubation (2, 3). Although not included in this definition, some patients may need intubation after developing severe HAP and should be similarly managed with patients with VAP. HCAP includes each patient who was admitted to an acute care hospital for two or more days within 90 days of the infection; stayed in a nursing home or long-term care facility; recent intravenous antibiotic therapy, chemotherapy or wound care in the last 30 days following the current infection; or visited a hospital or hemodialysis clinic (3, 4, 6). Although this document focuses more on HAP and VAP, most principles overlap with HCAP. Because most of the current data has been collected from patients with VAP, and microbiological data from unintated patients may be less accurate, most of our information is derived from patients with VAP, but extrapolation can apply to all patients with HAP, highlighting risk factors for infection with specific pathogens. This Directive is an update of the 1996 Consensus Statement on HAP published by the American Thoracic Society (5). The principles and recommendations are largely based on data presented by committee members at a conference jointly sponsored by the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA). The committee consisted of lung, critical care and infectious disease specialists with clinical and research interests in HAP, VAP and HCAP. All important aspects of epidemiology, pathogenesis, bacteriology, diagnosis and antimicrobial treatment were assessed by this group. Therapy recommendations are focused on antibiotic choice and patient stratification; additional, non-antibiotic therapy of pneumonia is not discussed, but information information this topic is available elsewhere (7). Recommendations to reduce the risk of pneumonia are limited in this document to important, modipherable risk factors associated with pneumonia pathogenesis to prevent redundancy with the more comprehensive guidelines for preventing health care-associated pneumonia, prepared by the Centers for Disease Control and Prevention (CDC) and the Hospital Infection Control Practices Advisory Committee (HICPAC) (3). The purpose of our document is to provide a framework for the initial evaluation and management of the immunocompetent, adult patient with bacterial causes of HAP, VAP, or HCAP, and excludes patients known to be immunosuppressed by HIV infection of the human immunodeficiency virus (HIV), hematologic malignancy, chemotherapy-induced neutropenia, organ transplantation, and so on. At first, the members of the ATS/IDSA Guideline Committee acknowledged that currently many patients with HAP, VAP or HCAP are infected with multidrug-resistant (MDR) bacterial pathogens that threaten the adequacy of initial empirical antibiotic therapy. At the same time, the committee members acknowledged that many studies have shown that excessive antibiotic use is an important factor contributing to an increased frequency of antibiotic-resistant pathogens. Four key principles underlie the management of HAP, VAP and HCAP: Avoid untreated or inadequately treated HAP, VAP or HCAP, as failure to initiate rapid appropriate and adequate therapy has been a consistent factor associated with increased mortality. Recognize the variability of bacteriology from one hospital to another, specific locations within the hospital and from one period to another, and use this information to modify the selection of a suitable antibiotic treatment regimen for a specific clinical environment. Avoid the overuse of antibiotics by focusing on accurate diagnosis, tailoring therapy to the results of lower respiratory cultures, and shortening the duration of therapy to the minimum effective period. Application of prevention strategies aimed at adaptable risk factors. The ATS/IDSA Directive has been drawn up for use in the initial treatment of patients suspected of HAP, VAP or HCAP. Therapeutic algorithms are presented based on the expected antimicrobial sensitivity of the common bacterial pathogens, and with therapeutic regimens that can often lead to initial adequate antibiotic management. This directive is not intended to replace clinical judgment, but to provide an organisational framework for patient management. Individual clinical situations can be very complex and the judgment of an expert with all available information on a specific is essential for optimal clinical management. As more laboratory and clinical data become available, therapy often needs to be streamlined or modified. Finally, our committee realises that these guidelines will change over time and that our current recommendations as new becomes available. The ATS/IDSA Guideline Committee originally met as a group, with each person assigned a topic for review and presentation to the entire group. Each subject in the directive was assessed by more than one committee member and, after the presentation of information, the committee discussed the data and formulated recommendations. Two committee members prepared each part of the document, and a draft document containing all sections was written and disseminated to the committee for review and suggestions. The guideline was then revised and circulated to the committee for final comment. This final statement represents the results of this process and the opinions of the majority of committee members. The assessment system for our evidence-based recommendations was previously used for the updated Pneumonia (CAP) statement acquired by the ATS, and high-level (level I), moderate level (level II) and low-level data (level III) are summarized in Table 1TABLE 1. Evidence-based grading system used to recommendEvidence LevelDefinitionLevel I (high)Evidence comes from well-conducted, randomized controlled trialsLevel II (moderate)Evidence comes from well-designed, controlled trials without randomization (including cohort, patient series, and case-control studies). Level II studies also include large case series in which systematic analysis of disease patterns and/or microbial etiology was conducted, as well as reports of new therapies not collected in a randomized mannerLevel III (layer) Evidence comes from case studies and expert advice. In some cases, therapy recommendations arise from data on the sensitivity of antibiotics without clinical observations (8). All available and relevant peer-reviewed studies published until July 2004 were considered. Much of the literature is observational, and only a few therapy trials have been conducted in a prospective, randomized manner. Almost all evidence-based data on risk factors for bacterial HAP have been collected from observational studies, which cannot distinguish between causation. Most studies focused on patients with VAP, but the committee extrapolated the relationship between risk factors and bacteriology to all patients with HAP, including patients with HCAP. Ultimately evidence of causality, and ideally the best strategies for the prevention of HAP, VAP, and HCAP, should be based on prospective, randomized trials. However, recommendations are further compromised when such trials produce conflicting results, often due to differences in definitions, study design and the specific population studied. In addition, evidence-based recommendations are dynamic and can change as therapies become available and as new interventions change the natural history of the disease. HAP is usually caused by bacteria, is currently the second most common nosocomial infection in the United States, and is associated with high high morbidity (3). The presence of HAP increases hospital stays by an average of 7 to 9 days per patient and has been reported to produce an excess of more than $40,000 per patient (9-11). Although HAP is not a reportable disease, the available data indicate that it happens at a rate of between 5 and 10 cases per 1,000 hospitalizations, with the incidence occurring by as much as 6- to 20-fold in mechanically ventilated patients (9, 12, 13). It is often difficult to define the exact incidence of VAP, as there may be an overlap with other lower respiratory tract infections, such as infectious tracheobronchitis in mechanically ventilated patients. The exact incidence varies greatly depending on the definition of pneumonia and the population being evaluated (14). For example, the incidence of VAP may be up to twice as high in patients diagnosed by qualitative or semi-biennial sputum cultures compared to quantitative cultures of lower respiratory secretions (9, 15). HAP accounts for up to 25% of all ICU infections and more than 50% of prescribed antibiotics (16). VAP occurs in 9-27% of all intubated patients (9, 11). In ICU patients, almost 90% of episodes occur during mechanical ventilation. In mechanically ventilated patients, the incidence increases with the duration of ventilation. The risk of VAP is highest early in the course of the hospital stay, and is estimated at 3%/day during the first 5 days of ventilation, 2%/day during day 5 to 10 of ventilation, and 1%/day thereafter (17). Because most mechanical ventilation is short-term, about half of all episodes of VAP occur within the first 4 days of mechanical ventilation. The intubation process itself contributes to the risk of infection and when patients with acute respiratory failure are managed with non-invasive ventilation, nosocomial pneumonia is less common (18-20). Time of onset of pneumonia is an important epidemiological variable and risk factor for specific pathogens and outcomes in patients with HAP and VAP. Early-onset HAP and VAP, defined as occurring within the first 4 days of hospitalization, typically carry a better prognosis, and are more likely to be caused by antibiotic-sensitive bacteria. Hap and VAP (5 days or more) are more commonly caused by multidrug-resistant (MDR) pathogens and are associated with increased patient mortality and morbidity. However, patients with early onset bite who have received prior antibiotics in the past 90 days or who have had prior hospitalization in the past 90 days are at greater risk of colonization and infection with MDR pathogens and should be treated similarly with patients with bite or VAP with late onset (Table 2)TABLE 2. Risk factors multidrug-resistant pathogens that cause hospital-acquired pneumonia, health-care-associated pneumonia, and respiratory-associated pneumonia• Antimicrobial therapy in prior 90 d• Current hospitalization of 5 d or more• High frequency of antibiotic resistance in the community in the specific hospital unit• Presence of risk factors for HCAP: Hospitalisation for 2 d or more in the previous 90 d Stay in a nursing home or extended care facility Home infusion therapy (including antibiotics) Chronic dialysis within 30 d Home wound care Family member with multi-resistant pathogen• Immunosuppressive disease and/or therapy (21). The raw mortality rate for HAP can be as high as 30 to 70%, but many of these seriously ill patients with HAP die from their underlying disease instead of pneumonia. Mortality associated with HAP or attributable mortality is estimated at between 33 and 50% in several case-matching studies from VAP. Increased mortality rates were associated with bacteremia, especially with Pseudomonas aeruginosa or Acinetobacter species, medical rather than surgical disease, and treatment with ineffective antibiotic therapy (22, 23). Other studies using similar methods could not identify attributable mortality due to VAP, indicating a variable outcome effect depending on the severity of the underlying medical conditions (24–26). HAP, VAP and HCAP may be caused by a broad spectrum of bacterial pathogens, may be polymicrobials and are rarely due to viral or fungal pathogens in immunocompetic hosts (9, 12, 27–32). Common pathogens include aerobic gram-negative germs, such as P. aeruginosa, Escherichia coli, Klebsiella pneumoniae, and Acinetobacter species. Infections due to gram-positive cocci, such as Staphylococcus aureus, especially methicillin-resistant S. aureus (MRSA), have quickly emerged in the United States (16, 33). Pneumonia due to S. aureus is more common in patients with diabetes mellitus, head trauma, and those included in IUs (34). Significant growth of orophary geal commensals (viridans group streptococci, coagulase-negative staphylococci, Neisseria species and Corynebacterium species) from distal bronchial specimens is difficult to interpret, but these organisms can cause infection in immune-compromised hosts and some immunocompete patient tent (35). Rates of polymicrobial infection vary widely, but appear to be increasing and are especially high in patients with adult respiratory distress syndrome (ARDS) (9, 12, 36–38). The frequency of specific MDR pathogens causing HAP may vary by hospital, patient population, antibiotic exposure, type of ICU patient, and time changes, emphasizing the need for timely local monitoring data (3, 8, 10, 21, 39-41). HAP with anaerobic organisms may track aspiration in uninubated patients, but is rare in patients with VAP (28, 42). Elderly patients represent a diverse population of patients with pneumonia, especially HCAP. Elderly residents of long-term have a spectrum of pathogens more similar to bite and VAP (30, 31). In a study of 104 patients aged 75 and over with severe pneumonia, El-Solh S. found aureus (29%), enteric gramnegative bars (15%), (15%), pneumoniae (9%) and Pseudomonas species (4%) as the most common causes of nursing home-acquired pneumonia (30). In another study of 52 long-term care residents aged 70 and over who did not respond to 72 hours of antibiotics, MRSA (33%), gram-negative enterics (24%) and Pseudomonas species (14%) were the most common pathogens isolated by invasive diagnostics (bronchoscopy) (31). In the last study, 72% had at least two comorbidities, while 23% had three or more. There is little data available on bacteriology and risk factors for specific pathogens in patients with HAP and HCAP, and which are not mechanically ventilated. Data from extensive hospital-wide monitoring of nosocomial infections at the University of North Carolina have described the pathogens causing both VAP and nosocomial pneumonia in uningubated patients during the years 2000-2003 (D. Weber and W. Rutala, unpublished data). Pathogens were isolated by 92% of mechanically ventilated patients with infection, and 77% of non-unfadicated patients with infection. In general, the bacteriology of non-un ventilated patients was similar to that of ventilated patients, including infection with MDR pathogens such as methicillin-resistant S. aureus (MRSA), P. aeruginosa, Acinetobacter species and K. pneumoniae. In fact, some organisms (MRSA and K. pneumoniae) were more common in non-ventilated than ventilated patients, while some resistant gramnegative bacilli were more common in patients with VAP (P. aeruginosa, Stenotrophomonas maltophilia and Acinetobacter species). However, the last group of more resistant gram-negative bacilli occurred in non-unventilated patients, so that the design of an empirical therapy regimen should take into account the design of an empirical therapy regimen. Studies in non-agitated patients have not determined whether this population has risk factors for MDR pathogens that differ from the risk factors present in ventilated patients. The rates of HAP due to MDR pathogens have increased dramatically in hospitalized patients, especially in intensive care and transplant patients (16). Risk factors for colonisation and infection with MDR pathogens are summarized in Table 2 (21, 43). Data on mechanisms of antibiotic resistance for specific bacterial pathogens have provided new insight into the adaptability of these pathogens. Pseudomonas aeruginosa. P. aeruginosa, the most common MDR gram-negative pathogenic pathogen that causes HAP/VAP, has intrinsic resistance to many antimicrobials (44–46). This resistance is mediated by multiple efflux pumps, which can be expressed all the time or can be filled by mutation (47). The resistance to ceftazidime, cefepime, other oxyimino-β-lactams, imipenem and meropenem, aminoglycosiden or fluoroquinolones is increasing in the United States (16). Reduced expression of an outer membrane pore (OprD) can cause resistance to both imipenem and meropenem or, depending on the change in OprD, specific resistance resistance but not other β-lactams (48). Currently, some MDR isolates of P. aeruginosa are only susceptible to polymyxin B.Although currently uncommon in the United States, there are concerns about the acquisition of plasmid-mediated metallo-β-lactamases active against carbapenems and antipseudomonal penicillins and cephalosporins (49). The first enzyme, IMP-1, appeared in Japan in 1991 and spread under P. aeruginosa and Serratia marcescens, and then to other gram-negative pathogens. Resistant strains of P. aeruginosa with IMP-type enzymes and other carbapenemases have been reported from other countries in the Far East, Europe, Canada, Brazil and most recently in the United States (50). Klebsiella, Enterobacter and Serratia species. Klebsiella species are intrinsically resistant to ampicillin and other aminopenicillins and can acquire resistance to cephalosporins and aztreonam by producing extensive spectrum β lactamases (ESBLs) (51). Plasmids coding ESBLs often carry resistance to aminoglycosides and other drugs, but ESBL-producing strains remain susceptible to carbapenems. Five to 10% of oxyimino-β-lactam-resistant K. pneumoniae do not produce ESBL, but a plasmid-mediated AmpC-type enzyme (52). Such strains are usually carbapenem susceptible, but can become resistant due to loss of an outer membrane porin (53). Enterobacter species have a chromosomal AmpC β-lactamase that is inducible and can also be easily expressed at a high level by mutation with resulting resistance to oxyimino-β-lactams and α-methoxy-β-lactams, such as cefotinxi and cefotetan, but remained the sensitivity to carbapenems. Citrobacter and Serratia species have the same inducible AmpC β-lactamase and the same potential for resistance development. Although the AmpC enzyme of E. coli is not inducible, it can occasionally become hyperexpressed. Plasmid-mediated resistance, such as ESBL production, is a more common mechanism for β lactam resistance in nosocomial isolates, and is increasingly recognized not only in isolates of K. pneumoniae and E. coli, but also Enterobacter species (54). Acinetobacter species, Stenotrophomonas maltophilia, and Burkholderia cepacia . Although acinetobacter species are generally less virulent than P. aeruginosa, they have become problem pathogens due to increasing resistance to commonly used antimicrobials (55). More than 85% of isolates are sensitive to carbapenems, but resistance is increased by imp-type metalloen enzymes or oxa-type carbapenemases (49). An alternative to therapy is sulbactam, usually used as an enzyme inhibitor, but with direct antibacterial activity against Acinetobacter species (56). S. moutophilia, which shares with B. cepacia a tendency to colonize the airways rather than cause invasive disease, is uniformly resistant to carbapenems, as of a ubiquitous metallo-β-lactamase. S. maltophilia and B. cepacia are likely to be susceptible to ticarcilline clavulanate, or fluoroquinolone (55). B. cepacia is also usually sensitive to ceftazidime and carbapenems. Methicillin-resistant Staphylococcus aureus. In the United States, more than 50% of ICU infections are caused by S. aureus with methicillin-resistant organisms (16, 33). MRSA produces a penicillin binding protein with reduced affinity for β-lactam antibiotics encoded by the mecA gene, which is carried by one of a family of four mobile genetic elements (57, 58). Strains with mecA are resistant to all commercially available β-lactams and many other antistaphylococcal drugs, with significant land-to-land variability (59, 60). Although vancomycin-intermediate S. aureus, with a minimum inhibitory concentration (MIC) of 8-16 μg/ml, and high level ofcomycin-resistant S. aureus, with a MIC of 32-1,024 μg/ml or more, are isolated from clinical specimens, none to date have caused respiratory infection and all are susceptible to linezolid (61, 62). Unfortunately, linezolid resistance originated in S. aureus, but is currently rare (63). Streptococcus pneumoniae and Haemophilus influenzae. S. pneumoniae and H. influenzae cause early-onset HAP in patients without other risk factors, are uncommon with late infection, and often the community are acquired. Currently, many strains of S. pneumoniae penicillin are resistant due to altered penicillin-binding proteins. Some such strains are also resistant to cephalosporins, macrolides, tetracyclines and clindamycin (64). Despite low and moderate resistance to penicillins and cephalosporins in vitro, the clinical results in patients with pneumococcal pneumonia and bacteremia treated with these drugs are satisfactory (65). All multidrug-resistant strains in the United States are currently susceptible to vancomycin or linezolid, and most remain sensitive to broad-spectrum quinolones. Resistance of H. influenzae to antibiotics other than penicillin and ampicillin is sufficiently rare to pose no problem in therapy. Legionella pneumophila. The evidence for Legionella pneumophila as a cause of HAP is variable, but is increased in immune-compromised patients, such as recipients of organ transplants or patients with HIV disease, as well as patients with diabetes mellitus, underlying lung disease or end-stage kidney disease (29, 66-69). HAP due to legionella species is more common in hospitals where the organism is present in the hospital water supply or where there is ongoing construction (3, 29, 66-69). Because detection is based on the widespread use of legionella urinary antiniges, rather than culture for legionella, disease due to serogroups other than serogroup 1 can be underdiagnosed. Detailed strategies for the prevention of legionella infections and eradication procedures for legionella species cooling towers and the hospital's water supply are described in the CDC/HICPAC guidelines for preventing health-associated pneumonia pneumonia due to fungi, such as Candida species and Aspergillus fumigatus, may occur in organ transplantation or immunocompromised, neutropenic patients, but is uncommon in immunocompetent patients (70-75). Nosocomial Aspergillus types of infections suggest possible airborne transmission by spores, and may be associated with an environmental source, such as contaminated air ducts or hospital construction. By comparison, isolation of Candida albicans and other Candida types of endotracheal aspirates is common, but usually represents colonization of the airways, rather than pneumonia in immunocompetent patients, and rarely requires treatment with antifungal therapy (70). The incidence of HAP and VAP due to viruses is also low in immunocompetent hosts. Outbreaks of HAP, VAP and HCAP due to viruses such as influenza, parainfluenza, adenovirus, measles and respiratory syncytial virus have been reported and are usually seasonal. Influenza, pararinfluenza, adenovirus and respiratory syncytial virus account for 70% of nosocomial viral cases of HAP, VAP and HCAP (3, 76-78). Respiratory syncytial virus outbreaks of bronchiolitis and pneumonia are more common in pediatric wards and are rare in immunocompetent adults (76). Diagnosis of these viral infections is often made by rapid antigen testing and viral culture or serologic assays. Influenza A is probably the most common viral cause of HAP and HCAP in adult patients. Pneumonia in patients with influenza A or B may be due to the virus, secondary bacterial infection, or both. Influenza is transmitted directly from person to person when infected individuals sneeze, cough, or talk or indirectly by person-fomite-person transmission (3, 79-81). The use of influenza vaccine, together with prophylaxis and early antiviral therapy in at-risk workers and at-risk patients with amantadine, rimantadine or one of the neuraminidase inhibitors (oseltamivir and zanamivir) dramatically reduces the spread of influenza within hospital and healthcare institutions (3, 81–90). Amantadine and rimantadine are only effective for treatment and prophylaxis against influenza A strains, while neuraminidase inhibitors are effective against both influenza A and B. Many patients with HAP, VAP and HCAP are at increased risk of colonization and infection with MDR pathogens (level II) (2-4, 6, 9, 11-13, 21, 22). It is often difficult to define the exact incidence of HAP and VAP, as there may be an overlap with other lower respiratory tract infections, such as tracheobronchitis, especially in mechanically ventilated patients (level III) (9, 12-14). The exact incidence of HAP is usually between 5 and 15 cases per 1,000 hospitalizations, depending on the case definition and study population; the exact incidence of VAP is 6- to 20-fold greater than in (level II) (9, 12-14). HAP and VAP are a frequent cause of nosocomial infection associated with higher (level II) (3, 9, 16). Patients with bite and VAP with late onset are more likely to be infected with MDR pathogens and have higher raw mortality than patients with early onset disease; patients with early onset bite who have recently been given antibiotics or have had an admission to a care facility are at risk of colonisation and infection with MDR pathogens (level II) (3, 9, 21, 22). An increase in raw and attributable mortality for HAP and VAP is associated with the presence of MDR pathogens (level II) (3, 5, 9–13, 21–23). Bacteria cause most cases of HAP, VAP, and HCAP and many infections are polymicrobial; patients with ARDS (level I) (2, 4, 6, 9, 12, 36–38). HAP, VAP and HCAP are often caused by aerobic gram negative bacilli, such as P. aeruginosa, K. pneumoniae and Acinetobacter species, or by gram-positive cocci, such as S. aureus, of which a large part is MRSA; anaerobic are an unusual cause of VAP (level II) (9, 12, 28, 36-40, 42, 91). Rates of L. pneumophila vary considerably between hospitals and disease is more common in serogroup 1 when the water supply is colonized or there is ongoing construction (level II) (29, 66-69). Nosocomial virus and fungal infections are unusual causes of HAP and VAP in immunocompetent patients. Outbreaks of influenza have occurred sporadically and the risk of infection can be significantly reduced with widespread effective infection control, vaccination and use of anti-influenza agents (level I) (3, 70-75, 79-90). The prevalence of MDR pathogens varies by patient population, hospital and type ICU, underlining the need for local surveillance data (level II) (3, 9, 41). MDR pathogens are more likely to be isolated from patients with severe, chronic underlying disease, patients with risk factors for HCAP and patients with bite or VAP (9, 21, 21, 30, 31, 39, 40, 91). For HAP occurrence, the delicate balance between host defense and microbial propensity for colonization and invasion must shift in favor of the ability of the pathogens to sustain and penetrate the lower airways. Sources of infection for HAP are health care or the environment (air, water, equipment and fomites) and may occur in the transmission of microorganisms between staff and patients (3, 9, 12, 13, 27, 66, 92, 93). A number of host and treatment-related colonisation factors, such as the severity of the patient's underlying disease, prior surgery, antibiotic exposure, other medications and exposure to invasive respiratory equipment and equipment, are important in the pathogenesis of HAP and VAP (40, 93, 94)HAP requires the entry of microbial pathogens into the lower respiratory tract, followed by colonization, which can then overwhelm the mechanical of the host (cyclicized epithelium and mucus) , (antibody and supplement), and cellular (polymorphic leukocytes, macrophages, and lymphocytes and their respective cytokines) defenses to diagnose infection (9, (9, of oropharnatal pathogens or leakage of bacteria around the endotracheal tube cuff is the primary route of bacterial entry into the trachea (95-98). The stomach and sinuses have been suggested as potential reservoirs for certain bacteria colonizing the oropharnate and trachea, but their importance remains controversial (99-104). Some researchers argue that colonization of the endotracheal tube with bacteria encased in biofilm can result in embolization in the alve vesicers during sucking or bronchoscopy (105, 106). Inhalation of pathogens of infected aerosols, and direct vaccination, are less common (107, 108). Hematogenic spread of infected intravascular catheters or bacterial translocation from gastrointestinal lumens are quite rare. Sources of pathogens for HAP are healthcare devices, the environment (air, water, equipment and fomites), and often the transmission of microorganisms between the patient and staff or other patients (level II) (3, 9, 12, 13, 27, 66, 92, 93). A number of host and treatment-related colonization factors, such as the severity of the patient's underlying disease, prior surgery, antibiotic exposure, and other medications and exposure to invasive respiratory equipment and equipment, are important in the pathogenesis of HAP and VAP (level II) (40, 93, 94). Aspiration of oropharnatal pathogens, or leakage of secretions that contain bacteria around the endotracheal tube cuff, are the main routes of bacterial entry into the lower respiratory tract (level II) (95-98). Inhalation or direct inoculation of pathogens in the lower respiratory tract, hematogenic spread of infected intravenous catheters and bacterial translocation from gastrointestinal ducts are unusual pathogenic mechanisms (level II) (107, 108). Infected biofilm in the endotracheal tube, with subsequent embolization of distal airways, may be important in the pathogenesis of VAP (level III) (105, 106). The stomach and sinuses may have potential reservoirs of nosocomial pathogens that contribute to bacterial colonization of the oropharnax, but their contribution is controversial, can vary by endangering the population, and may decrease with the changing natural history and management of HAP (Level II) (94, 99-104, 109). Risk factors for the development of HAP can be distinguished in adaptable and non-modifiable conditions. Risk factors may also be patient-related (male sex, pre-existing lung disease, or multiple organ failure) or treatment-related (intubation or enteral nutrition). Modipaed risk factors for HAP are clear goals for better management and prophylaxis in various studies and in the comprehensive guidelines for preventing health-associated pneumonia, published by

the Centers for Disease Control (3, 93, 110). strategies include strict infection control, alcohol-based hand disinfection, use of microbiological surveillance with timely availability of data on local MDR pathogens, MDR pathogens, removal of invasive devices and programs to reduce or change antibiotic prescribing practices (3, 92, 93, 100, 110–113). Intubation and mechanical ventilation increase the risk of HAP 6- to 21-fold and should therefore be avoided as much as possible (3, 94, 110, 114). Non-invasive positive pressure ventilation, using a face mask, is an attractive alternative for patients with acute exacerbations of chronic obstructive pulmonary disease or acute hypoxemic respiratory failure, and for some immune-suppressed patients with pulmonary infiltrates and respiratory failure (18, 20, 115–119). Data show that the use of non-invasive ventilation to prevent reclassification after the first extubation cannot be a good strategy (115). Specific strategies are recommended to shorten the duration of mechanical ventilation, such as improved sedation methods and the use of protocols to facilitate and accelerate weaning (120-124). These interventions depend on sufficient IC staff. Clean tubing should be avoided if possible, as the risk of VAP (114) increases. Attention to the specific type of endotracheal tube, its maintenance and the place of insertion can also be valuable. The use of oral endogastic tubes, instead of nasotracheal and nasogastric tubes, can reduce the frequency of nosocomial sinusitis and possibly HAP, although the causality between sinusitis and HAP is not firmly established (109, 125). Efforts to reduce the likelihood of aspiration of oropharnatal bacteria around the endotracheal cuff tube and in the lower respiratory tract include limiting the use of sedative and paralytic agents that suppress cough and other host-protective mechanisms, and maintaining endotracheal cuff pressure at more than 20 cm H2O (98, 126). Continuous aspiration of subglottic secretions, through the use of a specially designed endotracheal tube, has significantly reduced the incidence of early ong.com (97, 127-130). VAP may also be related to colonization of the fan circuit (131). A large number of prospective, randomized studies have shown that the frequency of fan circuit change does not affect the incidence of HAP, but condensate that collects in the fan circuit can become contaminated by patient secretions (98, 132-135). Therefore, vigilance is necessary to prevent the condensate from accidentally rinsing into the lower respiratory tract or for in-line medication prevents when the patient is turning or the movement is increased (98, 131-134, 136). Passive humidifiers or heat-moisture exchangers reduce the colonization of the fan circuit, but have not significantly reduced the incidence of VAP (128, 135-139). Supine patient positioning can also facilitate aspiration, which are reduced by a semi-recumbent positioning (140-142). Using radioactively labelled enteral nutrition, the cumulative numbers of endotracheal counts were higher when patients were placed in full supine position (0°) compared to a semi-overdue position (140, 141). A randomized study showed a threefold reduction in the incidence of THE ICU's hap in patients treated in the semi-posterior position compared to patients who were treated fully supine (143). Infection in patients in the supine position was strongly associated with the simultaneous administration of enteral nutrition. Intubated patients should therefore be managed in a semi-recumbent position, especially during feeding. Enteral diet is considered a risk factor for the development of HAP, mainly due to an increased risk of aspiration of stomach content (3, 144). However, the alternative, parenteral nutrition, is associated with higher risks for intravascular device-associated infections, complications of line insertions, higher costs, and loss of gut-like architecture, which can facilitate enteral microbial translocation. Although some have advised to feed seriously ill patients as early as possible, an early (i.e. day 1 of intubation and ventilation) was enteral nutrition, compared to late administration (i.e. day 5 of intubation), associated with a higher risk for ICU-acquired VAP (145, 146). Seven studies evaluated the risks for hap-acquired ICU in patients randomized for gastric or post-pylooristic foods (147). Although no significant differences were shown in any individual study, postpylooristic diets were associated with a significant reduction in the HAP acquired by the IC in meta-analysis (relative risk, 0.76; 95% confidence interval, 0.59 to 0.99) (147). The progression from colonization to tracheobronchitis to pneumonia is a dynamic balance and the ability to distinguish the different entities depends on the specificity of diagnostic instruments. Oropharyngeal colonization, either present at admission or acquired during the IC stay, has been identified as an independent risk factor for the development of ICU-acquired HAP caused by enteric gram-negative bacteria and P. aeruginosa (101). In a randomized study, DeRiso and colleagues showed that the use of oral antiseptic chlorhexidine significantly reduced the rates of nosocomial infection in patients undergoing bypass surgery (148). Modulation of oropharnatal colonization, by combinations of oral antibiotics, with or without systemic therapy, or by selective disinfection of the digestive tract (SDD), is also effective in significantly reducing the frequency of HAP, although the quality of the methodology study seemed to be inversely related to the extent of preventive effects (93, 149–155). In two prospective randomized trials, SDD was associated with higher ICU survival in patients receiving SDD (156, 157). In the first study patients with a midrange APACHE II score at admission lower ICU mortality, although the mortality rates of ICU mortality among all patients included did not differ significantly (156). In the largest study carried out to date, SDD was administered to 466 patients in one single icu mortality of 0.65 and a relative risk of hospital mortality of 0.78, compared to 472 patients admitted to a control unit (157). In addition, infections caused by antibiotic-resistant microorganisms were more common in the control department. Importantly, levels of antibiotic-resistant pathogens in both departments were low, with complete absence of MRSA. Moreover, a small already existing difference in result between two departments and the lack of a crossover design warrants confirmation of these beneficial effects of SDD. The preventive effects of selective disinfection of the digestive tract for HAP are also significantly lower in Ic's with high endemic levels of antibiotic resistance. In such an environment, selective disinfection of the digestive tract can increase the selective pressure for antibiotic-resistant microorganisms (158-164). Although selective disinfection of the digestive tract HAP reduces, routine prophylactic use of antibiotics should be discouraged, especially in hospital environments where there is a high degree of antibiotic resistance. The role of systemic antibiotics in the development of HAP is less clear. In one study, the prior administration of antibiotics had an adjusted odds ratio of 3.1 (95% confidence interval, 1.4–6.9) for the development of late-on-the-e.p.a., ICU-acquired HAP (165). In addition, antibiotics clearly pre-conceive patients for later colonization and infection with antibiotic-resistant pathogens (21). By contrast, previous exposure to antibiotics provided protection (risk ratio, 0.37; 95% confidence interval, 0.27-0.51) for bite at the ICU in another study (17). In addition, the use of antibiotics at the time of emerging intubation can prevent pneumonia within the first 48 hours after intubation (166). Preventive effects of intravenous antibiotics were evaluated in only one randomized study: administration of cefuroxim for 24 hours, at the time of intubation; and it reduced the incidence of early on-the-go, ICU-acquired HAP in patients with closed head injuries (167). However, circumstantial evidence of the efficacy of systemic antibiotics also follows from the results of meta-analyses of selective disinfection of the digestive tract, showing that the intravenous component of the regimens was largely responsible for better survival (149). In summary, prior administration of antibiotics for short duration may be beneficial in some patient groups, but when given for extended periods may well place others at risk for subsequent infection with antibiotic-resistant microorganisms. Both histamine Type 2 (H2) antagonists and antacids have been identified as independent risk factors for ICU-acquired HAP. Sucralfate has been used for stress bleeding prophylaxis, reduce non-intragastric acidity or significantly increase stomach volume. Numerous randomized trials, using different doses and different study populations, have produced controversial results on the benefits of specific stress bleeding stress bleeding agents regarding the increased risk of VAP (38, 99, 103, 104, 155, 168). A large randomized study comparing antacids, H2 blockers, and sucralfate reported no differences in rates of early-onset VAP, but rates of late-onset VAP were lower in patients treated with sucralfate (103). In a multicenter study of VAP in patients with ARDS, sucralfate and duration of exposure to sucralfate were associated with an increased risk of VAP (38). A large, double-blind, randomized study comparing ranitidine with sucralfate showed a trend toward lower rates of VAP with sucralfate, but clinically significant gastrointestinal bleeding was 4% higher in the sucralfate group (104). So, if stress ulcer proficlaxi is indicated, the risks and benefits of each regimen should be weighed before prescribing H2 blockers or sucralfate. A landmark prospective randomized study comparing liberal and conservative triggers with transfusion in ICU patients who do not have active bleeding and without underlying heart disease, showed that waiting for a hemoglobin level of 7.0 g/dl as opposed to a level of 9.0 g/dl for initiating transfusion resulted in less transfusion and no adverse effects on outcome (169). In fact, in those patients less seriously ill, as assessed by low APACHE II scores, mortality was improved in the limited transfusion group, a result thought to result from immunosuppressive effects of non-leukocyte-depleted red blood cell units resulting in an increased risk of infection. Multiple studies have identified exposure to allogeneic blood products as a risk factor for postoperative infection and postoperative pneumonia, and the duration of blood storage as another factor that modulates risk (170-174). In a prospective randomized control study, the use of depleted red blood cell transfusions resulted in a reduced incidence of postoperative infections, and specifically a reduced incidence of pneumonia in patients undergoing colorectal surgery (172). Routine red blood cell transfusion should be performed with a limited transfusion trigger policy. Whether the transfusions of leukocyte-depleted red blood cells will further reduce the incidence of pneumonia in broad populations of at-risk patients remains to be determined. Hyperglycemia, relative insulin deficiency, or both can directly or indirectly increase the risk of complications and poor outcomes in seriously ill patients. van den Berghe and colleagues randomised surgical intensive care unit patients to either receive intensive insulin therapy to maintain blood sugar levels between 80 and 110 mg/dl or to receive conventional treatment (175). The group receiving intensive insulin therapy had the mortality (4.6 vs. 8%, p&p; 0.04) and the difference was greater in patients who remained in intensive care for more than 5 days (10.6 vs. 20.2%, p = 0.005). Compared to the control group, those treated with intensive insulin therapy had a 46% 46% infections, reduced frequency of acute kidney failure that requires dialysis by 41%, fewer antibiotic treatment days, and significantly shorter length of mechanical ventilation and IC stay. While the same degree of benefit cannot be seen in patients with VAP as in other populations, aggressive treatment of hyperglycemia has both theoretical and clinical support. Effective measures to combat infection: staff information, compliance with alcohol-based hand disinfection and isolation to reduce cross-infection with MDR pathogens should be used routinely (level I) (level I) (3, 93, 100, 110, 111). Monitoring of ICU infections, the identification and quantification of endemic and new MDR pathogens, and the preparation of timely data for infection control and the guidance of appropriate, antimicrobial therapy in patients with suspected HAP or other nosocomial infections are recommended (level II) (level II) (3, 92, 93, 100, 110-113). Intubation and reclassification should be avoided if possible, as the risk of VAP (level I) (level I) (3, 12, 93, 94, 114) increases. Non-invasive ventilation should be used as far as possible in selected patients with respiratory failure (level I) (18, 20, 115-119). Orotracheal intubation and orogastrian tubes are preferred over nasotracheal intubation and nasogastric tubes to prevent nosocomial sinusitis and reduce the risk of VAP, although direct causality has not been proven (level II) (3, 93, 94, 109, 125). Continuous aspiration of subglottic secretions can reduce the risk of vap at an early onset and should be used, if available (level I) (97, 128, 130). The endotracheal tube cuff pressure should be maintained at more than 20 cm H2O to prevent leakage of bacterial pathogens around the cuff in the lower respiratory tract (level II) (98, 126). Contaminated condensate should be carefully emptied from respiratory circuits and condensate should be prevented from entering the endotracheal tube or in-line medication depositors (level II) (98, 131, 132). Passive humidifiers or heat-moisture exchangers reduce the colonization of the fan circuit, but have not consistently reduced the incidence of VAP, and therefore cannot be considered as a tool to prevent pneumonia (level I) (135-139). Reduced duration of intubation and mechanical ventilation can prevent VAP and can be achieved through protocols to improve the use of sedation and accelerate weaning (level II) (93, 120-122, 124). Maintaining sufficient staffing levels in the ICU can shorten the length of stay, improve infection control and reduce the duration of mechanical ventilation (level II) (121-124). Patients should be kept in the semi-recumbent position (30-45°) instead of supine in order to especially when receiving enteral nutrition (level I) (140-144). Enteral nutrition is preferred over parenteral nutrition to reduce the risk of complications associated with central intravenous catheters and prevent reflux villous atrophy of the intestinal mucosa that may increase the risk of bacterial translocation (level I) (3, 93, 93, 93, 146). Routine prophylaxis of HAP with oral antibiotics (selective disinfection of the digestive tract or SDD), with or without systemic antibiotics; reduces the incidence of IC-acquired VAP, has helped contain outbreaks of MDR bacteria (level I), but is not recommended for routine use, especially in patients who can be colonized with MDR pathogens (level II) (149-154, 156-159, 161–164, 176). Prior administration of systemic antibiotics has reduced the risk of nosocomial pneumonia in some patient groups, but if a history of prior administration is present at the time of onset of infection, there should be an increased suspicion of infection with MDR pathogens (level II) (157-159, 161–164). Prophylactic administration of systemic antibiotics for 24 hours at the time of emerging intubation has been shown to prevent ICU-acquired HAP in patients with closed head injuries in a study, but its routine use is not recommended until more data become available (level I) (167). Modulation of oropharyngeal colonization through the use of oral chlorhexidine has prevented HAP from being acquired in the ICU in selected patient populations, such as patients undergoing coronary bypass vaccination, but its routine use is not recommended until more data are available (level I) (148). Use daily interruption or relief from sedation to avoid constant heavy sedation and try to avoid crippling agents, which can reduce both coughs and thereby increase the risk of HAP (level II) (120). Comparative data from randomized studies suggest a trend toward reduced VAP with sucralfate, but there is a slightly higher rate of clinically significant gastric bleeding, compared to H2 antagonists. If necessary, stress bleeding prophylaxis with H2 antagonists or sucralfate is acceptable (level I) (99-104, 155, 177–179). Transfusion of red blood cells and other allogeneic blood products should follow a limited policy for the trigger of the transfusion trigger; leukocytes depleted red blood cell transfusions can help to reduce HAP in selected patient populations (level I) (169-174). Intensive insulin therapy is recommended to maintain serum glucose levels between 80 and 110 mg/dl in ICU patients to reduce nosocomial blood flow infections, duration of mechanical ventilation, ICU stay, morbidity and mortality (level I) (175). Diagnostic tests are ordered for two purposes: to determine whether a patient has pneumonia as the explanation for a constellation of new signs and symptoms and to determine the etiological pathogen when pneumonia is present. Unfortunately, currently available tools cannot always provide this information reliably. The diagnosis of HAP is suspected the patient will infiltrate a radiographic that is new or progressive, along with clinical findings suggesting infection, including the new onset of fever, purulent sputum, leukocytosis, and decrease in oxygenation. When fever, leukocytosis, purulent sputum and a positive culture of a sputum or tracheal suction are present without a new lung infiltration, lung infiltration, nosocomial tracheobronchitis should be considered (180). When this definition is applied to mechanically ventilated patients, nosocomial tracheobronchitis is associated with a longer duration of ICU stay and mechanical ventilation, without increased mortality (180). Antibiotic therapy may be beneficial in this group of patients (180, 181). In a prospective randomized study of intubated patients with community-acquired bronchial infection, the use of antibiotic therapy led to a reduced incidence of later pneumonia and mortality (181). Diagnosis of HAP is difficult, and most studies of non-deindubated patients relate to clinical diagnosis, with sputum culture, but bronchoscopy is used less frequently, making the reliability of bacteriological information uncertain and the specificity of the diagnosis undefined (182). The accuracy of VAP clinical diagnosis has been investigated on the basis of autopsy findings or quantitative cultures of either protected specimen brush (PSB) or bronchoalveolar lavage (BAL) samples as the standard for comparison (183-186). Some studies have examined the accuracy of a single clinical finding, while others have produced multiple criteria in their definition of pneumonia. These studies indicate that the diagnostic criteria of a radiographic infiltration and at least one clinical function (fever, leukocytosis, or purulent tracheal secretions) have high sensitivity but low specificity (especially for VAP). Combinations of signs and symptoms can increase specificity. A study in which the diagnostic standard was histology plus positive microbiological cultures of immediate postmortem lung samples, the presence of breast infiltrates, plus two of the three clinical criteria resulted in 69% sensitivity and 75% specificity (187). When the three clinical variables were used, sensitivity decreased, while the use of only one variable led to a decrease in specificity. For patients diagnosed with ARDS, the suspicion of pneumonia should be high and the presence of only one of the three described clinical criteria should lead to more diagnostic tests (188). A high index of suspicion should also be present in patients who have unexplained heodynamic instability or deterioration of blood gases during mechanical ventilation. In the absence of any of these findings, no further studies are required. The incidence of colonization in hospitalized patients in general and even more so in patients who require endotracheal intubation is high (107). Treatment with antibiotics of simple colonization is strongly discouraged. In a significant percentage of cases, it is also found that the routine monitoring of tracheal suction cultures to anticipate etiology a later pneumonia (189). Although these criteria should arouse the suspicion of HAP, confirmation of the presence of pneumonia is much more difficult and clinical parameters cannot be used to define the microbiological etiology of pneumonia. The The diagnosis generally requires a lower respiratory tract culture, but rarely can be made of blood or pleural fluid cultures. Respiratory cultures can include endotracheal suction, BAL or PSB specimens. In general, the sensitivity of blood cultures is less than 25%, and when positive, the organisms can come from an extractive source in a large percentage, even if VAP is also present (190). Although an etiological diagnosis is made of a respiratory tract culture, colonization of the trachea precedes the development of pneumonia in almost all cases of VAP, and thus a positive culture cannot always distinguish a pathogen from a colonizing organism. However, a sterile culture from the lower respiratory tract of an intubated patient, in the absence of a recent change in antibiotic therapy, is strong evidence that pneumonia is not present, and an extrapulmonary place of infection should be considered (191, 192). Moreover, the absence of MDR microorganisms from a lower respiratory sample in intubated patients, in the absence of a change in antibiotics in the past 72 hours, is strong evidence that they are not the cause. The time of clearance of these hard-to-treat microorganisms is usually slow, so even in the face of a recent change in antibiotic therapy sterile cultures may indicate that these organisms are not present (193). For these reasons, a lower respiratory tract sample for culture should be collected from all intubated patients when considering pneumonia. The diagnostic yield and negative predictive value of the expected sputum in undeindubated patients have not been determined. All patients must have obtained an extensive medical history and undergo physical examination to define the severity of HAP, exclude other potential sources of infection and reveal the presence of specific conditions that may affect the likely etiological pathogens (level II) (9, 16, 194). All patients should have a chest X-ray, preferably posteroanterior and lateral, if not intubated, because portable chest X-rays have limited accuracy. The X-ray can help to define the severity of pneumonia (multilobar or not) and the presence of complications, such as effusions or cavitation (level II) (5, 195). Purulent tracheobronchitis may mimic many of the clinical symptoms of HAP and VAP and may require antibiotic therapy, but prospective, randomized studies are needed (level III) (180). Tracheal colonization is common in intubated patients, but in the absence of clinical findings there is no sign of infection and does not require therapy or diagnostic evaluation (level II) (40, 107). Arterial should be measured in all patients to determine the need for additional oxygen. Arterial blood gas should be determined if there is concern about metabolic or respiratory acidosis, and this test is generally needed to manage patients who require mechanical ventilation. This together with other laboratory studies (full blood count, serum electrolytes, kidney and liver function) may indicate the presence of multiple organ dysfunction and thus help define the severity of the disease (level II) (38, 188). All patients with suspected VAP must have collected blood cultures, knowing that a positive result may indicate the presence of pneumonia or extrapulmonary infection (level II) (190). A diagnostic thoracentesis to rule out a complicating empyema or parapneumonic effusion should be performed if the patient has a large pleural effusion or if the patient with a pleural effusion appears toxic (level III) (5). Samples of subspiral pathway secretions should be obtained from all patients with suspected HAP and must be collected before antibiotics are modified. Samples may consist of an endotracheal suction, bronchoalveolaaire coil sample or protected sample (level II) (level II) (183, 184, 192, 196, 197). In the absence of a clinical suspicion of HAP or nosocomial tracheobronchitis, respiratory cultures may not be obtained (level III). A sterile culture of respiratory secretions in the absence of a new antibiotic in the past 72 hours virtually excludes the presence of bacterial pneumonia, but viral or legionella infection is still possible (level II) (192). If these patients have clinical signs of infection, an extrapulmonary site of infection should be investigated (level II) (190, 198). For patients with ARDS, for whom it is difficult to demonstrate deterioration of radiographic images, at least one of the three clinical criteria or other signs of pneumonia, such as hae radish or deterioration of blood gases, should lead to more diagnostic tests (level II) (38). Because the clinical suspicion of HAP/VAP is too sensitive, further diagnostic strategies are needed for optimal management. The objectives of diagnostic approaches in patients with suspected HAP are to determine which patients have lung infection; ensure that appropriate cultures are collected; promoting the use of early, effective antibiotic therapy, where it is possible to streamline or de-escalate where possible; patients who have an additional lung infection (Figure 1). The committee considered two different approaches to management, a clinical strategy and a bacteriological strategy and included characteristics of both in the final recommendations. When the clinical approach is used, the presence of pneumonia is defined by new lung infiltrates plus clinical evidence that infiltrating is an infectious origin. The presence of a new or progressive radiographic infiltrator plus two of the three clinical characteristics (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) represents the most accurate combination of criteria for starting empirical antibiotic therapy (187). Although susceptibility to the presence of pneumonia is increased if only one criterion is used, this is at the expense of leads to significantly more antibiotic treatment. Requiring all three clinical criteria is too insensitive and will result in many patients with real pneumonia who are not receiving therapy. The etiological cause of pneumonia is defined by semi-quantitative cultures of endotracheal aspirates or sputum with initial microscopic examination. Tracheal sucking cultures consistently grow more microorganisms than invasive quantitative cultures, and most microbiology laboratories report the results in a semi-quantitative way, describing growth as light, moderate or heavy. In general, it is rare that a tracheal sucking culture does not contain the pathogen(s) found in invasive quantitative cultures (191, 199, 200). Gram staining of polymoral leukocytes and macrophages and careful examination of the morphology of bacteria that appear to be present can improve diagnostic accuracy when correlated with culture results (201, 202). Conversely, a negative tracheal charge (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value (94%) vap (203). A reliably performed Gram stain of tracheal suctions has been shown to result in a low incidence of inappropriate therapy when used to accompany the first empirical antibiotic therapy (9, 198). The clinical strategy emphasizes rapid empirical therapy for all patients suspected of bite. The driving force behind this strategy is the consistent finding that delay in starting appropriate antibiotic therapy for patients with HAP is associated with increased mortality (37, 112, 204). The selection of the first antibiotic therapy is based on risk factors for specific pathogens, modified by knowledge of local patterns of antibiotic resistance and organism prevalence. The therapy is modified based on the clinical response on days 2 and 3 and the findings of semi-quantitative cultures of lower respiratory secretions. This approach does not require specialized microbiological methods, and all patients suspected of pneumonia are treated. This prevents the problem of not treating some infected individuals. The use of an ICU-specific, broad-spectrum empirical therapy regiment may reduce the incidence of inappropriate initial therapy to less than 10% (198, 205). The main limitation of the clinical approach is that it consistently leads to more antibiotic therapy than when therapy decisions are based on the findings (microscopy and quantitative cultures) of invasive (bronchoscopic) lower respiratory samples (198). The clinical approach is overly sensitive and patients can be treated for when another non-infectious process is responsible for the clinical findings. These processes may include congestive heart failure, atelectasis, pulmonary thromboembolism, pulmonary medication reactions, pulmonary hemorrhage or ARDS. Even if the patient has pneumonia, the dependence on semi-quantic cultures, which separating real pathogens from colonizers can lead to more or broader spectrum antibiotic therapy than with a quantitative approach (198). These cultures have their greatest value if they are negative and the patient has not received any new antibiotics in the last 72 hours. Another concern is that dependence on non-quantitative cultures could lead to a lack of additional lung infection to be recognized at an early time. In an effort to improve the specificity of clinical diagnosis, Pugin and colleagues developed the clinical lung infection score (CPIS), which combines clinical, radiographic, physiological and microbiological data into one numerical result (206). When CPIS was more than 6, a good correlation with the presence of pneumonia, as defined by quantitative cultures of bronchoscopic and non-bronschoscopic BAL specimens, was found. However, in a subsequent study using histology plus immediate postmortem quantitative long-term cultures as a reference standard, CPIS had a sensitivity of 77% and a specificity of 42% (187). A prospective study evaluated 79 episodes of suspected VAP, using the CPIS, and compared the findings with diagnoses established by BAL culture. Overall, the sensitivity and specificity of the score were low, although it improved if a Gram spot of a deep respiratory culture was added to the evaluation (201). The original description of the CPIS required microbiological data and therefore could not be used to screen for HAP. Singh and colleagues used a modified CPIS that was not dependent on culture data to guide clinical management (207). Another approach was to calculate the score using the results of a Gram stain from a BAL sample or blindly protected telescopic catheter sample, and score the findings as positive or negative. With this approach, CPIS for patients with confirmed VAP was significantly higher than the value for unconfirmed VAP (201). If a clinical strategy is used, a re-evaluation of the decision to use antibiotics based on serial clinical evaluations, on day 3 or earlier, is necessary, as patients who improve will have signs of a good clinical response by this time (193, 208). Singh and colleagues have shown that some patients with low clinical suspicion of VAP (CPIS of 6 or less) can safely discontinue antibiotics after 3 days, if the subsequent course suggests that the risk of pneumonia is still low (207). The modified CPIS used by Singh and colleagues seems to be an objective measure to define patients who may receive a short duration of therapy. A reliable tracheal suction stain gram can be used to direct initial empirical antimicrobial therapy and can value of cpis (level II) (191, 199, 201, 209). A negative tracheal suction (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value (94%) vap and should lead to a search for (level II) (203). The presence of a new or progressive radiographic infiltrator plus at least two of the three clinical characteristics (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) represent the most accurate clinical criteria for starting empirical antibiotic therapy (level II) (187). If a clinical strategy is used, a reassessment of the decision to use antibiotics based on the results of semi-quantifying lower respiratory organs and serial clinical evaluations, on day 3 or earlier, is necessary (level II) (193, 205, 207, 208). An amended CPIS of 6 or less for 3 days, proposed by Singh and colleagues, is an objective criterion for selecting patients at low risk for early cessation of empirical treatment of HAP, but still requires validation in patients with more severe forms of VAP (level I) (201, 207). The bacteriological strategy uses quantitative cultures of lower respiratory secretions (endotracheal suctions, BAL or PSB specimens collected with or without bronchoscope) to define both the presence of pneumonia and the etiological pathogen. Growth above a threshold concentration is necessary to diagnose VAP/HAP and determine the causal microorganism(s). Growth below the threshold is believed to be due to colonization or contagion. The bacteriological strategy has been used to steer decisions on whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobials should be used and whether therapy should continue. Because the bacteriological approach emphasizes avoiding the problem of overtreatment with antibiotics by trying to separate colonization from infecting pathogens, the use of this method has consistently led to finding fewer microorganisms that grow above the diagnostic threshold than are present in unqualified cultures of tracheal aspirates. When therapy decisions are based on this data, fewer patients were treated with antibiotics and a possible narrower spectrum of therapy was used, compared to the clinical approach (198, 210). Quantitative cultures have shown that they have a good diagnostic utility for the presence of pneumonia, especially in patients with low or unambiguous clinical suspicion of infection (211, 212). The main concern with the bacteriologic approach is that a false negative culture can lead to a failure to treat a specific patient or pathogen, and that the results are not always consistent and reproducible (213–215). An important factor causing false negative quantitative cultures is a recent onset or change antibiotic therapy, especially in the previous 24 hours, but up to 72 hours (192, 212). Therefore ideally, all quantitative cultures should be obtained before an antibiotic manipulation. This may not be possible in all situations, and in this setting a change in the diagnostic threshold may be useful (212). For BAL, the use of a threshold that is 10 times lower than normal can be a patients who received antibiotics before being tested. However, some patients with pneumonia will have the growth of the culture below the threshold, even without recent antibiotic changes, especially in early forms of infection (215-217). Methodology issues involved in the inconsistent results of published studies are summarized in a meta-analysis (184). These include the evaluation of patients who did not meet approved clinical criteria for the presence of pneumonia; longer time between carrying out a diagnostic test and collecting corroborating histopathological information; admission of patients who had undergone antibiotic therapy before diagnostic tests, often without correcting for the duration of antibiotic therapy; and intake of patients examined by BAL with insufficient lavage volume (less than 140 ml). A major problem with all studies of HAP diagnosis is the lack of a gold standard with which diagnostic results can be compared. Even the best criteria for the presence of pneumonia, immediate postmortem histological evaluation with microbiological confirmation of infection, may be incorrect. In addition, only a subgroup of patients with severe VAP is included in this type of study. In a prospective study of 148 patients on mechanical ventilators suspected of infectious pneumonia, Gibot and colleagues used a rapid immunoblot technique on BAL fluid, and found that levels of soluble triggering receptor expressed on myeloid cells (sTREM-1) were the strongest independent predictor of pneumonia (ratio, 41.5) (218). When this marker is commercially available, in combination with the classic clinical criteria and results of microbiological cultures, can be a valuable tool to increase specificity and maintain the sensitivity of bite diagnosis (197). Histological data have shown several characteristics of VAP that are relevant to diagnostic tests, such as the finding that the process is often multifocal, often involving both lungs, usually in the posterior and lower segments (191, 215, 216). Postmortem studies have also shown that VAP is often in multiple different stages of evolution at different locations at the same time (216). Prior antibiotic therapy can affect the number of bacteria found in lung tissue, and patients who have died despite long-term therapy are likely organisms resistant to the drugs used, while patients started therapy within 24 (and up to 72) hours may have negative cultures, especially if the therapy is adequate (192). The multifocal nature of VAP suggests that BAL and endotracheal suction may provide more representative samples than the protected specimen brush (PSB), which only has one segment. Due to the diffuse bilateral nature of VAP and the prevalence in dependent lung segments, blind BAL and PSB may be as accurate in some patients as bronchoscopic sampling (219). Another problem with the bacteriologic strategy is that that results are not immediately available. Additional tests such as Giemsa stain for intracellular microorganisms, gram stain, or differential cell counts can be used to increase the likelihood of a subsequent positive culture and can be used to guide the need for antibiotic therapy before culture results. In some studies, this approach has led to less use of antibiotics without adverse results and a tendency towards better mortality (198, 201). Not all researchers agree on the safety of withholding therapy until quantitative results are available, and positive, or with the withdrawal of therapy if cultures are negative, after empirically starting antimicrobials for suspected infection (198, 220-222). Clinically, these decisions are guided by the degree of certainty of diagnosing pneumonia at the time of testing (pretest probability), and on the severity of the patient's disease (198). For example, most researchers agree that patients with signs of infection, who are clinically unstable, should receive therapy regardless of the initial bronchoscopic findings (198, 212). The diagnostic threshold to distinguish infection from colonization varies with the technique used, and possibly due to the clinical risk of infection (212). The threshold can be lowered if the patient has recently had a change in antibiotic therapy or if the risk of infection is high. Endotracheal aspirates can be grown quantitatively, and with a threshold of 106 cfu/ml or more, the sensitivity of this method to the presence of pneumonia ranged from 38 to 82%, with an average of 76 ± 9%, and with a specificity ranging from 72 to 85%, with an average of 75 ± 28% (209). Bronchoscopic BAL studies have typically used a diagnostic threshold of 104 or 105 cfu/ml. Samples contaminated with upper airway secretions, as reflected by a high percentage of paving litheel cells, should be used carefully. Some studies have shown that the technique is reproducible, but not all bacteria are recovered above the diagnostic threshold when the procedure is repeated in the same patient at the same location (223). An evidence-based review of 23 prospective studies of BAL in suspected VAP showed a sensitivity of 42-93%, with an average of 73 ± 18% (186), and a specificity of 45-100%, with an average of 82 ± 19%. In 12 studies, the detection of intracellular organisms in 2-5% of recovered cells was used to diagnose pneumonia, with an average sensitivity of 69 ± 20% and a specificity of 75 ± 28% (186). The advantage of searching for intracellular organisms is the ability to obtain information of high predictive value in a fast time frame, without waiting for the results of to define the presence of pneumonia, although not the specific identity of the etiologic pathogene. Quantitative cultures of PSB samples have used a diagnostic threshold of 103 cfu/ml or more. The quality of the PSB sample is difficult to measure, and the reproducibility is not exact, with as much as 25% of the results on the diagnostic threshold, when comparing two samples collected from the same patient at the same location (183). Sensitivity and specificity range from 33 to 100% (average, 66 ± 19%) 50 to 100% (90 ± 15%). PSB seems more specific than sensitive to the presence of pneumonia, and a positive result greatly increases the risk of pneumonia (186). The bacteriological strategy requires specialized laboratory and clinical skills. In many clinical environments, bronchoscopy is not immediately available, especially in the evening, and collecting blind, non-sourceschoscopic samples is an attractive alternative. Blind sampling can be done by BAL or PSB, or a blind bronchial suction sample can be taken. When BAL samples are obtained non-sourceschoscopic, the threshold varies by technique and may differ from that of bronchoscopic BAL. The sensitivities of blind bronchial suction, blind mini-BAL and blind PSB are 74-97, 63-100 and 58-86% respectively(224). The specificity of these methods ranged from 74 to 100% for blind bronchial suction, from 66 to 96% for mini-BAL and from 71 to 100% for blind PSB. In general, these techniques provide data similar to those of samples collected bronchoscopicly, although with a trend towards more cultures above the diagnostic threshold. Side effects should not be greater and possibly less than in bronchoscopicly collected samples. Quantitative cultures can be performed on endotracheal suction or samples collected either bronchoscopic or nonbronchoscopic, and each technique has its own diagnostic threshold and methodology limitations. The choice of method depends on local expertise, experience, availability and cost (level II) (197, 198, 214, 224). To date, several decision analyses, one retrospective study and four prospective studies have evaluated the effect of diagnostic strategies on antibiotic use and the results of patients with suspected VAP (198, 211, 212, 220-222, 225). In three randomized single-center studies, no differences in mortality were found when invasive techniques (PSB and/or BAL) were compared with quantitative or semi-quantial endotracheal suction techniques (220-222). However, these studies included few patients (51, 76 and 88, respectively) and antibiotics were continued in all patients, even patients with negative cultures, denying any of the potential benefits of the bacteriological strategy. In fact, several prospective studies have concluded that antibiotics can be safely stopped in patients with negative quantitative cultures, without adversely affecting mortality (15, 198, 226). A large, prospective randomized study was found to have an advantage for the quantitative approach, compared to a clinical approach in a multicenter study of 413 patients suspected of hap (198). Compared to patients who were clinically managed, those who received invasive management had lower on day 14 (16 and 25%; p = 0.02), but not on day 28, and lower average sepsis-related organ failure ratings on days 3 and 7 (p = 0.04). After 28 days, the quantitative breeding group had significantly more antibiotic-free days (11 ± 9 vs. 7 ± 7 days; p&0.001), but only a multivariate analysis showed a significant difference in mortality (hazard ratio, 1.54; 95% confidence interval, 1.10 to 2.16; p = 0.01). A strength of the study was that a high percentage of patients in both arms received adequate initial antibiotics, although

more patients in the invasive group received adequate therapy than in the clinical group, and the impact of this difference on the mortality differences observed was uncertain. Another important consequence of quantitative culture results was that the presence of clinical symptoms of infection in patients with negative cultures was often an indication that an extrapulmonary site of infection was present. This study clearly showed that the quantitative approach could be applied safely, leading to less antibiotic use and possibly a reduction in mortality. In the study, approximately 10% of patients who received a quantitative strategy under control received antibiotic therapy, regardless of bronchoscopic findings due to the presence of clinical instability and signs of sepsis. Given the available methods of diagnostic testing and the objectives of the timely use of the appropriate therapy, without overuse of antibiotics, the Committee has combined characteristics of the clinical and bacteriological approach into an algorithm shown in Figure 1. The decision to discontinue antibiotics, using this algorithm, may vary depending on the type of respiratory sample that is collected and whether the culture results are reported in quantitative or semiquantitative terms. Proponents of the bacteriological approach support the cessation of antibiotics in clinically stable patients whose quantitative culture results of deep lung samples (BAL or PSB) fall below a diagnostic threshold. The usefulness of quantitative endotracheal sucking up to this decision is not so well defined. Proponents of the clinical strategy generally decide on the cessation of antibiotics based on the patient's clinical course, supplemented by data from quantitative or semi-natal cultures from a lower respiratory tract sample, including an endotracheal sucking, as well as a BAL or PSB sample. A patient with a suspected VAP should have a lower respiratory sample followed for culture and extrapulmonary infection should be excluded as part of the pre-administration evaluation of antibiotic therapy (level II) (198). If there is a high risk of pneumonia, or in the 10% of patients with evidence of rapid therapy is required regardless of whether bacteria are found on microscopic examination of lower respiratory tract samples (level II) (197, 198). Diagnostic techniques that cause etiological pathogens to the basis of qualitative cultures will lead to therapy for more organisms than diagnostic techniques based on quantitative cultures (level I) (198, 220-222). Semi-protein cultures of tracheal aspirates cannot be used as reliably as quantitative cultures to define the presence of pneumonia and the need for antibiotic therapy (level I) (198, 220-222). If bronchoscopic sampling is not immediately available, non-sourceschoscopic sampling can reliably obtain lower respiratory separations for quantitative cultures, which can be used to steer decisions on antibiotic therapy (level II) (224). The use of a bronchoscopic bacteriological strategy has been shown to reduce 14-day mortality, compared to a clinical strategy, in a study of suspected VAP (level I) (198). Delays in starting appropriate antibiotic therapy may increase VAP mortality and therefore therapy should not be delayed for the purpose of conducting diagnostic studies in patients who are clinically unstable (level II) (37, 111, 198). Once the clinical decision has been made to start therapy, the general approach to therapy for suspicious HAP is shown in Figure 2. The selection of antibiotics for each patient should be based on the risk factors for MDR pathogens, summarized in Table 2. The algorithms in Figures 1 and 2 provide the pathways for the selection of suitable antibiotics for the initial management of HAP, VAP and HCAP based on the time of onset of the disease and the risk for MDR pathogens, as described in Tables 3 and 4TABLE 3. First empirical antibiotic therapy for hospital-acquired pneumonia or respiratory pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and possible severity of the diseasePotential PathogenRecommended Antibiotic*Streptococcus pneumoniae†CeftriaxoneHaemophilus influenzae orMethicillin-sensitive Staphylococcusreus auLevoflocin, moxifloxatin, or ciprofloxacinAntibiotic-sensitive enteric gramnegative bacilli or Escherichia coliAmpicillin/sulbactam Klebsiella pneumoniae or Enterobacter speciesErtapenem Proteus species Serratia marcescensTABLE 4. First empirical therapy for hospital-acquired pneumonia, respiratory-related pneumonia, and healthcare-associated pneumonia in patients with late illness or risk factors for multidrug-resistant pathogens and all severity of the diseasePotential PathogensCombination Antibiotic Therapy*Pathogens listed in Table 3 and MDR pathogensAntipseudomonal cephalosporin (cefepime, ceftazidime) Pseudomonas aeruginosaor Klebsiella pneumoniae (ESBL+)†Antipseudomonal carbepenem Acinetobacter species†(imipenem or meropenem)or β-Lact am/β-lactamasemmer (piperacillin–tazobactam) Antipseudomonale fluoroquinolone† (ciprofloxacine of levofloxacin)of Aminoglycoside (amikacine, gentamicine, of tobramycine)plus Methicilline-resistente Staphylococcus aureus (MRSA)Linezolid of vancomycine· Legionella pneumophila†. De adequate dosering van antibiotica voor empirische therapie voor MDR-pathogenen wordt samengevat in in 5TABLE 5. First intravenous, adult doses of antibiotics for empirical therapy of hospital-acquired pneumonia, including respiratory-related pneumonia, and healthcare-associated pneumonia in patients with late illness or risk factors for multidrug-resistant pathogensAntibio ticDosage *Antipseudomonal cephalosporin Cefepime1–2 g every 8-12 hours Ceftazidime2 g every 8 hCarbepenems Imipenem5 00 mg every 6 hours or 1 g every 8 hours Meropenem1 g every 8 hβ-Lactam/β-lactamase inhibitor Piperacillin–tazobactam4,5 g every 6 hAminoglycosiden Gentamicin7 mg/kg per d† Tobramycin7 mg/kg per d† Amikacin20 mg/kg per d†Antipseudomonal quinolones Levofloxacin750 mg each d Ciprofloxacin400 mg every 8 hVancomciney15 mg/kg every 12 h· Linezolid600 mg every 12 o'clock. Broad-spectrum empirical antibiotic therapy should be accompanied by a commitment to de-escalate antibiotics, based on serial clinical and microbiological data, to limit the onset of resistance in the hospital. The antimicrobial spectrum of activity, effective doses of antibiotics, pharmacokinetic profiles, adverse effects of individual antimicrobials and the role of monotherapy were carefully assessed by the consensus committee. Where possible, antibiotic recommendations were based on well-designed, controlled clinical trials, but when such data were not available, the spectrum of activity, pharmacokinetic data and reported clinical experience were taken into account. These initial recommendations for empirical therapy require modification based on knowledge of the predominant pathogens in a specific clinical environment and local patterns of antibiotic sensitivity. Moreover, as soon as the results of respiratory and blood cultures become available, therapy can often be targeted or narrowed (i.e. de-escalation) based on the identity of specific pathogens and their sensitivity to specific antibiotics (Figure 1). The algorithm in Figure 2 will lead many patients to receive initial broad spectrum therapy, as risk factors for MDR pathogens are common, and therefore it is important to use serial clinical evaluations and microbiological data to de-decalize therapy where possible. The most important decision in the first empirical therapy is whether the patient has risk factors for MDR organisms. Previously, the time of the onset of HAP was used to classify patients as early beginnings or late beginnings, depending on whether the infection began within the first 4 days of hospitalization or later (5). However, many patients are admitted after a recent hospitalization or from a health care-associated facility (nursing home, dialysis center, etc.). These patients should be classified as a risk for MDR pathogens, regardless of when, in the time run of the current hospitalization, pneumonia Health-related infections are bacteriologically similar to hospital infections (4, 6, 43, 227). HCAP is defined by a positive respiratory culture, obtained within 48 hours of admission, in the case of a patient who has set out the criteria in Table 2 (43). Most patients with HCAP are at risk of infection with MDR organisms, but studies of HAP and VAP require hospitalization for at least 5 days to increase the risk of infection with these organisms (21, 103). One of the consequences of increasing antimicrobial resistance is an increased risk of inappropriate initial empirical antimicrobial treatment of infections (228). Inappropriate antimicrobial treatment represents the use of antibiotics with poor or no in vitro activity against the identified microorganisms that cause infection at the tissue site of infection (e.g. empirical treatment with nafcilline for pneumonia that has later been documented as MRSA). Because delays in the administration of appropriate therapy have been associated with excessive hospital mortality in HAP (37, 111, 112, 229, 230), the rapid administration of empirical therapy for patients likely to have VAP is essential. Alvarez-Lerma showed that, among 490 episodes of pneumonia acquired in the ICU institution, 214 episodes (43.7%) required change to the initial antibiotic regimen due to either isolation of a resistant microorganism (62.1%) lack of clinical response to therapy (36.0%) (204). The attributable mortality of HAP was significantly lower in patients receiving initial appropriate antibiotic treatment compared to patients who needed a change in treatment (16.2 versus 24.7%; p = 0.034). Iregui and colleagues also documented an adverse outcome with initially delayed appropriate antimicrobial therapy in 107 patients with VAP and examined factors leading to such delays (112). Thirty-three (30.8%) patients received appropriate antibiotic treatment that was delayed for 24 hours or more after patients initially met diagnostic criteria for VAP, often due to a delay in the doctor's recognition of vap presence and writing antimicrobial treatment orders (n = 25; 75.8%). Patients receiving delayed antimicrobial treatment had greater hospital mortality compared to patients without delay (69.7 vs. 28.4%; p&0.001). Delays in the administration of appropriate antibiotic treatment have also been associated with increased mortality for patients with severe sepsis, and with higher hospital costs and length of stay for patients with VAP (231, 232). A consistent factor leading to delays in proper therapy in these studies is the presence of resistant organisms, stressing once again that these pathogens should anticipate when selecting the first therapy in at-risk patients (205, 228). Changing antimicrobial therapy as soon as the culture results are available can excess risk of hospital mortality associated with inappropriate initial treatment with antibiotic therapy (37, 204, 233). Therefore, the selection of the first suitable therapy (i.e. getting antibiotic treatment right the first time) is an important aspect of care for hospitalized patients with serious infections. The The and adequate doses listed in Table 5 are therefore targeted at the pathogens normally associated with inappropriate initial empirical antimicrobial therapy. The most common pathogens are P. aeruginosa, Acinetobacter species, K. pneumoniae, Enterobacter species, and MRSA (37, 111, 204, 228-230, 233). Patients at risk of infection with these organisms should initially be given a combination of drugs that can provide a broad spectrum of coverage to minimize the risk of inappropriate antibiotic treatment. In the therapy of suspected pseudomonal infection, the therapy should include a selected β-lactam plus an antipseudomonal quinolone or an aminoglycoside. The choice of drugs should be based on local patterns of antimicrobial sensitivity, and expected side effects, and should also take into account which therapies patients have recently received (in the past 2 weeks), aim not to repeat the same antimicrobial class, if possible. For the first antimicrobial therapy regimen to take into account local bacteriological patterns, each hospital and each ICU should ideally have their own antibiogram, which is updated as often as possible. Variability in the microorganisms associated with hospital infections between hospitals, as well as within the wards of large hospitals, has been shown to occur (41, 234). In addition, changing temporal patterns of nosocomial pathogens and antimicrobial sensitivity have been described (235). Having current, and often updated knowledge of such data may increase the likelihood that the appropriate initial treatment with antibiotics will be prescribed (205, 235). When patients at risk of infection with MDR pathogens are identified, empirical therapy should be performed with drugs known to be effective against these organisms. Trouillet and colleagues found that 57% of the 135 consecutive episodes were caused by potentially resistant organisms (21). According to the logistic regression analysis, three variables predicted potentially resistant bacterial etiology for VAP: duration of mechanical ventilation, 7 days or more (odds ratio, 6.0); prior antibiotic use (odds ratio, 13.5); and prior use of broad-spectrum medicines (third generation cephalosporin, fluoroquinolon and/or carbapenem) (odds ratio, 4.1). Of 15 different antimicrobial regimens, the combination of a carbapenem, amikacin, and vancomycin provided the widest in vitro coverage against the spectrum of bacteria found in their IC. Ibrahim and colleagues found that the first coverage for P. aeruginosa and methicillin-resistant S. aureus (MRSA), the two most common pathogens causing VAP in their IC, required combination antimicrobial treatment with vancomycin, a carbapenem, and a fluoroquinolone to be in vitro more than 90% of all bacterial isolates (205). These studies suggest that each ICU should collect similar data to establish its own best empirical therapy regimen, tailored to antibiotic sensitivity sensitivity of the local flora. If patients develop HAP during or shortly after antibiotic treatment for another infection, empirical therapy should likely include a drug from another antibiotic class. Recent exposure to a class of antibiotics can predict subsequent resistance to a variety of drugs, usually to the same class, but occasionally to other classes of agents (236). Protocols for the first empirical therapy have emerged as a potentially effective means to prevent unnecessary administration of antibiotics, while increasing the likelihood of initially appropriate therapy. The potential benefits of antibiotic therapy guidelines, through the use of an automated system guiding antibiotic choice based on knowledge of local microbiology and general pharmacological principles, have been demonstrated (113). This system reduced inappropriate empirical antibiotic administration compared to individual physician prescribing practices (237). The use of the automated directive also significantly reduced orders for medicines for which patients were allergic, reduced the overall side effects of antibiotics, reduced the total number of prescribed anti-infectious doses and reduced medical costs associated with antimicrobials (113). Non-automated or partially automated protocols, often driven by hospital-based quality improvement teams, have also demonstrated efficacy. Bailey and colleagues randomized patients at two teaching hospitals to have their doctors contacted by pharmacists with consensus recommendations to stop intravenous antibiotics versus no intervention (238). The intervention significantly reduced antibiotic doses administered and mean antibiotic costs, but was associated with higher labor costs. Similarly, Leibovici and colleagues developed a problem-based database decision support system that significantly reduced the unnecessary use of antibiotics and reduced the administration of inappropriate antibiotics, particularly for patients infected with multidrug-resistant gram-negative isolates, enterococcal and S. aureus (239). Ibrahim and colleagues compared the treatment of 50 patients with VAP in a period without an antibiotic protocol with 52 patients with VAP administered by an ICU-specific protocol (205). The protocol-oriented therapy required initial intravenous combination antimicrobial treatment with vancomycin, imipenem, and ciprofloxacin. The directive also required that antibiotic treatment should be amended after 48 hours on the basis of the available cultural results. De-escalation was achieved in 61.5% of patients. An additional feature of the protocol was an attempt to limit the therapy to a 7-day course of suitable antibiotics for patients with VAP. Administration antimicrobials after day 7 was only recommended for patients with persistent signs and symptoms consistent with active infection (e.g. fever greater than 38.3°C, circulating leukocyte number greater than 10,000 mm-3, lack of x-ray, continued purulent sputum). The use of the Directive was accompanied by a statistically significant increase in the administration of appropriate antimicrobial treatment and a decrease in the development of secondary episodes of antibiotic-resistant VAP. The total duration of antimicrobial treatment decreased significantly to 8.1 ± 5.1 days from 14.8 ± 8.1 days (p&o; 0.001). Use the algorithm in Figure 2 to select an initial empirical therapy based on the absence or presence of risk factors for MDR pathogens (tables 2–4) (level III). These risk factors include a longer duration of hospitalization (5 days or more), admission from a health care-related facility and recent long-term antibiotic therapy (level II) (21, 43). The choice of specific agents should be determined by local microbiology, cost, availability and formula restrictions (level II) (41, 205, 234). Patients with healthcare-related pneumonia should be treated for potentially resistant organisms, regardless of when pneumonia begins during hospital stay (level II) (43). Inappropriate therapy (failure of the etiological pathogen sensitive to the antibiotic administered) is a major risk factor for excessive mortality and length of stay for patients with HAP, and antibiotic-resistant organisms are the pathogens most commonly associated with inappropriate therapy (level II) (228). When selecting empirical therapy for patients who have recently received an antibiotic, it is appropriate to pre-use a drug from another class of antibiotics, as recent therapy increases the likelihood of inappropriate therapy and may be susceptible to resistance to that same class of antibiotics (level III) (236). The first antibiotic therapy should be given immediately, as delays in administration may lead to excessive mortality due to VAP (level II) (37, 112, 231, 232). Initial empirical therapy is more appropriate if a protocol for antibiotic selection is developed based on the recommendations in tables 2–4, but adapted to local patterns of antibiotic resistance, with each IC collecting this information and updating it regularly (level II) (205). Optimal outcome in patients with HAP can best be achieved with the combination of appropriate initial therapy (the etiological organism is sensitive to the therapeutic agent) and an adequate therapy regimen. In order to achieve adequate therapy, it is necessary not only to use the right antibiotic, but also the optimal dose and the correct route of administration (oral, intravenous or aerosol) to ensure that the antibiotic penetrates to the site of infection and to use combination therapy if necessary. When managing VAP, it is important to use doses of antibiotics clinical studies have shown efficacy. For the empirical therapy of severe VAP, the correct doses of commonly used drugs for patients with normal kidney function are thus shown in Table 5 (240–247). Pharmacodynamic properties of van antibiotics should also be considered when selecting an appropriate dosing regimen. Some antibiotics penetrate well and reach high local concentrations in the lungs, while others do not. For example, most β-lactam antibiotics achieve less than 50% of their serum concentration in the lungs, while fluoroquinolones and linezolid are equal to or exceed their serum concentration in bronchial secretions (5, 248). The relevance of these findings to the results in therapy has yet to be defined. The mechanism of action of certain agents may also affect dosage regimens, efficacy and toxicity. Some antimicrobials are bactericide, while others are bacteriostatic. Even among the bactericide agents, various mechanisms of killing may be present. Agents such as aminoglycosides and quinolones are bactericide in a concentration-dependent manner, killing faster at high concentrations. Other agents, such as vancomycin and the β-lactams, are also bactericide, but in a more time-dependent way, with the degree of killing depending on the time the serum concentration is above the minimum inhibitory concentration of the organism (MIC). Another difference is that some antibiotics have a post-antibiotic effect (PAE), which means that these drugs are able to suppress bacterial growth even after the antibiotic level falls below the organism's MIC (5, 249, 250). Gram-negative bacilli have a long-term PAE with the use of aminoglycosides and quinolones. No PAE, or a short PAE against gram-negative germs, is seen with β-lactam antibiotics. An exception is carbepenem antibiotics (imipenem or meropenem), which have shown a post-antibiotic effect against gram-negative bacilli such as P. aeruginosa (5, 251). These pharmacodynamic effects lead to drug-specific dosing regimes. The β-lactams, with minimal concentration-dependent deaths and a limited post-antibiotic effect, are most effective if the levels remain above the MIC of the infecting organism for as long as possible (247). This requires frequent dosing, or even continuous infusion. On the other hand, quinolones and aminoglycosides are less likely to be sedated due to the long-term post-antibiotic effect. In addition, due to their concentration-dependent killing mechanism, efficacy can be improved by using a regimen that maximizes initial serum concentrations. Combining an all-day therapy in a single daily (every 24 hours) dose can benefit from both the concentration-dependent killing mechanism and the post-antibiotic effect. This type of dosing regimen has been applied to the aminoglycosides to maximize efficacy and minimize toxicity, but clinical trials have yielded conflicting results on the success of achieving these goals (252). All HAP and VAP should initially receive intravenous therapy, but conversion to oral/enteral therapy may be possible in certain responsive patients. The quinolones and linezolid have oral formulations with bioavailability equivalent to the this can facilitate conversion to oral therapy in patients with good clinical response (below) and intact gastrointestinal tract function. Studies with quinolones have shown that early step-down to oral therapy is safe and effective (253, 254). Local instillation or aerosolization is a way to improve antibiotic penetration to the lower respiratory tract. In the past, the drugs usually administered and studied in this way are the aminoglycosides and polymyxin B (255, 256). Only one prospective randomized study examined the impact of the additional use of locally instilled tobramycin with intravenous therapy in the treatment of VAP (256). Although the addition of endotracheal tobramycin did not improve clinical outcome compared to placebo, microbiological eradication was significantly greater in patients receiving aerosolized antibiotics. The small number of patients in this study suggests that more data is needed on this type of therapy before its value is determined. Aerosolized antibiotics may also be useful for the treatment of microorganisms that, based on high MIC levels, are resistant to systemic therapy. Anecdotal reports have appeared of patients with VAP due to MDR P. aeruginosa who do not respond to systemic antibiotics, but who have been improved with the addition of aerosolized aminoglycosides or polymyxin B (255). Concerns about aerosolized antibiotics leading to an increased risk of pneumonia due to resistant microorganisms were heightened when these drugs were used as prophylaxis, not as therapy (257). A side effect of aerosolized antibiotics is bronchospasm, which can be caused by the antibiotic or associated dilution substances present in certain preparations. The committee considered that further research into the use of aerosolized antibiotics is warranted.Combination therapy is common in the therapy of suspicious and proven gram-negative HAP. The oft-cited reason for using combination therapy is to achieve synergy in the therapy of P. aeruginosa. However, synergy is clearly documented to be valuable only in vitro and in patients with neutropenia or bacteremmic infection, which is uncommon in VAP (5, 258). The in vitro finding of synergy has been shown to be inconsistent and difficult to demonstrate as clinically relevant (258, 259). Combination regimens are also recommended as a method to prevent the onset of resistance during therapy, a common phenomenon when P. aeruginosa is treated with a variety of individual drugs and when Enterobacter is treated with third-generation cephalosporins (240, 260). Prevention of this type of antibiotic resistance through combination therapy is not well documented (261). A metalyse all prospective randomized trials with β-lactam monotherapy evaluated compared to β-lactam-aminoglycoside combination regimens in patients with sepsis, of whom at least 1,200 of the reported 7,586 patients had HAP or VAP (262). In this clinical failure was more common in combination therapy and there was no benefit in the therapy of P. aeruginosa infections, compared to monotherapy. Moreover, combination therapy did not prevent the onset of resistance during therapy, but led to a significantly higher rate of nephrotoxicity. Despite this data, another reason to use combination therapy, particularly for patients treated according to the regimens in Table 4, is to provide a broad spectrum empirical regimen that is likely to contain at least one drug active against the often MDR etiologicus agent(s). Combination therapy should include drugs from different classes of antibiotics to prevent antagonism from therapeutic mechanisms. For gram negatives, regimens typically involve combinations of two drugs from the β-lactam, quinolone, or aminoglycoside classes. Although quinolones can penetrate the lung better than aminoglycosides and have less potential for nephrotoxicity, a trend towards improved survival has been seen with aminoglycoside-containing, but not with quinolone-containing combinations (259). In some studies, combination therapy has continued less than the entire course of therapy, with discontinuation of the aminoglycoside after 5 days as the patient improves (235). Monotherapy should be used when possible, as combination therapy is often expensive and exposes patients to unnecessary antibiotics, increasing the risk of MDR pathogens and side effects. Patients who develop nosocomial pneumonia without risk factors for resistant organisms may respond to monotherapy with the antibiotics listed in Table 3. Monotherapy is also the standard when gram-positive HAP, including MRSA, is documented. Monotherapy with ciprofloxaline has been successful in patients with mild HAP (defined as a CPIS of 6 or less), but is less effective in severe HAP (207, 240). Drugs that have been shown to be effective as monotherapy in patients with moderately severe HAP not due to MDR pathogens include ciprofloxatin, levofloxatin, imipenem, meropenem, cefepime and piperacillin tazobactam (240, 242–247). For monotherapy, these drugs should be optimally sedated, as discussed above. To use monotherapy in patients with severe VAP, the committee considered that patients should initially receive combination therapy as described in Table 4, but the therapy can be targeted at one drug if the lower respiratory organs did not show a resistant pathogen (205). Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of response to therapy. Dennesen and colleagues showed that when VAP was caused by H. influenzae and S. pneumoniae, the organisms could quickly eradicated from tracheal insusceptions, while Enterobacteriaceae, S. aureus and P. aeruginosa persisted despite in vitro sensitivity to the antibiotics administered (193). For all parameters, usually within the first 6 days after the onset of antibiotics. The result of prolonged therapy up to 14 days or more was newly acquired colonization, especially with P. aeruginosa and Enterobacteriaceae, generally during the second week of therapy. Luna and colleagues, using serial CPIS measurements, found that patients who survived VAP after receiving adequate therapy tended to have a clinical improvement by day 3-5, primarily reflected by an improved PaO2/FiO2 ratio, while non-antirespondent patients had no such response during the same period (208). These data support the assumption that most patients with VAP, who receive the right antimicrobial therapy, have a good clinical response within the first 6 days. Long-term therapy simply leads to colonization with antibiotic-resistant bacteria, which may precede a recurring episode of VAP. Reducing the duration of therapy in patients with VAP has led to good results with less antibiotic use with a variety of different strategies. Singh and colleagues used a modification of the CPIS system to identify low-risk patients (CPIS of 6 or less) with suspected VAP who could be treated with 3 days of antibiotics as opposed to conventional practice of 10 to 21 days of antibiotic therapy (207). Patients receiving the shorter course of antibiotic therapy had better clinical outcomes than patients who received longer therapy, with fewer subsequent superinfections attributed to antibiotic-resistant pathogens, although many of these patients may not have had pneumonia. A multicenter, randomized, controlled trial showed that patients receiving the appropriate, first empirical therapy from VAP for 8 days had results similar to those of patients receiving therapy for 14 days (210). A trend toward greater rates of relapse for short-term therapy was seen as the etiologic agent was P. aeruginosa or an Acinetobacter strain. Empirical therapy of patients with severe HAP or VAP requires the use of antibiotics at optimal doses, to ensure maximum efficacy (level I) (240, 242-247). The first therapy should be administered intravenously to all patients, with a switch to oral/enteral therapy in selected patients with a good clinical response and a functioning intestinal tract. Highly bioavailable drugs, such as the quinolones and linezolid, can easily be switched to oral therapy in such patients (level II) (248, 253, 254). Aerosolized antibiotics have not been proven to have value in vap therapy (level I) (256). However, they may be considered as complementary therapy in patients with MDR gramnegatives who do not respond to therapy (level III) (255). Combination therapy should be used if patients are likely to be infected with MDR pathogens (level II) (21, 205). No data have documented the superiority of this approach compared to monotherapy, except to increase the likelihood of initially appropriate empirical therapy (level I) (262). If patients receive combination therapy with a regimen, the aminoglycoside can be stopped after 5-7 days in responding patients (level III) (235). Monotherapy with selected drugs can be used for patients with severe HAP and VAP in the absence of resistant pathogens (level I) (240, 242-247). Patients in this risk group should initially receive combination therapy until the results of the lower respiratory cultures are known and confirm that one drug can be used (level II). If patients are given an initially appropriate antibiotic regimen, efforts should be made to shorten the duration of treatment from the traditional 14 to 21 days to 7-day periods, provided that the etiological pathogen is not P. aeruginosa, and that the patient has a good clinical response with resolution of clinical characteristics of infection (level I) (210). Although the initial therapy is empirical, it may be possible, based on the recommendations in Tables 3 and 4, modified by knowledge of local microbiological data, to choose a specific agent when an etiological pathogen is identified. Recommended empirical therapy and optimal doses appear in Table 5. The choice of specific agents is determined by the results of sensitivity tests, the availability of these agents, and cost and formula constraint issues. Four MDR pathogens deserve special discussion.P. aeruginosa has the capacity to easily develop resistance to all known classes of antibiotics, and resistance may develop in 30-50% of patients currently receiving monotherapy, but no data show that this problem can be avoided through the use of combination therapy (240, 261). Cross-infection is also a serious problem and the antibiotics given to adjacent patients can affect the risk of infection with an antibiotic-resistant strain. As mentioned, the benefits of combination therapy are unclear, with the only data supporting this practice coming from a study of P. aeruginosa bacteremia (of which few were due to pneumonia) showing that patients receiving combination therapy were less likely to die (258). A prospective study of an aminoglycoside added to a carbapenem showed no improved outcome or difference in the rate of developing resistance during therapy, compared to monotherapy with a carbapenem (261). In another prospective study, combination therapy with β-lactam and twice-daily aminoglycosiden showed an unacceptable 39% success rate for patients with VAP due to P. aeruginosa (263). A metalyse that evaluated the addition of an aminoglycoside to β-lactam monotherapy showed no benefit for the treatment of P. aeruginosa in patients with sepsis (262). All studies of combination therapy an aminoglycoside with a β-lactam, but has not used any daily dosage of the aminoglycoside, nor have they used the maximum effective dose. While a quinolone could be an alternative to an aminoglycoside, with the theoretical benefit of improved respiratory penetration, no prospective study has compared a fluoroquinolone-based combination with β-lactam monotherapy. If a quinolone is used in combination therapy for P. aeruginosa, ciprofloxatin or levofloxatin may be used on the basis of in vitro activity, but should only be used if local sensitivity data show the activity of these agents. This remains a problem because a significant decrease in P. aeruginosa sensitivity to quinolones resulted with widespread use of these drugs in the hospital (264, 265). In these reports, levofloxatin was used at a dosage of 500 mg/day and the effect of using higher dosages (750 mg per day) on resistance patterns is unknown (243). As mentioned, some anecdotal experience has suggested a value of aerosolized antibiotics as a supplement to systemic therapy in patients with highly resistant P. aeruginosa pneumonia (255). The antibiotic armamentarium for the treatment of Acinetobacter is limited because of the native resistance to many classes of antibiotics. The most consistently effective antibiotics are the carbapenems, the sulbactam component of ampicillin sulbactam, and the polymyxins. Although no randomized study has been conducted, a publication of the case series has shown that there are equivalent rates of clinical healing in a population of trauma surgery with ampicillin sulbactam compared to imipenem, including patients with imitable isolates (56). The emergence of karbapenem-resistant clones suggests that optimal doses of carbapenems should be used. The significant nephrotoxicity of the polymyxins limits widespread intravenous use, but there are reports of efficacy with acceptable toxicity, and these drugs can also be used as aerosolized therapy (255, 266). Sensitivity to aminoglycosides is variable and penetration may limit the supply of sufficient tissue levels of antibiotics, indicating a possible role for the supply of aerosols of these agents for selected patients with Acinetobacter pneumonia. One report documented the efficacy and safety of colistin in patients with Acinetobacter VAP who were not sensitive to carbapenems (266). Colistin therapy led to a clinical cure in 57% of patients, and none had prolonged neuromuscular blockage as a side effect of therapy. The characteristic of ESBL-producing Enterobacteriaceae is a variable response to cephalosporins and should therefore be avoided as monotherapy when these pathogens are suspected or isolated (267). In particular, a third generation of cephalosporin should not be used for Enterobacter species due to the documented high frequency of resistance that develops in therapy (260). The use of fourth generation cefepime for this infection is controversial and the safety of the use of cefepime in previously exposed to third-generation cephalosporins is not well documented (267, 268). A reliable choice is a carbapenem, which is generally active against these organisms (269). Because these microorganisms are also likely to demonstrate resistance to aminoglycoides and fluoroquinolones, the benefit of combination therapy is uncertain. Uncertain. has been used to treat VAP, but its efficacy against ESBL+ organisms is uncertain and should be used with caution and at appropriate doses (Table 5) (270). In a prospective analysis of hospital mortality associated with VAP, Fowler and colleagues found that the use of an antipseudomonal penicillin with a β-lactamase inhibitor for VAP was associated with a lower risk of death (hazard ratio, 0.41; 95% confidence interval, 0.21-0.80; p = 0.009) than when other antibiotics were used (259). Although vancomycin is the accepted standard of therapy for this pathogen, both industry-sponsored clinical trials and studies of individual centers have consistently reported clinical failure rates of 40% or more with a standard dose (1 g every 12 hours) ofcomycin for MRSA pneumonia (271-273). Combination therapy with other drugs, such as rifampin (274), aminoglycosides, and others, has been tried, but no prospective clinical data have documented the value of this approach. Retrospective pharmacokinetic modeling has suggested that vancomycin failures may be related to insufficient dosing (272). Many doctors have therefore tried to achieve a trough concentration of 15 mg/L or more, but no prospective clinical data have shown the value of this practice. The use of continuous vancomycin infusions has not been clearly beneficial compared to twice-daily dosing (275). Two new drugs for severe gram-positive infections have been studied in patients with MRSA pneumonia. A prospective randomized study of quinupristin-dalfopristin for gram-positive nosocomial pneumonia found worse clinical success rates than with vancomycin for MRSA HAP (271). Two large multicenter studies with linezolid, on the other hand, showed equivalence in vancomycin in patients with HAP (241, 276). When the two studies were combined and analyzed by multivariate techniques, Linezolid was found to have a significant association with both clinical healing and lower mortality, especially for patients with VAP due to MRSA (241). This benefit may be due to the higher penetration of linezolid into the epithelial lining fluid than with vancomycin (248, 277). However, optimal dosage of vancomycin may not have been achieved in all patients, and potential confirmation of these results is needed. Although linezolid superiority over vancomycin for VAP due to MRSA still requires further validation, linezolid may be preferred in several clinical settings. In patients at risk of, or already having, kidney insufficiency, doctors have a strong tendency to underdose vancomycin, dosing vancomycin in patients with fluctuating kidney function is difficult and requires frequent monitoring of levels. The renal insufficiency was an important predictor of vancomycinphate in a multivariate analysis of patients with VAP (241). Related care is an increased risk of nephrotoxicity in patients with MRSA pneumonia who, along with other other medications, in particular aminoglycosides (275, 278, 279). Antibiotic cycling or rotation has been advocated as a potential strategy for reducing the rise of antimicrobial resistance (280). In theory, a class of antibiotics or a specific antibiotic is taken out of use for a certain period of time and reintroduced at a later date in an attempt to limit bacterial resistance to the cycled antimicrobial agents. When outbreaks of infection with a specific strain of resistant bacteria have occurred, limited access to specific antibiotics has successfully managed the problem, with generally no impact on the overall frequency of resistance (281). However, if disproportionate use of another antibiotic results, resistance rates may be affected. Rahal and colleagues restricted use of third-generation cephalosporins to fight an outbreak of ESBL+ Klebsiella infections (281). Restriction of cephalosporins was accompanied by a 44% reduction in infection and colonization with the ESBL+ Klebsiella. However, the use of imipenem increased by 140% during the intervention year and was associated with a 69% increase in the incidence of imipenem-resistant P. aeruginosa throughout the medical center. The clinical benefit of shifting resistance from one pathogen to another was uncertain. Gerding and colleagues evaluated cycling from aminoglycosides for more than 10 years at minneapolis veterans affairs medical center, cycling amikacin and gentamicin (282). Using cycle times of 12 to 51 months, these researchers found significantly reduced resistance to gentamicin when amikacin was used. Return of resistance with the rapid reintroduction of gentamicin took place, while subsequent, more gradual reintroduction of gentamicin took place without increased resistance levels. This experience suggests that cycling antibiotics within the same drug class, in some circumstances, could be an effective strategy to counter antimicrobial resistance. Kollef and colleagues investigated the influence of a planned change in the preferred antibiotic for empirical therapy of infection on the incidence of nosocomial infections in cardiac surgical ICU (283). A period of 6 months before, during which the traditional practice was to use ceftazidime for the empirical treatment of gram-negative bacterial infections, was followed by a period of 6 months after period, in which ciprofloxaline was replaced. Unexpectedly, the overall incidence of VAP was significantly reduced in the post-period, primarily due to a significant reduction in the incidence of VAP attributed to antibiotic-resistant gram-negative bacteria. Also in the post-period, a lower incidence of antibiotic-resistant gramnegic bacteremia This experience was followed by a series of planned antibiotic changes to treat suspected gram-negative bacterial infections in patients admitted to medical and surgical IUs (284). The result of this policy was an overall improvement in the antimicrobial therapy as MDR infections. Gruson and colleagues observed a decrease in vap incidence following the introduction of an antimicrobial program consisting of guided rotation and limited use of ceftazidime and ciprofloxazale (235). The antibiotic selection was based on monthly assessments of the pathogens isolated from the intensive care unit and their antibiotic sensitivity patterns. They found a decrease in vap incidence, primarily due to a decrease in the number of episodes attributed to antibiotic-resistant gramnegative bacteria, including P. aeruginosa, B. cepacia, S. maltophilia and Acinetobacter baumannii. Their first results could be maintained over a period of 5 years (285). If P. aeruginosa pneumonia is documented, combination therapy is recommended. The main justification is the high frequency of the development of resistance to monotherapy (240). Although combination therapy will not necessarily prevent the development of resistance, combination therapy is more likely to prevent inappropriate and ineffective treatment of patients (level II) (205). If Acinetobacter species are documented to be present,

the most active substances are the carbapenems, sulbactam, colistin, and polymyxin. There is no data documenting an improved result if these organisms are treated with a combination regimen (level II) (56, 266). If ESBL+ Enterobacteriaceae are isolated, monotherapy with a third generation cephalosporin should be avoided. The most active agents are the carbapenems (level II) (267). Additional therapy with an inhaled aminoglycoside or polymyxine for MDR gramnegative pneumonia should be considered, especially in patients who do not improve with systemic therapy (level III) (255). More studies of this type of therapy are needed. Linezolid is an alternative to vancomycin for the treatment of MRSA VAP and may be preferred based on a subset analysis of two prospective randomized studies (level II) (241, 276, 286). This medicine may also be preferable if patients have renal insufficiency or receive other nephrotoxic drugs, but more data are needed (level III). Antibiotic restriction can limit infection epidemics with specific resistant pathogens. Heterogeneity of antibiotic prescriptions, including formal antibiotic cycling, may be able to reduce the overall frequency of antibiotic resistance. However, the long-term impact of this practice is unknown (level II) (284, 285). Empirical antibiotics may need to be adapted as soon as the results of blood or respiratory cultures are available (Figure 1). Modification may be necessary if a resistant or unsuspected pathogen is found in a non-resistant patient. Alternatively, therapy is descaled or narrowed if an expected organism (such as P. aeruginosa or an Acinetobacter species) was not recovered or if the isolated organism is susceptible to a less broad-spectrum antibiotic than was used in the original regimen. Crucial for the use of one of the proposed empirical antibiotic regimens is the ability to recognize when a patient does not respond adequately. Unfortunately, little information is available about the natural course of HAP resolution. In addition, the natural history of the supposed HAP, due to its unreliability in diagnosing the infection, may vary depending on which disease process is actually present in a particular patient. Clinical response may also be related to patient factors (such as age and comorbidity), bacterial factors (such as antimicrobial resistance patterns and virulence) and other events that may occur in the course of HAP. HAP resolution can be defined clinically or microbiologically. Clinical endpoints such as improvement, resolution, delayed resolution, relapse, failure and death can be defined (287). With the help of this approach, clinical improvement is usually apparent after the first 48-72 hours of therapy and therefore the selected antimicrobial regimen should not be altered during this period unless progressive deterioration is noted or initial microbiological studies require it (208, 287). Suitable respiratory organs can be used to define microbiological resolution. Serial cultures can be used to define endpoints, such as bacterial eradication, superinfection (infection with a new organism), recurrent infection (elimination, then return, of the original organism), or microbiological persistence. Serial quantitative microbiological studies of lower respiratory secretions can also define resolution endpoints (193). In one such study, repeat PSB samples collected 72 hours after starting therapy were used to define the bacteriological response to the therapy. The results of these microbiological evaluations were compared with the clinical outcome (288). When the follow-up PSB sample showed no growth or less than 103 cfu/ml, clinical failure occurred only 7% of the time, while a finding of more than 103 cfu/ml (microbiological failure to eradicate) was associated with clinical failure in 55.8% of patients. At present, the use of early recognition of a microbiological non-response to changing therapy has not been prospectively investigated. Breast X-rays are of limited value for defining clinical improvement in severe pneumonia, and the initial radiographic deterioration is common, especially in patients who are bacteremic or infected with highly virulent organisms. Moreover, radiographic improvement often lags behind clinical parameters, especially in the elderly and in people with coexisting diseases (e.g. chronic obstructive pulmonary disease) (208). The finding of a rapidly deteriorating pattern, with a follow-up breast radiography showing progression towards multilobar involvement, an increase of more than 50% in the extent of infiltration within 48 hours, the development of cavitary diseases or significant pleural effusion, should raise concerns (5). Clinical parameters, including white white cell count and measurements of oxygenation and core temperature have been used in several studies to define hap's normal resolution pattern. Dennesen and colleagues showed that in patients treated with the first appropriate antibiotic therapy, clinical improvement of these parameters gradually occurred during the first week of antibiotic treatment (193). Little further improvement in fever, the number of white blood cells, or the PaO2/FiO2 ratio occurred after 7 days of antibiotic treatment. Similarly, Luna and colleagues used changes in CPIS as a measure of resolution or deterioration in patients with VAP, rather than its traditional application as a tool to diagnose pneumonia (208). Improving CPIS during the first 3 days of empirical treatment was associated with hospital survival, while a lack of improvement in CPIS predicted mortality. Inappropriate treatment with vap antibiotics was also associated with a lack of clinical improvement in CPIS, particularly in serial measurements of arterial oxygen. There are several possible causes for rapid deterioration or failure to improve. These include the possibility that the process being treated is not pneumonia or that certain host, bacterial and therapeutic (antibiotic) factors have not been taken into account (Figure 3). Many non-infectious processes can be wrongly labeled hap, including atelectasis, congestive heart failure, pulmonary embolism with infarction, lung contusion (in trauma patients), and chemical pneumonitis of aspiration. Patients with ARDS may have fibroproliferative diffuse alveolar damage, while any mechanically ventilated patient may have a pulmonary hemorrhage (195, 289). In one series, 26 of the 69 ventilated patients with new lung infiltrates had a pulmonary hemorrhage during the autopsy, sometimes in combination with pneumonia (195). Host factors associated with a failure to improve during empirical therapy include the presence of a condition known to increase mortality. These include prolonged mechanical ventilation, respiratory failure, an underlying fatal condition, age greater than 60 years, bilateral radiographic infiltrators, prior antibiotic therapy, prior pneumonia (i.e., the current episode represents superinfection), and/or chronic lung disease (12, 13, 287, 290). Bacterial variables may also be associated with a negative outcome of the first therapy. The infecting pathogen may initially be resistant to the chosen antibiotic or may gain resistance during therapy, in particular P. aeruginosa treated with a single agent (240). Some organisms are inherently difficult to eradicate, even with effective therapy (288). In a study of P. aeruginosa pneumonia on IC, 20 of the 34 patients survived an initial episode of infection. However, among survivors, recurrent infection, as defined by clinical, radiographic and bacteriological criteria, developed in 50% (291). Certain types of infections are associated with a bad outcome, outcome, those with gram-negative bacilli, polymicrobial flora, or bacteria that have acquired antibiotic resistance (10, 290). In patients who are mechanically ventilated, superinfection with P. aeruginosa or Acinetobacter species has a particularly high mortality rate, which is approaching 90% in some series (292). Finally, pneumonia may be due to other pathogens (i.e. Mycobacterium tuberculosis, fungi or respiratory viruses) or an unusual bacterial pathogen not included in the original empirical regimen. In addition, some patients may have clinically unrecognized immunosuppression (e.g. acquired immunodeficiency syndrome), and unrecognized pneumocystis carinii pneumonia may be a cause of unresponsive therapy. Certain complications during therapy can also lead to an apparent failure in response to therapy. Some patients with HAP may have other sources of fever at the same time, in particular sinusitis, vascular catheter-related infection, pseudomembranous enterocolitis or urinary tract infections (109, 293). Complications of the original pneumonia can also lead to failure, including the development of lung abscess or empyema. Other considerations for persistent fever or pulmonary infiltrates include drug fever, sepsis with multiple organ failure of the system, or pulmonary embolism with secondary infarction. For patients who are rapidly deteriorating or unresponsive to the first therapy (figures 1 and 3), it may be necessary to broaden antimicrobial coverage pending the results of cultures and other diagnostic studies. An aggressive evaluation is required for this type of individual, starting with careful differential diagnosis and repeated sampling of lower respiratory secretions for culture and antimicrobial sensitivity patterns. This can be done by collecting an endotracheal supplement if the patient is intubated, or by a bronchoscopic procedure with quantitative cultures for both intubated and unintated patients. Although patients are given antibiotics in this clinical environment, recovery with invasive methods of organisms at high concentrations may indicate that infection with a resistant organism is present (192). If cultures exhibit a resistant or unusual pathogen, the therapy can be changed appropriately. If cultures do not exhibit a resistant or unsuspected pathogen, attention to a non-infectious process or one of the previously discussed complicating problems is appropriate. This requires changing vascular access catheters and growing blood, catheter line tips that have been removed, and urine, as well as other easily accessible sites. Specialized radiological procedures can be useful in identifying anatomical reasons for failure. Lateral pressure ulcer chest ultrasound, or automated tomographic scanning can reveal pleural fluid, which must be evaluated to exclude empyema. In addition, automated tomographic scanning can separate pleural fluid from parenchymal disease and can adenopathy, and lung masses. Automated tomographic scanning of extrathoracic sites can also help to identify other areas of infection, and particular attention should be focused on the abdomen in patients taking ARDS (294). An often infected site in patients with nasotracheal or nasogastric tubes in place is the sinuses, and automated tomographic scanning can identify opacification or the presence of an air-fluid level in the sinuses. When these findings are present, sinusaspiration and culture may be necessary and may define the presence of infection, which can often exist alongside HAP (109). Evaluation for pulmonary embolism may be necessary for selected patients, because a lung infarction can be confused with pneumonia. If this microbiological and radiographic evaluation is negative, it should be decided whether the patient should be observed while continuing or empirically altering antibiotics or performing an open lung biopsy to obtain the diagnosis of an unusual pathogen or of a non-contagious disease that mimics pneumonia. There is debate about the value of open lung biopsy in non-immune patients with suspected HAP, VAP or HCAP. The available evidence does not indicate a clear result advantage, and therefore the decision should be individualised. Bronchoscopy that does not demonstrate unusual or resistant organisms, along with an aggressive but non-performing search for extralong infectious foci, should be performed before performing an open lung biopsy. Even if bronchoscopic cultures and other diagnostic tests are not useful, the decision to perform an open biopsy should be guided by the patient's clinical status. If there is slow but progressive improvement, close observation alone can be the most appropriate course. If the patient remains hemorrnamically stable, but shows no evidence of clinical improvement, and does not reveal bronchoscopic and radiological evaluations, a change in antibiotics or initiation of inflammatory therapy (corticosteroids) may be appropriate before proceeding with an open biopsy. However, if the patient deteriorates early (within the first 48-72 hours of therapy) or is initially improved, but then deteriorates, additional antibiotics targeting resistant or unusual bacteria can be added while doing aggressive radiographic and microbiological evaluations. A serial assessment of clinical parameters should be used to define the response to the first empirical therapy (level II) (193, 208). Changes in empirical therapy should be made on the basis of this information, in combination with microbiological data (level III). Clinical improvement usually takes 48-72 hours, and so therapy should not be changed at this time unless there is a clinical decline (level III). Failure to respond to therapy is usually evident on day 3, using an assessment of clinical parameters (level II) (193, 208). Responding patient must have de-escalation of antibiotics, narrowing therapy narrowing therapy the most targeted regime possible based on culture data (level II) (205). The non-resistant patient should be assessed for non-contagious imitations of pneumonia, unsuspected or resistant organisms, additional lung sites of infection, and complications of pneumonia and its therapy. Diagnostic tests should be directed at which of these causes is likely (level III) (293). Hap guidelines circulate to the right medical staff (quality and safety administrators, doctors and nurses) for assessment. Provide epidemiological data on prevalence and types of MDR pathogens in intensive care ward patients and current antibiotics to select the appropriate initial antibiotic therapy. Select specific parts of the guideline for implementation by medical and surgical services, including intensive care units, and check compliance with HAP patient outcome guidelines. Identify modipaable risk factors for HAP and develop programs to reduce the risk of pneumonia by changing these risk factors. Co-CHAIRS: MICHAEL S. NIEDERMAN, M.D.* and DONALD E. CRAVEN, M.D.*#Committee Members MARC J. BONTEN, M.D.*#JEAN CHASTRE, M.D.*#WILLIAM A. CRAIG, M.D.#JEAN-YVES FAGON, M.D.*#JESSE Hall, M.D.*GEORGE A. JACOBY, M.D.#MARIN H. KOLLEF, M.D.*CARLOS M. LUNA, M.D.*LIONEL A. MANDELL, M.D.#ANTONIO TORRES, M.D.* #RICHARD G. WUNDERINK, M.D.**ATS member#ISDA member1. Niederman MS. Guidelines for managing respiratory infection: why do we need them, how should they be developed and can they be useful? Curr Opin Pulm Med 1996;2:161–165. 2. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatal accident in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 1986;133:792–796. 3. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R, Healthcare Infection Control Practices Advisory Committee, Centers for Disease Control and Prevention. 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