CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

ETIOLOGY DIAGNOSIS AND MANAGEMENT OF SEVERE PNEUMONIA IN INTENSIVE CARE UNIT

[1]-Abdullah Ahmed Bawazir
[2]-Sakhr Mohammed Alghamdi
[3] - Jamal Sharaf Alzahrani
[4]- awad hassan alamri
[5]- Roaa Khaled Alhelfawi
[6]- Abdulhamid Abdulnaeim Alsaigh
[7]-Salha Abdulghani Abdullah
[8]-Abdullah Abdulghani Abdullah

Article Received: August 2022 **Accepted:** September 2022 **Published: September** 2022

Abstract:
Severe pneumonia is a common condition encountered by intensive care clinicians. Recent results regarding microbiology, diagnosis, and treatment, particularly the care of critically ill patients with acute respiratory failure, are highlighted in this article. Comprehensive search through electronic databases; PubMed and Embase for all relevant articles published in English language up to the middle of 2022. Despite advances in antimicrobial and life-supporting treatments, severe pneumonia remains the leading cause of admission to the intensive care unit (ICU) and death. Immediate and effective antimicrobial treatment is necessary.

Corresponding author:
Abdullah Ahmed Bawazir,

QR code

Please cite this article in ***Abdullah Ahmed Bawazir*** *et al,* ***Etiology Diagnosis And Management Of Severe Pneumonia In Intensive Care Unit.,*** *Indo Am. J. P. Sci, 2022; 09(09).*

INTRODUCTION:

The high mortality and morbidity rate attributed to severe pneumonia episodes in intensive care unit (ICU) patients is a serious concern for clinicians [1,2]. During the past several decades, numerous measures have been introduced to maximize the prognosis of patients with severe lung infections, with a portion of these efforts centered on the need to identify and predict sickness severity as accurately as possible [3,4]. In addition to other clinical scores, the most recent Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines have evaluated major and minor criteria that appear to best define the severity of community-acquired pneumonia (CAP) and determine the need for ICU admission [5,6].

Gram-negative germs remain the leading cause of ventilator-associated pneumonia (VAP). In this community, Pseudomonas aeruginosa and Acinetobacter baumani are among the most common isolates. These microorganisms are associated with greater mortality rates than other microorganisms (71% versus 41% in one study); they typically appear in individuals who have been treated with antibiotics; and they are frequently resistant to multiple drugs [1]. Staphylococcus aureus is now equally prevalent in various locations and is associated with 20% to 33% of VAP patients. Compared to methicillin-sensitive S. aureus, methicillin-resistant strains (MRSA) are associated with a greater incidence of bacteremia, shock, and mortality (54.5% versus 2.6%, respectively) [6]. Similar to P. aeruginosa, past antibiotic treatment is a significant risk factor for MRSA pneumonia. A greater prevalence of MRSA in the community is also cause for concern. In up to forty percent of cases, polymicrobial infections can complicate therapy. Even though they are uncommon, epidemics can develop in hospitals due to polluted water (legionellosis), respiratory equipment (Pseudomonas), or viral outbreaks. If patients develop pneumonia symptoms within the first 48 to 72 hours of hospitalization, community-acquired pathogens must be examined (early onset VAP)

VAP risk factors include shock, multiorgan failure, progressive respiratory failure, underlying illness that is eventually or swiftly deadly, age over 60, supine position, and improper or past antibiotic treatment. On a ventilator, the risk of developing pneumonia is estimated to be roughly 1% every day for the first 30 days [5]. There are few data about long-term dangers beyond this point.

Notably, these scores were developed for severe CAP (SCAP), and their relevance to other categories of severe pneumonia must be extrapolated. In addition, it may be challenging to determine whether a pneumonia is truly community-acquired (CAP), healthcare-associated (HCAP), or hospital-acquired (HAP). [7,8]. ICU-admitted critically sick patients may develop severe pneumonia [9] [ventilator-associated pneumonia (VAP); nonventilator ICU-acquired pneumonia (NV-ICUAP)]. Both nosocomial and community-acquired pneumonia can proceed to acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), which are linked with a death rate of over 50% [10].

This review aims to discuss the proper management approaches of sever pneumonia for those patients admitted to intensive care unit.

DISCUSSION:

Agents causing severe pneumonia may vary widely, primarily based on demographic and clinical characteristics (Table 1). Up to 10% of hospitalized CAP patients require severe treatment due to respiratory failure necessitating mechanical ventilation and/or septic shock [11]. The prevalence of microbiologically confirmed CAP among in-patients is around 25%, although the proportion of isolated pathogens in SCAP may be higher due to the availability and extensive use of more accurate diagnostic methods in ICU [12,13]. In a recent cohort study, Restrepo et al. [1] identified Streptococcus pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa as the most prevalent pathogens isolated from patients admitted to the intensive care unit (ICU) with severe pneumonia. S. pneumoniae, historically known as 'Captain of Men of Death' [14], harbors virulence factors that can induce an unbalanced systemic inflammatory response syndrome (SIRS) responsible for the severity of the disease, and this condition has been shown to be associated with specific host genotypes [15]. Legionella pneumophila is a well-known causative agent of SCAP, and immune-mediated extrapulmonary involvement [16] is frequently documented. Due to its propensity to create several virulence factors and protective biofilms [17], the mortality rate of Pseudomonas SCAP may be very high. S. aureus, the causal agent of SCAP, can be isolated from influenza patients. In addition, the rate of methicillin resistance among patients with severe community-acquired lung infections is steadily increasing [18]. 79% of the 128 patients with S. aureus CAP investigated by Taneja et al. [19] were hospitalized to the intensive care unit, and 24 died. 43

individuals showed positive first cultures for methicillin-resistant strains [19]. Viruses such as adenovirus, respiratory syncytial virus, seasonal influenza, and parainfluenza are frequently found in respiratory samples, frequently in conjunction with mixed bacterial infections. In 214 countries, influenza A (H1N1 2009) of swine origin caused 18,000 deaths among middle-aged patients (20–40 years), whereas obesity and pregnancy revealed to be significant risk factors for the development of severe respiratory complications (ALI/ARDS) [20]. Other pulmonary pathogens, including bacteria, viruses (herpesviruses), fungi (Aspergillus spp., Pneumocystis jiroveci, particularly in patients with human immunodeficiency virus, Cryptococcus neoformans, and endemic mycoses), and parasites, may cause respiratory insufficiency in immunocompromised patients [21]. The true bacterial epidemiology of HCAP remains problematic, as approximately fifty percent of these pneumonia cases are culture-negative [22]. Nonetheless, episodes severe enough to necessitate intensive therapy are better documented microbiologically and are typically caused by multidrug-resistant (MDR) bacteria [23]. A quarter of HCAP patients die as a result of the severity of the condition [24,25]. Schreiber et al. [26] retrospectively studied 190 cases of severe pneumonia (ARDS rate of 37%) and found that the most frequently isolated bacteria in HCAP episodes were methicillin-resistant S. aureus (MRSA) and P. aeruginosa. S. pneumoniae and S. aureus sensitive to methicillin were the most frequently isolated pathogens in SCAP patients. Six major MDR bacterial species have been identified as HAP/VAP causal agents: S. aureus, P. aeruginosa, Klebsiella spp., Escherichia coli, Acinetobacter baumannii, and Enterobacter spp. Despite ICU admission, the high incidence of medication resistance and the presence of several comorbidities are responsible for significant fatality rates [27]. Recently, Esperatti et al. [28] observed in a large prospective cohort of ICU-acquired pneumonia that the causal agents (mostly P. aeruginosa and S. aureus) in non-ventilated patients were identical to those causing VAP., with similar mortality rate (42 vs. 36%; P ¼ 0.4).

TABLE 1: Most common causes of severe pneumonia

SCAP (mainly drug-susceptible strains)	Severe HCAP/HAP/'late onset' VAP (mainly multidrug-resistant strains)
• *Streptococcus pneumoniae*	• *Pseudomonas aeruginosa*
• *Staphylococcus aureus*	• Enterobacteriaceae (*Klebsiella pneumoniae*; *Escherichia coli*; *Enterobacter* spp.)
• *Legionella* spp.	• *Staphylococcus aureus*
• Gram-negative bacilli	
• Virus and fungi (mainly in immmunosuppressed population)	

HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; SCAP, severe community-acquired pneumonia; SP, severe pneumonia; VAP, ventilator-associated pneumonia.

Blood and lower respiratory tract samples for culture should be taken from all patients with severe pneumonia prior to treatment [29]. In a recent retrospective study with 3116 consecutive patients with CAP, Falguera et al. [30] created a six-variable score for predicting the probability of bacteremia. Patients with a score value of at least 2 exhibited a bloodstream infection rate between 16 and 63%, according to the investigators. Urinary antigen tests to detect S. pneumoniae and L. pneumophila infections are available [5]. High diagnostic accuracy, fast availability of results, and strong performance under antibiotic therapy are the primary benefits of their use. The Legionella urine antigen test has great specificity (0.99), but lower sensitivity (0.74), according to a meta-analysis; nonetheless, the authors noted poor study quality and publication bias [31]. A recent prospective study of 171 adult patients hospitalized with CAP (ICU admission, 8%) found that the pneumococcal urine antigen test has a sensitivity of 71% and a specificity of 96% [32]. The diagnostic reliability of deep cough-produced sputum and nasopharyngeal aspirates is questionable [33] in patients with severe pneumonia who have not yet received endotracheal intubation (ETI). Noninvasive ventilation (NIV) permits fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) in hypoxemic patients with pneumonia without increasing the work of breathing during FOB [34,35]. Many writers discourage the routine use of endotracheal aspirate for microbiological sampling in patients undergoing ETI. Protected specimen brushing

(PSB) and FOB with BAL or miniBAL (done without fiberoptic guiding) are invasive techniques used to diagnose severe pneumonia microbiologically in ICU patients. Literature-based evidence does not support the use of bronchoscopic procedures over 'blind' techniques; hence, the decision is solely dependent on institutional resources and experience. The Gram stain of respiratory samples, which is accessible within a few hours, can assist doctors in restricting or expanding the antimicrobial spectrum [11]. Current research supports the use of quantitative cultures in diagnosing bacterial pneumonia in intubated patients [36]. Early molecular detection approaches, predominantly utilizing polymerase chain reactions (PCRs) in real-time, are being developed [37]. Regarding the bacterial etiology, multiplex amplification assays may discover commonly involved species, and in situations of hospital-acquired infections, resistance gene targets may also be detected [38]. A recent Swedish study from the Karolinska University Hospital compared traditional diagnostic methods with PCR-based methods in 124 patients with CAP (6% were treated in the ICU) [38]. The scientists discovered that the deployment of this molecular method resulted in a greater microbiological yield, with S. pneumoniae and respiratory viruses coexisting often. Despite the potentially immense benefits of PCR-based diagnostic procedures (rapidity, sensitivity, and simplicity), there are some drawbacks, such as the need for a quantitative cutoff to discriminate.

Diagnostic and management approaches:

The use of invasive vs noninvasive procedures to diagnose and whether the invasive approach has a demonstrated impact on patient outcome are major grounds of debate. Clinical criteria for determining the presence or absence of pneumonia have a relatively low predictive value, which has sparked the dispute. (A) new or worsening infiltrates, (B) fever, (C) purulent sputum or tracheal secretions, and (D) peripheral leukocytosis or leukopenia were the traditional diagnostic criteria for pneumonia. The diagnostic threshold for pneumonia is three out of four. In the ICU, however, these markers are utilized less frequently. Noninfectious causes of fever include medications, systemic inflammatory response syndrome (SIRS), pulmonary thromboembolic disease (PTE), and extrapulmonary infections. Similarly, the chest radiograph's sensitivity and specificity may be greatly diminished. Pulmonary contusions, aspirated blood, pulmonary infarctions, and atelectasis are all examples of potentially confusing results. Frequently, the quality of portable films is low, which further diminishes their utility. Acute lung damage or ARDS is a particularly worrisome finding. In an autopsy analysis of 47 ARDS patients, Bell et al. [39] found a 10% false-positive rate for pneumonia and a 62% false-negative rate when clinical suspicion was used as the diagnostic criterion. In the same study, antibiotic response did not predict the presence or absence of infection at autopsy. Gram staining and culture of endotracheal aspirates cannot differentiate between colonization and infection. Standard Gram staining or culture has been linked to overtreatment, putting patients at risk for infection with highly resistant pathogens such as P. aeruginosa or MRSA.

Invasive and noninvasive procedures

To increase diagnostic accuracy, invasive bronchoscopy procedures such as protected specimen brushing (PSB) and bronchoalveolar lavage were developed (BAL). Bronchoscopy enables one to circumvent potential contamination from the upper airway and proximal tracheobronchial tree. PSB utilizes a microbiologic brush designed to collect about 0.1 mL of respiratory secretions. Single or double lumen catheters with a wax stopper to prevent contamination are available. Under direct visualization, the catheter is guided to the target region by the working channel. The brush is advanced, dislodging the plug, which then evaporates, and bronchial secretions of interest are sampled. The brush is retracted back into the catheter and then the bronchoscope is removed. The brush tip is removed with sterile scissors, placed in 1 mL of preservative-free saline, manually vortexed, and transported to the microbiology lab for quantitative culture [39,40].

Empirical therapy:

The selection of empiric antibiotic coverage for VAP is influenced by suspected pathogens and local resistance tendencies. In most series, including the comprehensive National Nosocomial Infection Surveillance Program data, P. aeruginosa and S. aureus are the major causes of VAP. Initial coverage must include antimicrobial medicines active against these pathogens [40].

Gram-negative bacilli: The standard treatment for pseudomonal pneumonias has been a combination of a b-lactam and an aminoglycoside to take advantage of the synergistic action of both medications. Known issues with aminoglycosides include renal and ototoxicity. In order to reduce renal damage while retaining antimicrobial activity, once-daily dosage has been utilized. This approach exploits the delayed post-antibiotic action of aminoglycosides on gram-negative bacteria. Fluoroquinolones may be substituted for aminoglycosides to prevent renal damage in high-risk

patients. It has been shown that b-lactams and fluoroquinolones exhibit synergistic action in vitro. Ciprofloxacin has the strongest activity against P. aeruginosa among the currently available fluoroquinolones and is the medication of choice in this class [41].

In terms of survival, studies using VAP have failed to provide a clear advantage for either monotherapy or double coverage. Possible exception is A. baumani, which, like Pseudomonas, has a tendency to develop resistance during monotherapy. In some circumstances, the presence of multi-resistant gram-negative pathogens in some intensive care units is a challenging concern. In such cases, empiric coverage may entail the use of two or even three antibiotics in order to ensure treatment with an appropriate drug. Similar to what is done for tuberculosis, some authorities have recommended utilizing multidrug therapy to prevent the establishment of resistance. There are currently no statistics to support such a strategy. In addition, in contrast to outpatient tuberculosis treatment, the ICU population is typically very unwell, has multiorgan failure, and is more prone to pharmaceutical side effects. These patients are also taking numerous drugs that can interact in a negative way [41].

Gram-positive organisms have superseded gram-negative organisms as the most prevalent pathogen in certain regions. Gram-positive organisms are becoming increasingly widespread as causes of nosocomial infection. S. aureus and P. aeruginosa co-occur in 20% to 30% of all instances of ventilator-associated pneumonia (VAP). Due to the high prevalence of MRSA and its relationship with higher morbidity and mortality, empiric coverage with vancomycin is required. The rise of resistant enterococci explains the reluctance to suggest vancomycin for prophylactic usage. There are currently isolated instances of staphylococcal isolates with low levels of vancomycin resistance. Although methicillin-resistant staphylococci are adequately treated with bactericidal penicillins, it is sometimes feared that vancomycin's therapeutic efficacy in treating MRSA is inadequate. Although this may be a result of host response rather than the drug itself, there is a definite need for new effective anti-MRSA medications, particularly if vancomycin resistance becomes a clinical reality. For the treatment of severe MRSA infections, some experts propose adding rifampin or an aminoglycoside to vancomycin. In certain clinical scenarios, additional empiric coverage may be added, such as anaerobic coverage if large aspiration is part of the clinical picture or antiviral or legionella coverage in cases of known nosocomial epidemics. Response to treatment can vary widely amongst patients. It is typical for 48 to 72 hours to pass before clinical improvement develops in response to successful medication. Initial selection is the most significant predictor of survival. Before proclaiming a treatment failure, a reasonable amount of time should elapse, unless objective proof implicates a novel or resistant organism.

CONCLUSION:

Severe pneumonia is a frequent cause of ICU admission. Given the necessity of early treatment of critically sick patients, a rapid recognition of those illnesses that require ICU management is vital. Depending on epidemiological and individual risk variables, causative agents can vary significantly. Rapid microbiological diagnosis is necessary in order to avoid incorrect empirical treatment and early clinical failures. By applying pharmacodynamic/pharmacokinetic criteria, it is possible to optimize the efficacy of antimicrobials. Few data are available to support the use of pharmacological therapies other than traditional antibacterial therapy. Patients with severe pneumonia often develop severe acute respiratory failure needing invasive or noninvasive mechanical ventilation. Innovative measures, such as extracorporeal oxygenation, are currently accessible and may represent the treatment of the future for a historically prevalent disease.

REFERENCES:

1. Restrepo MI, Mortensen EM, Velez JA, et al. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. Chest 2008; 133:610–617.
2. Kollef KE, Schramm GE, Wills AR, et al. Predictors of 30-day mortality and hospital costs in patients with ventilator-associated pneumonia attributed to potentially antibiotic-resistant Gram-negative bacteria. Chest 2008; 134:281– 287.
3. Restrepo MI, Anzueto A. Severe community-acquired pneumonia. Infect Dis Clin North Am 2009; 23:503–520.
4. Brown SM, Dean NC. Defining and predicting severe community-acquired pneumonia. Curr Opin Infect Dis 2010; 23:158–164. In this review new predictive models and approaches aimed to describe pneumonia severity are discussed.
5. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases

Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44 (2 Suppl): 27–72.
6. Chalmers JD, Taylor JK, Mandal P, et al. Validation of the Infectious Diseases Society of America/American Thoracic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. Clin Infect Dis 2011; 53:503–511.
7. Restrepo MI, Jorgensen JH, Mortensen EM, Anzueto A. Severe community acquired pneumonia: current outcomes, epidemiology, etiology, and therapy. Curr Opin Infect Dis 2001; 14:703–709.
8. Zilberberg MD, Shorr AF. Healthcare-associated pneumonia: the state of evidence to date. Curr Opin Pulm Med 2011; 17:142–147. A comprehensive review on ongoing concerns regarding the management of HCAP.
9. Muscedere JG, Day A, Heyland DK. Mortality, attributable mortality, and clinical events as end points for clinical trials of ventilator-associated pneumonia and hospital-acquired pneumonia. Clin Infect Dis 2010; 51 (1 Suppl): 120–125.
10. Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome: a clinical review. Lancet 2007; 369:1553–1564.
11. Niederman MS. Recent advances in community-acquired pneumonia: inpatient and outpatient. Chest 2007; 131:1205–1215.
12. Paganin F, Lilienthal F, Bourdin A, et al. Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. Eur Respir J 2004; 24:779–785.
13. Yoshimoto A, Nakamura H, Fujimura M, Nakao S. Severe community-acquired pneumonia in an intensive care unit: risk factors for mortality. Intern Med 2005; 44:710–716.
14. Osler W. The principles and practice of medicine. 4th ed. New York: Appleton; 1901. p. 108.
15. Calbo E, Garau J. Factors affecting the development of systemic inflammatory response syndrome in pneumococcal infections. Curr Opin Infect Dis 2011; 24:241–247. This recent review analyzes those factors influencing the severity of systemic inflammatory response syndrome during pneumococcal infection.
16. Carratala` J, Garcia-Vidal C. An update on Legionella. Curr Opin Infect Dis 2010; 23:152–157.
17. Rello J, Rodriguez A, Torres A, et al. Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. Eur Respir J 2006; 27:1210–1216.
18. Garau J, Bouza E, Chastre J, et al. Management of methicillin-resistant Staphylococcus aureus infections. Clin Microbiol Infect 2009; 15:125–136.
19. Taneja C, Haque N, Oster G, et al. Clinical and economic outcomes in patients with community-acquired Staphylococcus aureus pneumonia. J Hosp Med 2010; 5:528–534.
20. Ramsey C, Kumar A. H1N1: viral pneumonia as a cause of acute respiratory distress syndrome. Curr Opin Crit Care 2011; 17:64–71. The authors review the literature on novel H1N1 viral pneumonia causing ARDS.
21. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357:2601–2614.
22. Labelle AJ, Arnold H, Reichley RM, et al. A comparison of culture-positive and culture-negative health-care-associated pneumonia. Chest 2010; 137:1130–1137.
23. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for healthcare-associated pneumonia. Arch Intern Med 2008; 168:2205–2210.
24. Micek ST, Kollef KE, Reichley RM, et al. Healthcare-associated pneumonia and community-acquired pneumonia: a single-center experience. Antimicrob Agents Chemother 2007; 51:3568–3573.
25. Venditti M, Falcone M, Corrao, et al. Study Group of the Italian Society of Internal Medicine. Outcomes of patients hospitalized with community acquired, healthcare-associated, and hospital-acquired pneumonia. Ann Intern Med 2009; 150:19–26.
26. Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: is it time to refine the definition of healthcare-associated pneumonia? Chest 2010; 137:1283–1288.
27. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis 2010; 51 (1 Suppl): 81–87.
28. Esperatti M, Ferrer M, Theessen A, et al. Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients. Am J Respir Crit Care Med 2010; 182:1533–1539.
29. Woodhead M, Blasi F, Ewig S, et al. Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology

and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections: full version. Clin Microbiol Infect 2011; 176:E1–E59.

30. Falguera M, Trujillano J, Caro S, et al. NAC-CALIDAD (Proyecto Integrado de Investigacio´ n de la Sociedad Espan˜ola de Patologı´a del Aparato Respiratorio sobre Infecciones Respiratorias de Vı´as Bajas) Study Group. A prediction rule for estimating the risk of bacteremia in patients with community-acquired pneumonia. Clin Infect Dis 2009; 49:409–416.
31. Shimada T, Noguchi Y, Jackson JL, et al. Systematic review and meta-analysis: urinary antigen tests for legionellosis. Chest 2009; 136:1576–1585.
32. Sorde´ R, Falco´ V, Lowak M, et al. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med 2011; 171:166–172.
33. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis 2011; 52 (4 Suppl):296–304. 37. Antonelli M, Conti G, Rocco M, et al. Noninvasive positive-pressure ventilation vs. conventional oxygen supplementation in hypoxemic patients undergoing diagnostic bronchoscopy. Chest 2002; 121:1149–1154.
34. Azoulay E, Mokart D, Lambert J, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med 2010; 182:1038–1046.
35. Chastre J, Trouillet JL, Combes A, Luyt CE. Diagnostic techniques and procedures for establishing the microbial etiology of ventilator-associated pneumonia for clinical trials: the pros for quantitative cultures. Clin Infect Dis 2010; 51 (1 Suppl):88–92.
36. Caliendo AM. Multiplex PCR and emerging technologies for the detection of respiratory pathogens. Clin Infect Dis 2011; 52 (4 Suppl):326– 330.
37. Tenover FC. Developing molecular amplification methods for rapid diagnosis of respiratory tract infections caused by bacterial pathogens. Clin Infect Dis 2011; 52 (4 Suppl):338–345.
38. Johansson N, Kalin M, Tiveljung-Lindell A, et al. Etiology of community acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis 2010; 50:202–209.
39. Bell RC, Coalson JJ, Smith JD, Johanson WG Jr. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983;99:293 – 8.
40. Chastre J, Fagon JY, Bornet-Lecso M, Calvat S, Dombret MC, Al Khani R, et al. Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 1995;152:231 – 40.
41. Meduri GU, Baselski V. The role of bronchoalveolar lavage in diagnosing nonopportunistic bacterial pneumonia. Chest 1991;100:179 – 90.