Evaluation of Non-responding Patients with Ventilator-associated Pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) is a major challenge in the intensive care unit (ICU), with an incidence varying between 5 and 50% in mechanically ventilated patients [1, 2]. Because of its high mortality rate (around 30%) [3, 4], aggressive evaluation of patients who fail to improve during the first days of treatment is indicated.

Lack of response to empirical antibiotic treatment should be recognized early and an operative strategy to evaluate the causes of failure should be started. The most important questions arising in this situation are:

- what is the most appropriate moment to evaluate the response/non-response of VAP to antibiotic treatment and based on which criteria?
- what are the possible causes of non-response?
- what are the basic investigations to perform in order to detect the alternative causes and to optimize therapy?

Response of Ventilator-Associated Pneumonia to Empirical Antibiotic Treatment: Timing and Criteria for Evaluation

Because of the severity of the disease and the high mortality rate, the evaluation of the response of VAP to empirical antibiotic treatment should be performed early and be based on objective criteria.

Apparently, the most suitable moment for assessment is 72 hours after initial diagnosis. This timing is justified by the study of Montravers et al. [5], who reported that 67% of patients with VAP had sterile secretions, obtained by protected specimen brush (PSB), after 3 days of antibiotic therapy and another 21% had microbial growth below the 10^3 colony-forming units (CFU)/ml threshold. Clinical improvement was associated with bacterial eradication in 96% of cases, while only 44% of patients with persistent growth over the threshold showed a favorable evolution. In addition, complete results of initial microbial investigations are available after 72 hours, allowing the adequacy of empirical treatment to be checked.

The evaluation of the response of VAP to the empirical antibiotic treatment should rely basically on the same criteria used for the initial diagnosis of VAP, namely: presence of fever or hypothermia; leukocytosis or leukopenia; purulent tracheobronchial secretions; and radiographic pulmonary infiltrates. It is known that the diagnosis of VAP based on all these criteria has a good specificity but with the cost of a loss in sensitivity. The most reasonable diagnostic accuracy is provided by the combination of radiographic infiltrates and two of three clinical criteria [6].

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An additional benefit for evaluation could be obtained by using the clinical pulmonary infection score (CPIS) [7]. This score includes the traditional parameters (fever, leukocytes, tracheal secretions, oxygenation, radiograph abnormalities). However, because the score also takes into account the culture results of tracheal aspirates, the VAP evaluation may be delayed at least 24 hours. In addition, using the cut-off of 6 points, it appears that a fall below 6, which was compatible with clinical improvement, was observed only after 5 days of antibiotic treatment [8].

Useful tools to improve the accuracy of the follow-up evaluation could be clinical scores such as the lung injury score (LIS), focusing exclusively on lung parameters in ventilated patients (radiographic infiltrates, oxygenation, compliance, positive end-expiratory pressure [PEEP]), and the multiple organ dysfunction score (MODS), allowing concomitant disorders to be monitored also.

In practice, the persistence of fever and/or leukocytosis and/or purulent secretions or the progression of the radiographic infiltrate (increase of the initial opacity, cavitation, pleural effusion), reflect an abnormal evolution of VAP under antibiotic treatment. Additional functional pulmonary parameters, such as oxygenation, compliance, or need of PEEP, must be considered, as well as certain parameters of other organ dysfunction, such as creatinine, bilirubin, thrombocytes, Glasgow coma score, blood pressure, or central venous pressure.

Causes of Non-Response of VAP to Empirical Antibiotic Treatment

The causes of non-response of VAP to the empirical antibiotic treatment are various (Table 1) and can be divided into three categories:
1) causes related to the antibiotic treatment or to the responsible microorganism;
2) infections other than VAP; and
3) non-infectious conditions.

Despite the large numbers of possible causes, few are common in clinical practice, facilitating the diagnostic approach.

Table 1. Causes of non-response of ventilator-associated pneumonia (VAP) to empirical antibiotic treatment. ARDS: acute respiratory distress syndrome; BOOP: bronchiolitis obliterans organizing pneumonia; CMV: cytomegalovirus

Causes related to the antibiotic treatment or to the responsible microorganism	Infections other than VAP	Non-infectious conditions
▪ Inappropriate election/combination of antibiotics	▪ Sinusitis	▪ ARDS
▪ Low dosage/serum level of antibiotics	▪ Vascular catheter-related sepsis	▪ Atelectasis
▪ Resistance to antibiotics (MRSA, *P. aeruginosa*, *Acinetobacter* spp, *S. maltophilia*)	▪ Abdominal sepsis (cholecystitis, pancreatitis, colitis)	▪ BOOP
▪ Microorganisms not covered by the empiric antibiotic treatment (*Candida* spp, *Aspergillus* spp, CMV, *Legionella* spp, *P. carinii*)	▪ Pulmonary abscess	▪ Pulmonary hemorrhage
▪ Superinfection	▪ Pleural effusion/empyema	▪ Pulmonary embolism
	▪ Urinary sepsis	▪ Congestive heart failure
		▪ Lung contusion
		▪ Pulmonary edema after lung resection
		▪ Drug-related fever

Causes Related to the Antibiotic Treatment or the Etiological Microorganism

The most frequent situation is lack of response due to the persistence of the etiological microorganism. This situation occurs in the following circumstances: inadequate treatment (inappropriate empirical selection of antibiotics, inappropriate dosage, low blood level of antibiotics) or infection caused by microorganisms not covered by the initial therapy (i.e., resistance to antibiotics or infection by unusual organisms).

Initial resistance of the microorganism to antibiotics or inappropriate dosage or combination of antibiotics could result in microbial persistence and lack of clinical resolution. Over the last decade, lung infections caused by strains with multiple resistance to the usual antibiotics, like *Pseudomonas aeruginosa*, *Acinetobacter* spp, and methicillin-resistant *Staphylococcus aureus* (MRSA), have become a common problem in ICUs, being responsible for more than 50% of VAP episodes [2, 9, 10].

The American Thoracic Society recommendation [11] for the treatment of hospital-acquired pneumonia, and other subsequent studies [10], have described a number of risk factors related to infections by multiresistant strains and have made suggestions for optimal empirical antibiotic coverage in these situations. Thus, this approach allows the clinician to safely avoid possible non-response related to antibiotic resistance or inappropriate drug strategy. In fact, several studies [12, 13] support the importance of adequate initial therapy, reporting a statistically significant difference in mortality rate between patients receiving correct antibiotic therapy versus those with inadequate treatment.

Although the persistence of the microorganism can be proved only by a second bacterial investigation, the results of the initial microbial investigation are already available at 72 hours, and treatment should be adjusted accordingly. A second respiratory sampling could reveal a superinfection with another microorganism that is not covered by the initial antibiotic treatment, for example MRSA.

The initial infection, or the superinfection, with MRSA could be a cause of non-response in a significant number of cases, because vancomycin is not usually administered empirically. The fear of developing vancomycin-resistant strains justifies this conservative attitude, but if certain risk factors (i.e., head trauma or low level of consciousness [14] are present, empirical vancomycin is more than appropriate. In addition, the increasing proportion of methicillin-resistant staphylococci in the ICU and the promising new agents against Gram-positive organisms both support the empirical use of vancomycin [15].

Infections with unusual microorganims such as *Aspergillus* spp, *Legionella pneumophila*, *Candida* spp, or *Cytomegalovirus* (CMV) are frequently associated with an immunocompromised condition (solid organ transplant, hematological disorder, prolonged corticosteroid therapy) [16, 17] and must be considered in these particular situations. Rapid techniques of antigen detection may facilitate diagnosis in cases of infection with CMV, *Aspergillus* spp or *L. pneumophila*. Due to its presence in normal flora, infection with *Candida* spp should be considered only in patients with multiple courses of antibiotics and more than 10 days of ICU stay [18], and if no other microorganism is isolated in the respiratory samples.

Infections other than VAP

A concomitant infection in a patient with VAP is not uncommon and can contribute to the persistence of the systemic inflammatory response syndrome (SIRS) and especially to the persistence of fever. In addition, fever in critically ill patients

could be related to a variety of non-infectious causes (i.e., myocardial infarction, gastrointestinal bleeding) but in these cases it does not usually exceed 38.9 °C. Therefore, we will focus only on the most frequent nosocomial infections that can occur in an ICU patient.

Nosocomial Sinusitis. Nosocomial sinusitis is commonly associated with nasotracheal intubation and nasogastric tubes but also with head trauma and neurological disorders [19, 20]. It usually occurs after 7 days of nasal intubation, in up to 85% of patients [21, 22]. However, apparently only 20–40% of patients with radiological evidence of maxillary sinusitis have true infectious sinusitis, namely with the presence of pus and positive cultures of the responsible microorganism [21]. Infectious sinusitis seems to be a risk factor for subsequent infections of the lower respiratory tract, supported by a recent study in an animal model [23]. Furthermore, Rouby et al. [21] reported an incidence of nosocomial pneumonia of 67% in patients with infectious nosocomial sinusitis.

The diagnosis of sinusitis is based on computed tomography (CT) scan rather than on the classic x-ray. Microorganisms frequently associated with nosocomial sinusitis in mechanically ventilated patients are *P. aeruginosa*, *Acinetobacter* spp, *Staph. aureus* and anaerobes [19, 20]. Treatment consists of removal of nasal tube, if possible, and maxillary sinus drainage and lavage. Antibiotic treatment is controversial but still recommended.

Vascular Catheter-related Sepsis. Vascular catheter-related sepsis should be considered in patients with positive blood culture and persistent fever. The incidence of catheter-related bacteremia ranges between <1 and 18% [24], depending mainly on the number of days of catheterization (usually more than 2 days), the frequency of manipulation, and the number of ports. The most common microorganisms isolated in blood cultures and in the culture of the catheter tip are the staphylococci, with *Staph. epidermidis* accounting for 50% [25]. Removal of the catheter with reinsertion in a different site is recommended if catheter-related sepsis is suspected.

Abdominal Sepsis. Cholecystitis occurs in 1.5% of critically-ill patients [26] as a result of several non-infectious mechanisms such as gallbladder ischemia, bile stasis, use of PEEP, or parenteral nutrition [27]. Bacterial invasion is just a secondary phenomenon. The diagnosis is particularly difficult in intubated patients and usually occurs when the gallbladder is perforated. Therefore, a persistent fever without evident focus of infection should indicate, among others, a radiological investigation of the gallbladder. Ultrasound and CT scan both provide good diagnostic accuracy. The therapeutic approach in these patients is somewhat controversial. The procedure of choice seems to be percutaneous cholecystectomy and open cholecystectomy is only recommended if this fails [28].

Pancreatitis is sometimes associated with left pleural effusion and has been related also to the development of acute respiratory distress syndrome (ARDS) [29]. Therefore, a new pulmonary infiltrate in patients with a diagnosis of pancreatitis should alert to the possibility of ARDS rather than a pneumonia.

Pseudomembranous colitis caused by *Clostridium difficile* occurs in 20% of all hospitalized patients and about one third of them develop diarrhea [30]. Cephalosporins and clindamycin are usually associated with the development of pseudomembranous colitis [31]. Diagnosis is based on ELISA test for *C. difficile* toxins and/or on CT scan of the abdomen.

Urinary Sepsis. Urinary tract infection (UTI) is a common event in ICU patients, with a reported incidence of 50% of all nosocomial infections. Bacteriuria usually occurs in 30% of catheterized hospitalized patients [32], although this condition does not always imply a real UTI. The differentiation between colonization and infection is not clear, while the bacterial load ($>10^5$ CFU/ml) is similar in both cases. Furthermore, only 3% of these patients develop bacteremia with the same microorganism as isolated in the urine. Therefore, treatment is recommended only if there is ultrasound evidence of stones or urinary tract obstruction.

Pulmonary Abscess. A cavitating image on standard radiograph or CT scan suggests a pulmonary abscess, a condition that prevents good penetration of antibiotics into the lung tissue and can results in the persistence of VAP. In this situation, antibiotic treatment should be revised in order to provide a better coverage for anaerobes and an adequate drainage technique should be considered.

Pleural Effusion/Empyema. Pleural effusion may be associated with VAP [33], contributing to the persistence of clinical and radiological manifestations of pulmonary infection despite adequate antibiotic treatment. A CT scan or ultrasound are often required to reveal pleural effusion in VAP patients. When a significant amount of pleural effusion is present, thoracentesis is mandatory in order to rule out an empyema. Grossly purulent fluid or a pH <7.20 and positive Gram stain and culture are indications for chest tube insertion.

Non-infectious Causes

Different non-infectious conditions can mimic or complicate VAP. The diagnosis is often difficult because these conditions are usually responsible for the lack of resolution of the pulmonary infiltrate and can also be accompanied by fever or other manifestations of SIRS. The most frequent non-infectious situations that should be considered in case of non-response of VAP are listed in Table 1.

ARDS. The distinction between ARDS and VAP is not always easy, especially in post-operative or trauma patients. Fever and leukocytosis can be present in the late phase of ARDS as a consequence of the fibroproliferative changes [34]. Furthermore, these two findings along with the radiographic infiltrate are also criteria to suspect the diagnosis of VAP. On the other hand, pneumonia is one of the main direct lung injuries related to the development of ARDS [29]. However, the presence of a bilateral radiographic infiltrate and severe hypoxemia associated with one of the accepted risk factors for ARDS (i.e., trauma, multiple transfusion, cardiopulmonary bypass, acute pancreatitis) could facilitate the distinction from pneumonia. In addition, a negative or under cut-off microbiologic result usually rules out a respiratory infection in these particular situations.

The relationship between these two conditions is bilateral, some studies reporting an incidence of nosocomial pneumonia varying between 15 [35] and 60% [36] in patients with ARDS. Because critically ill patients usually present with two or more criteria of SIRS [37] and become rapidly colonized with potential pathogenic microorganisms, the diagnosis of pneumonia in ARDS patients should be based on suggestive microbiological findings.

Atelectasis. The mechanical effect of the decubitus and the increased volume of tracheobronchial secretions facilitate the occurrence of atelectasis in ventilated patients. This circumstance could result in a progression of the initial radiological infiltrate. In addition, atelectasis could be associated with fever [38]. Appropriate hydration and physiotherapy may prevent the development of atelectasis in intubated patients.

Bronchiolitis Obliterans Organizing Pneumonia. Bronchiolitis obliterans organizing pneumonia (BOOP) is usually related to specific conditions such as collagen vascular diseases, viral infection, aspiration of gastric contents, lung irradiation, drugs or lung transplant [39]. Clinical presentation may mimic pneumonia and the presence of bilateral radiographic infiltrates is common. Diagnosis is usually delayed but a persistent infiltrate with negative microbial cultures and lack of clinical improvement with antibiotic treatment should alert to this alternative. Although it does not provide diagnostic findings, CT scan investigation can be useful, while open lung biopsy is the last option in mechanically ventilated patients. The administration of corticosteroids usually results in rapid clinical and radiological improvement.

Pulmonary Hemorrhage. Pulmonary hemorrhage is more frequent in patients with hematological disorders or receiving immunosuppressive therapy [40] and should be considered as a differential diagnosis in intubated patients with marked thrombocytopenia. Nevertheless, pulmonary infection in these particular patients could also result in bleeding into the alveolar space [41], so that microbiological investigation of the respiratory sample is mandatory.

Pulmonary Embolism. Pulmonary embolism should be suspected in postoperative patients, patients with prolonged bed-stay or signs of thrombophlebitis. The development of a new pulmonary infiltrate in these patients, associated with a marked deterioration in gas exchange and hemodynamic instability should raise the suspicion of embolism and a supplemental investigation by ventilation-perfusion scintigraphy or pulmonary artery arteriography should be performed.

Congestive Heart Failure. The classical radiographic image of pulmonary edema and high central venous pressure facilitate the diagnosis, but asymmetric patterns of pulmonary edema are not infrequently observed, for example in patients with chronic obstructive pulmonary disease (COPD) or with mitral valve insufficiency. Echocardiography and pulmonary artery catheterization may be helpful in the management of these patients.

Pulmonary Contusion. Probably the most challenging condition in ICU is trauma, because of the frequent presence of SIRS and multiple evident or masked injuries, which make the diagnosis of VAP rather difficult. Thoracic trauma with lung contusion may be followed by infection of the injured pulmonary region with poor radiological improvement and apparent lack of response to antibiotic treatment.

Pulmonary Edema After Pulmonary Resection. Pulmonary edema after pulmonary resection is defined by lung injury after pneumonectomy, lobectomy or bilobectomy [42]. It occurs in approximately 7% of lung resections [43], usually developing 1 to 3 days after surgery [44], and its clinical and pathological manifestations are very similar to ARDS. The diagnosis of pneumonia in the postoperative patient with

pulmonary resection is particularly difficult, because fever in the first 48 hours after surgery is a common event and a new pulmonary infiltrate may reflect post-resection lung injury.

Drug-induced Fever. Drug-induced fever is associated with antibiotics, antiarrhythmic drugs, and phenytoin [45]. Although these drugs are frequently administered in the ICU, their role as a cause of fever must be consider only when all possible foci of infection have been ruled out and when blood eosinophilia is present.

Basic Investigations in Non-responding Patients With VAP

The evaluation of the response of VAP to empirical antibiotic treatment should be practical and performed early (Fig. 1). The first approach in cases who fail to improve should be the assessment of the antibiotic treatment based on the microbiological results of the respiratory samples collected on the day of the diagnosis. Therefore, a microbial investigation prior to initiation of the empirical therapy is extremely useful. Although some authors recommend bronchoscopic invasive techniques (PSB, bronchoalveolar lavage [BAL]) [46], the quantitative endotracheal aspirate seems to have similar diagnostic yield [47], is less expensive, and is easier to perform. Complete bacteriological results (Gram stain, cultures, and susceptibility tests) are usually available after 72 hours, facilitating the evaluation of the adequacy of the empirical therapy.

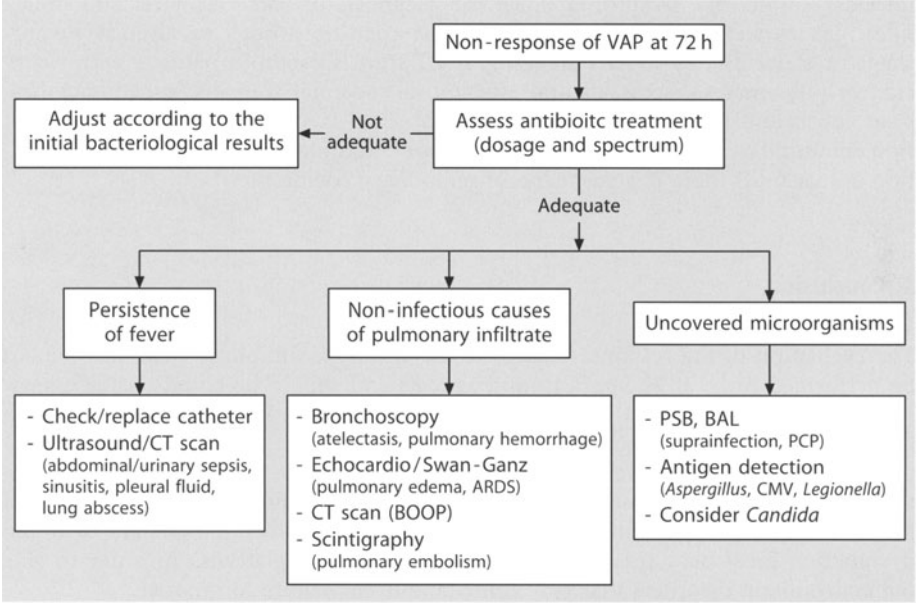

Fig. 1. Basic investigations to be considered in patients with non-responding ventilator associated pneumonia (VAP) after 72 hours of empirical antibiotic treatment. PSB: protected specimen brush; BAL: bronchoalveolar lavage; ARDS: acute respiratory distress syndrome; BOOP: bronchiolitis obliterans organizing pneumonia; CMV: cytomegalovirus; PCP: *Pneumocystis carinii* pneumonia

If the antibiotic treatment is inadequate in terms of spectrum, dosage or serum level, it should be correctly readjusted. If the empirical antibiotic treatment is adequate, the investigation should move on towards the next step and consider: 1) an infection/superinfection due to a microorganism not covered by the initial therapy; and, 2) causes of non-response other than VAP.

In the first case, a new microbial investigation, preferably by invasive methods (i.e., bronchoscopy with PSB and BAL) is recommended. The antigen detection techniques for *Aspergillus* spp, *Legionella*, and CMV are useful, especially in immunocompromised patients (hematological disorders, organ transplants). An infection by *Pneumocystis carinii* should be considered in patients at risk of human immunodeficiency virus (HIV) infection.

Other causes of non-response (infectious or non-infectious) require further investigations, based mainly on the suspicion of the most common alternative diagnosis compatible with the clinical and radiological manifestations (Fig. 1). Fever $>38.9\,^{\circ}C$ is usually associated with an infection [48], and the investigation must focus on the possible sources of pathogens. If a bacteremia is caused by staphylococci, vascular catheters should be replaced. A thoracic and abdominal ultrasound investigation may reveal a possible pleural effusion or abdominal source of sepsis. A progression of a pulmonary infiltrate under correct antibiotic treatment or a bilateral radiological pattern should mandate the investigation of other alternative causes, especially non-infectious. Because 72 hours is too early to observe any radiological improvement, the persistence of the initial infiltrate should indicate further investigation only if it is accompanied by the persistence of other clinical signs (fever, purulent tracheobronchial secretion or leukocytosis). Fiberoptic bronchoscopy represents the cornerstone for the investigation of the pulmonary infiltrates. Respiratory samples facilitate the diagnosis of bacterial, viral and fungal infections as well as of other non-infectious conditions such as alveolar hemorrhage or atelectasis by mucus plugging. A CT scan is useful in patients with suspicion of pulmonary abscess, pleural effusion, nosocomial sinusitis, pseudomembranous colitis and BOOP. When pulmonary embolism is suspected, ventilation-perfusion scintigraphy is required. Echocardiography and pulmonary artery catheterization are useful if there is a suspicion of pulmonary edema.

Conclusion

The evaluation of the response of VAP to the empirical antibiotic treatment should be performed early, at 72 hours from diagnosis and should be based on the assessment of the initial criteria of diagnosis and on certain additional scores of organ function (LIS, MODS). Lack of response to the antibiotic treatment must be suspected in the following circumstances: persistence of fever, purulent tracheal secretions, leukocytosis; progression of the radiographic pulmonary infiltrate; lack of improvement or further impairment of gas exchange. Other parameters of organ dysfunction must be assessed (i.e., creatinine, bilirubin, platelets) in order to rule out concomitant disorders that may contribute to the failure to improve.

The first approach in case of non-response consists of revising the antibiotic treatment based on the initial bacteriological results and adjusting the combination and dosage, if necessary. Some microorganisms that are not covered by the empirical treatment (MRSA, fungi, *Legionella* spp, CMV) must be consider when risk fac-

tors are present (i.e., head trauma for MRSA, immunocompromised condition for fungi and viruses). Other frequent causes of fever in critically ill patients could be concomitant to VAP, like catheter-related sepsis, sinusitis or urinary infection. The radiographic pulmonary infiltrate in critically ill patients could be related to ARDS, atelectasis, BOOP, pulmonary embolism or pulmonary edema after lung resection. Fiberoptic bronchoscopy with respiratory sampling (PSB, BAL), ultrasound, CT scan, echocardiography and pulmonary scintigraphy are the basic investigations recommended when a condition other than VAP is suspected to be responsible for the lack of improvement of the patient with VAP.

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