A New Approach to Ventilator-associated Pneumonia Based on the PIRO System

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Introduction

Several new scoring systems have been developed over recent years to assess the degree of organ failure (e.g., Acute Physiology and Chronic Health Evaluation [APACHE] II, APACHE III, Sequential Organ Failure Assessment [SOFA], Simplified Acute Physiology Score [SAPS] II, and Multiple Organ Dysfunction Score [MODS]). Most of these were models generated based on the concepts of sepsis, severe sepsis and septic shock. In 2001, an International Sepsis Definition Conference updated these terms in order to facilitate standardized enrolment into clinical trials, but due to their simplicity and easy use physicians rapidly adopted them for daily clinical practice [1].

However, few of these scoring systems are focused on ventilator-associated pneumonia (VAP), the leading cause of nosocomial infection in critically ill patients requiring mechanical ventilation [2]. The approach to VAP severity has been traditionally based on three clinical items: The underlying disease, the time of onset, and the causative microorganism. The VAP-PIRO score (**Table 1**) [3], based on the PIRO system (predisposition, insult, response, organ dysfunction), has been recently developed by our group and endeavors to identify different risk levels for VAP. This score stratifies patients with VAP into mortality risk groups and correlates these with health-care resource use in VAP patients. The PIRO concept, a conceptual framework for understanding sepsis [1], is a classification scheme that could stratify patients based on their predisposing conditions, the nature and extent of the insult, the nature and magnitude of the host response, and the degree of the concomitant organ dysfunction. Conceptually, PIRO was

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Table 1. Summary of the main components of the VAP-PIRO scoring system

P	I	R	O

• COPD
• Immunocompromised host
• Trauma patient
• Genetic factors
	• Bacteremia
	• Pathogens
	  – MRSA
	  – *Pseudomonas* spp.
	  – *Aanetobacter* spp.
	• *Candida* spp.
	• VAT
	• Blood transfusions
		• Clinical resolution
		• Biomarkers
		• Compartimentalization
		• Shock
		• Immunoparalysis, macrolides
			• Renal failure
			• ARDS

VAT: ventilator-associated tracheobronchitis; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; MRSA: methicillin-resistant *Staphylococcus aureus*
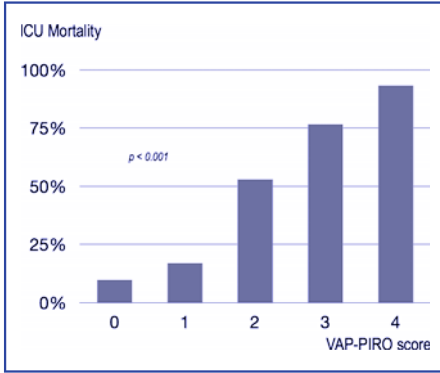
Fig. 1. Intensive care unit (ICU) mortality according to the VAP-PIRO score classification. (adapted from [3])

modeled on the TNM (tumor, nodes, metastases) classification [4] which has been successfully used to define prognostic indicators in clinical oncology. PIRO was introduced as a hypothesis-generating model for future research, but its practical applications were limited. The aim of this chapter is to describe a new approach to the prognosis of VAP based on the PIRO concept focusing in its main components and their relative impact on VAP severity and prognosis.

Figure 1 shows the mortality rate in ICU patients with VAP classified according to the VAP-PIRO score.

Components of the VAP-PIRO Score: Predisposition

Genetic Factors

Despite considerable advances in our understanding of the biology of pneumonia, improvements in clinical outcomes have been sporadic and, with few notable exceptions, because of improvements in supportive care rather than specific therapies. As a result, morbidity, mortality, and costs remain high.

Although it is clear that gene sequencing and manipulation of experimental models have provided a better approach for insight into the biology of the inflammatory response to infection, these technologies and their application to the study of naturally occurring human genetic variation have yet to provide the same insight or clinical benefit. Variations in genes encoding important components of the inflammatory response and the microbial recognition system are likely to be involved in the development of pneumonia. In contrast to entities such as community-acquired pneumonia (CAP) or meningitis where 'the genetic approach' is being developed with some success, there are still scarce data that link VAP to genetic variability [5–9].

In addition, genetics may explain the wide variation in the individual response to infection that has puzzled clinicians for long. VAP phenotypes can range from septic shock to a very well compartmentalized consolidation on x-ray accompanied by low grade hypoxemia. Fortunately, novel therapeutic strategies are currently being developed in experimental models to modulate the inflammatory response in the host and may be available at the bedside in the near future.

Underlying Diseases

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a risk factor for nosocomial lower respiratory tract infections. The incidence of VAP in intubated COPD patients has been estimated to range between 6 and 33 % [10]. Tracheo-bronchial colonization, local and systemic immunosuppression and frequent antibiotic treatment are factors predisposing to VAP in these patients. However, the impact of COPD on VAP mortality remains controversial. Our group [11] demonstrated that COPD was associated with higher mortality rates in patients with VAP. However, after adjustment for confounding factors, COPD was not independently associated with mortality in these patients. In contrast, Nseir et al. [12] reported that VAP was associated with higher mortality rates and longer duration of mechanical ventilation and intensive care unit (ICU) stay in COPD patients, and was independently associated with ICU mortality.

Immunocompromised host

A huge number of immunocompromised patients are admitted to the ICU and immunosuppression has been recognized as an independent risk factor for infectious morbidity and mortality [13]. In addition, immunosuppression represents a risk factor for multidrug-resistant pathogens in VAP and should be considered in treatment decisions. As has been described by Nseir et al. [12], a significantly greater proportion of immunosuppressed patients received antibiotic therapy before and during ICU admission, being more likely to be colonized and/or infected by multidrug resistant organisms. However, despite the evidence available, current guidelines for treatment of VAP and or hospital-acquired pneumonia (HAP)/VAP do not consider patients who are known to be immunosuppressed because of human immunodeficiency virus (HIV) infection, hematologic malignancy, chemotherapy-induced neutropenia or organ transplantation [14], factors likely to determine prognosis.

Trauma patients

Trauma deaths have a classic trimodal distribution. Late death (3 days to 3 weeks postinjury) occurs in more than 25 % of the patients, in whom infection is the principal cause of death and is associated with high rates of extracranial complications, like pneumonia, that determine the final outcome. In fact, Bronchard et al. [15], in trauma patients, described that for patients developing pneumonia there was a higher risk of secondary cerebral injury, increased intra-cranial pressure, hypotension, fever and hypoxemia that would worsen outcomes in such patients. Therefore, in trauma patients, early identification of subjects at a high risk of developing VAP reduces morbidity and costs.

Trauma patients exhibit greater incidences of early-onset VAP, which accounts for 30–40 % of cases [15]. Most reports regarding microorganisms indicate that methicillin-sensitive *Staphylococcus aureus* (MSSA) is the predominant pathogen in multiple-trauma patients in coma, and nasal MSSA colonization at the time of severe injury may increase the risk of MSSA pneumonia [16]. As length of stay increases, causal pathogens are likely to switch to antibiotic-resistant bacteria. Rangel et al. [17] reported that the presence of multi-drug resistance (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and methicillin-resistant *S. aureus* [MRSA]) in respiratory isolates increased from

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27 % to 52 % after 5 days of admission. Therefore, in comatose patients, coverage with a beta-lactam active against MSSA is mandatory when early VAP is suspected, however treatment of late onset VAP should be based on local bacteriologic patterns and antimicrobial susceptibility.

Components of the VAP-PIRO Score: Insult

Bacteremia

In HAP, bacteremia occurs in 8 to 20 % of the episodes [18] and is associated with high mortality rates [19], but because many of these studies were not designed to investigate attributable mortality, little is known regarding its real impact on VAP patients. Agbaht et al. [20] found that bacteremic-VAP was independently associated with increased ICU mortality. Moreover bacteremic episodes occurred later during the ICU stay and were more frequent in previously hospitalized patients. MRSA was found to be an independent risk factor for bacteremia and Depuydt et al. [21] reported a high mortality rate in MRSA bacteremia associated with nosocomial pneumonia,

Pathogens

Consideration of the particularities of each ICU's ecology should provide a more rational basis for selecting initial therapy for VAP patients before culture results are available. As we reported [22], the observed differences in pathogen etiology across institutions reflected differences in antibiotic use and local patterns of resistance, which prompted the development of a more patient specific antibiotic management.

The impact of multidrug resistant pathogens, including *P. aeruginosa* and MRSA, causing nosocomial infection is ever-increasing and is now recognized as a major health problem. Multidrug resistant pathogens have been recognized as contributing to unfavorable clinical outcome and increased resource utilization [23]. The greater associated hospital mortality has been attributed to the virulence of these bacteria and the increased occurrence of inadequate initial antibiotic treatment of VAP due to the presence of antibiotic resistance. However, the impact of multidrug resistance is difficult to assess because of the presence of multiple patient characteristics that may confound uniform analysis.

P. aeruginosa, MRSA and *A. baumannii* represent the three most important microorganisms in VAP.

Pseudomonas aeruginosa

P. aeruginosa represents the most prevalent microorganism in VAP in different series and is associated with high mortality rates [24]. Some surface factors, by either injecting cytotoxin to damaged epithelial cells or by rupturing epithelial integrity or by mechanisms like the type III secretion system, increase *P. aeruginosa*'s virulence, particularly exoU. The type III secretion system induces the translocation of toxins from the bacterial cytoplasm into the cytosol of host cells directly. *P. aeruginosa* strains producing type III secreted proteins are linked with worse outcome [25].

Zhuo et al. [26] reported that patients with large burdens of *P. aeruginosa* had an increased risk of death and possessed more virulent strains. Therefore, a high

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burden of *P. aeruginosa* may be a marker of inadequate host defense and its presence may also further compromise target host immune cells, for example, macrophages and neutrophils, allowing organisms to evade the immune response and often reducing the number of viable host defense cells.

Staphylococcus aureus

S. aureus is the most important Gram-positive pathogen in VAP. In the recent European multicenter study [27], EUVAP, the most common isolate was *S. aureus* in 32.3 % of cases; 16.3 % were MSSA and 16.0 % MRSA. Virulence and therapy-related factors, such as inappropriate antibiotic prescription, have been consistently associated with increased mortality. There are several factors linked with MRSA isolation in VAP episodes: Administration of antibiotics before the development of VAP [28] and length of hospital stay, rather than the period of mechanical ventilation, were strongly associated with MRSA isolation [29]. Vidaur et al. [30] found that MRSA VAP treated with appropriate therapy resolved more slowly than VAP due to *Haemophilus influenzae*, MSSA, and *P. aeruginosa* treated with appropriate therapy. The risk of death in MRSA episodes is 20 times higher than in episodes caused by MSSA strains treated with beta-lactams [31] and a recent report showed that MRSA-VAP episodes were independently associated with prolonged hospitalization and higher costs than MSSA VAP episodes, even when therapy was appropriate [32].

Acinetobacter baumannii

Several studies have investigated the attributable mortality of *A. baumannii* and found controversial results. Fagon et al. [33] reported higher mortality in cases with VAP caused by *A. baumannii* and *P. aeruginosa* than in controls with bronchial colonization. In contrast, Garnacho-Montero et al. [34], found that VAP due to *A. baumannii* was not associated with worse outcomes than other causes of VAP in a matched case-control study. *A. baumannii* exhibits intrinsic resistance to multiple antimicrobial agents and generates continuing controversy about whether VAP caused by this microorganism increases morbidity and mortality independently of the effects of other confounding factors in ICU setting.

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Candida species

In immunocompetent mechanically ventilated patients, isolation of *Candida* spp. from the respiratory tract is relatively common. Olaechea et al. [35] found an association with *Candida* spp. isolation and longer ICU and hospital stays and resource utilization. Azoulay et al. [36] reported that *Candida* spp. colonization was associated with an increased risk of *P. aeruginosa* VAP. *Candida* spp. and *P. aeruginosa* were among the most common microorganisms retrieved from endotracheal tube biofilm and tracheal secretions in patients with VAP. This can be explained because both microorganisms have identical functional enzymes, such as 2' phosphotransferase, acting in concert with ligase to splice transfer RNA molecules. Preemptive treatment with local or systemic therapy has been proposed in order to reduce the incidence of *P. aeruginosa* VAP [37].

Ventilator-associated Tracheobronchitis (VAT) as an Intermediate Insult for VAP

VAT might represent an intermediate process between colonization and VAP [38] and probably is a continuum between bronchitis and pneumonia in mechanically

ventilated patients. Host defenses can be overwhelmed by a large aspirated inoculum or an inherently virulent organism and the main reason for developing infection in the upper airways is the imbalance between host defenses and excess of mucus. Recent studies have shown that bronchial/tracheal epithelial cells are functionally different and represent a first step of injury [39]. VAT represents an interesting target for treatment since it may prevent the progression to VAP, shorten the use of antibiotics that reduce cost and minimize the selective pressure on ICU ecology [40].

Blood Transfusion

The majority of critically ill patients require a transfusion of packed red blood cells (RBCs) at some point during their ICU stay. The incidence of blood transfusion during the ICU stay has been reported to be as frequent as 37.0 % [42]. Nevertheless, transfusion of packed RBCs is not without risk since it represents an insult to the host's immune system with enhancement of cytokine response. Anti-inflamatory (interleukin [IL]-10) and pleiotropic (IL-6) cytokines are increased during transfusion of packed RBCs. Blood transfusion has been associated with nosocomial infection-like surgical site infections and potentiates the risk for catheter-related blood stream infection but also increases the risk of developing VAP.

Shorr et al. [42] reported that transfusion was independently associated with an increased risk for VAP, the effect of transfusion on late-onset VAP being more pronounced and dose-response dependent. Therefore, blood transfusion needs to be considered cautiously in critical care patients in order to evaluate potential adverse events and to acknowledge that the burden of proof is shifting to suggest that transfusion avoidance may be the safer paradigm [43].

Components of the VAP-PIRO Score: Response

Clinical Resolution

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Early clinical recognition of therapeutic failure is of paramount importance if corrective measures are to be taken. While this will intuitively make sense to clinicians, data available on this issue are very limited. Several studies have suggested that improvement in oxygenation is the most reliable criteria to distinguish patients who are responding to antibiotic treatment from those who are not. Luna et al. [44] evaluated the performance of the Clinical Pulmonary Infection Score (CPIS) in identifying which patients with VAP respond to therapy. These authors discovered that only the PaO_2/FiO_2 ratio could distinguish survivors from non-survivors, as early as day 3 of therapy for VAP. Moreover they reported that the PaO_2/FiO_2 ratio improved above 250 mmHg in survivors, and this improvement happened before improvement in the other components of the score (white blood cell count, fever, secretions, and radiographic abnormalities). Thus, the PaO_2/FiO_2 ratio may represent a very accurate and rapid measure of the patient's response to therapy and can help tailor appropriate duration of therapy. However, Vidaur et al. [45] reported that improvement in oxygenation was unreliable in patients with the acute respiratory distress syndrome (ARDS), and only fever was delayed compared with non-ARDS patients. At days 7–8 of treatment, when antibiotics for VAP are commonly discontinued [46], Chastre et al. reported that more than 35 % of ARDS patients with VAP remain febrile.

Clinical patterns, such as fever and hypoxemia, are clinical variables that can be easily followed at the bedside of the patient simply by physical examination to monitor clinical response and to individualize and shorten the duration of antibiotic therapy.

Use of Biomarkers to Quantify the Response to VAP

Several biomarkers have been proposed as the most promising candidates, such as leukocyte count, C-reactive protein (CRP) and procalcitonin (PCT), for correlating with the prognosis of VAP [47]. Seligman et al. [48] reported that decreases in either serum PCT or CRP levels between onset and the fourth day of treatment could predict survival of VAP patients. Similarly, Luyt et al. [49] reported different procalcitonin levels as strong predictors of unfavorable outcome (death, recurrent VAP or development of extrapulmonary infection) by a point-of-care test at days 1, 3 and 7 in patients with VAP. However, neither PCT nor CRP threshold values nor their kinetics could predict the development of septic shock in VAP patients [50].

Recently, other biomarkers such us midregional pro-atrial natriuretic peptide (MR-proANP) and copeptin have been suggested and tested as prognostic markers, but their function in VAP resolution is still unproven [51, 52].

Compartmentalization

The response to VAP may vary from compartmentalized forms that account for a local response with minor systemic compromise to systemic spillover or escape of inflammation leading to septic shock and uninfected multiorgan failure.

Cytokines are the key factors in the pathogenesis of pneumonia and add complexity of signaling during VAP development. Millo et al. [53] reported that the production of cytokines and cytokine inhibitors was compartmentalized within the lungs in patients who developed VAP. They reported a significant increase in concentration of tumor necrosis factor (TNF)-α, soluble TNF-α receptors [sTNFaRI], IL-1α, and IL-1β in non-directed bronchoalveolar lavage (BAL) fluid.

Similarly, VAP is characterized by a shift in the local hemostatic balance to the procoagulant side, which precedes the clinical diagnosis of VAP. Fibrin deposits enhance inflammatory responses by increasing vascular permeability, activating endothelial cells to produce pro-inflammatory mediators, and eliciting recruitment and activation of neutrophils; eventually, these effects will disrupt normal gas exchange by creating intrapulmonary shunts and ventilation-perfusion mismatches.

As has been reported by Schultz et al. [54], patients with VAP, before the clinical manifestation, had a dramatic increase in procoagulant activity, increased BAL levels of thrombin-antithrombin III complex (TAT), and decreased fibrinolysis, as reflected by a gradual fall in BAL levels of plasminogen activator activity.

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Shock

The inflammatory response of the host to an infection is associated with increased circulating levels of pro-inflammatory cytokines, such as IL-6 and IL-8. The clinical presentation of VAP varies widely, from a relatively benign illness to

a devastating illness resulting in septic shock. The incidence of septic shock among VAP patients can be as high as 50 % in reported series [48]. Bonten et al. [55] reported that high circulating levels of IL-6 and IL-8 were associated with higher mortality rates and with a clinical presentation of severe sepsis or septic shock. Moreover soluble triggering receptor expressed on myeloid cells (sTREM)-1 is particularly increased on evolution from sepsis or severe sepsis to septic shock in patients with VAP. Its sustained increase might be an indicator for poor outcome [56].

Our group reported that septic shock was an independent variable associated with ICU mortality (OR 4.40 CI 2.71 – 7.15) [3]. The early stages of VAP may be accompanied by circulatory insufficiency resulting from hypovolemia, myocardial depression, increased metabolic rate, and vasoregulatory perfusion abnormalities. As a consequence, a variety of hemodynamic combinations create a systemic imbalance between tissue oxygen supply and demand, leading to global tissue hypoxia and shock. Early correction of septic shock is crucial for patient outcomes, for which reason consensus guidelines now recommend early goal-directed therapy [57] for the first six hours of sepsis resuscitation.

Immunoparalysis

In the past, immodulatory therapies in sepsis were driven by the assumption that the adverse outcomes were related to an overly exuberant inflammatory response. However, over the last few years, new evidence on cytokine production in response to bacterial antigens, lymphocyte proliferation in response to recall antigens, or new antigen presentation as a marker of immune function has been released. For example, low HLA-DR expression has been correlated with the development of nosocomial infections, and persistence of abnormally low levels of HLA-DR in the late phase of septic shock (day 5 – 7) has been linked to death [58]. New studies based on HLA-DR modulation in patients with VAP might improve the understanding of the response to VAP.

XII   Immunomodulatory Effects of Macrolides

Compelling evidence has shown that appropriate antibiotic therapy is the cornerstone of success in the treatment of patients with VAP [59]. However, despite early diagnosis and prompt initiation of antibiotics, mortality remains high in severe sepsis [60]. Recent studies suggest that macrolides may have beneficial effects for patients at risk of certain infections due to their immunomodulatory effects rather than their antimicrobial properties [61]. Based on favorable results in experimental models of sepsis caused by Gram-negative organisms, Giamarellos-Bourboulis et al. [62] conducted a randomized controlled trial (RCT) in 200 patients with VAP who were randomly assigned to receive either placebo or clarithromycin. They showed that despite no differences in 28-day mortality rates between the two groups, clarithromycin accelerated the resolution of VAP and weaning from mechanical ventilation in surviving patients and delayed death in those who died of sepsis. The explanation can be based on the regulation of leukocyte function and production of inflammatory mediators, control of mucus hypersecretion, resolution of inflammation, and modulation of host defense mechanisms or on bacterial quorum sensing in *P. aeruginosa* infections. Moreover, some evidence suggests that macrolides might facilitate the killing of micro-

organisms in acute respiratory infections through the stimulation of neutrophil activation, whereas blood monocytes release lower amounts of TNF-α without any change in tissue bacterial load [63].

Components of the VAP-PIRO Score: Organ Dysfunction

Renal Failure

VAP is a risk factor for the development of acute renal failure. The incidence of acute renal failure for the population at risk has been reported to be around 38 % [64]. In this study, VAP caused by multidrug resistant pathogens and sepsis were independent risk factors for the development of acute renal failure. However, there is not yet enough evidence in the published data to explain the relationship between multidrug resistant infections and the development of acute renal failure.

Acute Respiratory Distress Syndrome

Nosocomial pneumonia is a frequent complication of ARDS and *vice versa*. Epidemiologic studies have reported that VAP was present in 20 – 75 % of patients dying of ARDS [65]. Fibrin deposition within the air space is one of the hallmarks of ARDS. Alveolar fibrin deposits appear to contribute to the magnitude of the inflammatory response by virtue of the ability of their cleavage and degradation products to promote chemotaxis, to increase vascular permeability, and to exert modulatory effects on various immune cells. In addition, fibrin may participate in the resolution phase of ARDS, possibly contributing to lung fibrosis by providing a matrix for macrophage migration and by promoting angiogenesis and collagen deposition [66].

Conclusion

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Despite recent advances in VAP management, VAP cannot yet be prevented. Some risk factors for developing VAP are not modifiable and the etiology of each episode varies markedly according to the time to pneumonia onset and underlying diseases in the host. The VAP-PIRO approach takes into account these risk factors and the consideration of predisposing conditions, the nature and extent of insult, the nature and magnitude of the host response; in addition, the degree of concomitant organ dysfunction provides a useful and novel approach to VAP. The VAP-PIRO approach may improve the understanding of the natural history and the stratification of patients according to severity of each VAP episode. VAP-PIRO could be useful both for benchmarking and for balancing sickness severity in future randomized clinical trials.

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