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Nosocomial pneumonia in the intensive care unit: how should treatment failure be predicted?

Pneumonia nosocomial na unidade de terapia intensiva: é possível prever a falha do tratamento?

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INTRODUCTION

Intensive care unit-acquired pneumonia (ICUAP) is the most common infection acquired by critically ill patients and leads to poor patient outcomes, such as prolonged hospital stays and high associated costs.[1,2] ICUAP includes pneumonia acquired during ICU stays of patients under mechanical ventilation (ventilator-associated pneumonia, or VAP), as well as of non-ventilated patients (NV-ICUAP). Although the current literature contains few studies examining NV-ICUAP, it has been suggested that both diagnoses present with similar pathogens and, depending on case-mix, similar outcomes.[1]

ICUAP remains a major cause of morbidity and mortality[1,2] despite advances in antimicrobial therapy, supportive care, and the use of a broad range of preventive measures.[2,3] Several factors that likely play a role in the poor outcomes of ICUAP patients include illness severity, the presence of pre-existing conditions, and the host response to infection.[3,4] Early and adequate empirical treatment is also a crucial prognostic determinant. The weight that each of these factors has on influencing final patient outcomes has been a matter of debate for decades, with recent studies reporting a small attributable mortality to VAP after applying appropriate analysis.[5]

The treatment of ICUAP is challenging for attending physicians in the ICU, as they must integrate the clinical decision-making process with low-quality images, interference from other invasive devices, and lung infiltrates secondary to other syndromes. This is a more common problem for mechanically ventilated patients, as clinical, laboratory, and microbiologic findings can be related to a myriad of factors in addition to pneumonia.[2]

One of the key determinants of ICUAP patient outcomes is the appropriate initiation of antibiotic treatment.[6] Early and adequate antibiotic administration is a main factor in obtaining good outcomes; however, prescribing effective empirical antibiotics has been challenging. The problem lies within a clinician's ability to balance selection of the correct initial antibiotic, which many times leads to excessive use of broader spectrum drugs, as opposed to selection of narrow spectrum antibiotics, which may increase the risk of error in choosing empirical coverage. Additionally, because of competing events in the critical care scenario, some clinical and laboratory changes following initial treatment cannot always be attributable to pneumonia treatment.

Natural course of intensive care unit-acquired pneumonia

The evolution of ICUAP episodes in patients receiving adequate antibiotic treatment should be considered when defining what is considered adequate management of the condition.[7] Determinations of ICUAP improvement or resolution can be based on either clinical or microbiological end-points. Both approaches are recommended by current guidelines, and utilizing a combination of them is likely the most advisable course of action for the clinician.[2]

To define clinical resolution, we can evaluate leukocytosis, body temperature, purulence of secretions, hypoxemia (such as PaO_2/FiO_2), and radiological findings.[2,7,8] One score that encompasses all of these parameters is the Clinical Pulmonary Infection Score (CPIS), which was originally validated for the diagnosis of VAP.[9,10] Alternatively, microbiologic resolution is defined by the eradication of causative pathogens. Reliance on this end point has been a subject of debate, considering the difficulties inherent in separating colonization from infection in airway diseases, as well as the cost-effectiveness of repeated sampling for culture.[2,7]

Though it is not well defined in the current literature, some studies have helped to elucidate the correct timeline for determining ICUAP resolution. In a cohort of 27 patients with VAP who were considered adequately treated upon diagnosis, the first normalized parameter was fever after 5 days, then oxygenation (defined as PaO_2/FiO_2 ratio>250) after 6 days, and finally leukocyte count after 8 days post treatment initiation.[11] Microbiological resolution was achieved later (after 10 days). The mean time to resolution was 6 days when considering the clinical response and 10 days when including microbiological parameters. Similar findings were reported in another study of 401 patients who were also adequately treated upon VAP diagnosis: they presented improvement in fever, leukocytosis, radiological findings and oxygenation following the first week of treatment.[12]

CPIS scores can also be used to define clinical resolution of ICUAP.[7,9,10] According to current findings, CPIS scores decrease progressively until day 9 in adequately treated ICUAP patients, with a value of less than 6 points following the 5th day of treatment. Outcome measurements of patients presenting with specific diseases such as acute respiratory distress syndorme and multiple trauma require special consideration: although temperature remains an early marker of ICUAP resolution in such patients, their percentage of leucocyte and oxygenation abnormalities remains high following the first week of treatment, while clearance of secretions and radiological resolution are considered delayed end-points.

Recently, the assessment of lung re-aeration in 30 patients with adequately treated VAP was described. Data obtained from chest radiography, lung ultrasound and lung computed tomography (CT) were compared for clinical utility. Lung ultrasound and CT proved to be useful tools for evaluating ICUAP resolution; however, chest radiography was not. Indeed, in all patients who exhibited clinical response, there was a CT-demonstrated improvement in aeration. Conversely, chest radiography was variable among responder patients, remaining unchanged in 10% of the study group, improving in 50% and deteriorating in 40%. For non-responders, chest radiography produced random results.[13]

The evaluation of various biomarkers has also been used to determine patient responses to ICUAP treatment regimens. C-reactive protein and procalcitonin have been the most widely studied in this regard.[14,15] A lack of decrease in these biomarkers at 72 hours post initial treatment is associated with poor outcomes, such as mortality and treatment failure. Some patients also present with a complex time course for these biomarkers.

Microbiologic evolution is usually correlated with clinical response, and its definition depends on respiratory sample collection methodology. In evaluating serial cultures, it was demonstrated that at 72 hours following treatment, almost 70% of patients present sterilization and that persistence of bacterial growth in the small airway at this point was associated with poor outcomes.[7] However, it is not yet established whether non-sterilized patients require treatment modification. For instance, 20% of patients presenting with low-grade bacterial growth following treatment exhibited only small differences in outcome when compared to the sterilization group. While the clinical usefulness of this information remains unclear, it has been described that some pathogens appear to be risk factors for persistence or relapse, such as non-fermenting Gram-negative bacteria.

Identifying intensive care unit-acquired pneumonia treatment failure

A main difficulty faced by clinicians in identifying ICUAP treatment failure is an understanding of the

length of time that can safely elapse before deciding that a modification to the treatment regimen is necessary. In general, it is suggested that patients be re-evaluated at 48 to 72 hours following initial treatment. This is a pragmatic time frame for many reasons, including the availability of microbiological results. It is also the amount of time required for the prescribed antibiotic to kill a significant amount of colonies, as well as enough time for potential differential diagnoses to become more evident.[9,16]

For the reasons stated above, recognizing variables associated with poor clinical outcomes in patients with ICUAP at early time points can be valuable. Towards this end, our group has established[16] and validated[9] a set of predictors for adverse ICUAP events (including mortality, ventilator free-days, and ICU stay). The Predictors of Adverse Outcomes (PAO) are described in table 1. PAO were evaluated at 72 and 96 hours following antibiotic treatment, and it was found that the presence of at least one criterion increased the risk of poor patient outcomes. The parameter most consistently associated with mortality was oxygenation, which agrees with current studies indicating

this parameter as being the most accurate diagnostic and dynamic parameter for ICUAP.

The attending clinician should consider the natural history of ICUAP to better manage these patients. Additionally, the recognition of early predictors of adverse events seems to be very useful in examining patient response to antibiotic treatment. Despite this information, medication agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMEA) still propose 28-day mortality as the primary end-point in evaluating antibiotic efficacy for ICUAP, through a non-inferiority design.[17] The consequence of staying with this end-point and design is the need for very large sample sizes, which may not only unnecessarily prolong the study but also risk unintentional evaluation of factors other than antibiotic treatment. Given that treatment failure at 96 hours is more than reasonably associated with mortality, this may be a better end-point for investigating antibiotic efficiency, especially in the current era wherein the need for new antimicrobials is urgent.

Table 1 - Predictors of adverse outcomes in intensive care unit-acquired pneumonia

Criteria	Definition
No improvement of the PaO_2/FiO_2 ratio	Defined as the PaO_2/FiO_2 ratio at 72 hours equal or lower than the PaO_2/FiO_2 ratio at the onset of pneumonia*
Need for intubation due to NV-ICUAP	Defined as need for intubation at least 24 hours after starting antibiotics
Persistence of fever or hypothermia AND purulent secretions	Defined as persistence of fever (>38° C) or hypothermia (<35.5° C) together with purulent respiratory secretions
Worsening of radiologic infiltrate by >50%	Defined as greater than or equal to a 50% increase in the pulmonary infiltrates on chest radiograph
Development of septic shock or multiple organ failure following treatment	Defined as occurrence of septic shock or multiple organ dysfunction syndrome (defined as three or more organ system failures) not present on day 1

* This measurement must be performed in the absence of other potential causes of alterations to the PaO_2/FiO_2 ratio, such as new development of atelectasis, patient-ventilator asynchrony, or respiratory secretions. PaO_2/FiO_2 - partial pressure of oxygen/fraction of inspired oxygen; NV-ICUAP - non-ventilated patients.

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