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Intensive care unit-acquired pneumonia due to *Pseudomonas aeruginosa* with and without multidrug resistance☆

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Summary *Objective: Pseudomonas aeruginosa* often presents multi-drug resistance (MDR) in intensive care unit (ICU)-acquired pneumonia (ICUAP), possibly resulting in inappropriate empiric treatment and worse outcomes. We aimed to identify patients with ICUAP at risk for these pathogens in order to improve treatment selection and outcomes.
Methods: We prospectively assessed 222 consecutive immunocompetent ICUAP patients confirmed microbiologically. We determined the characteristics, risk factors, systemic inflammatory response and outcomes of *P. aeruginosa* pneumonia (Pa-ICUAP), compared to other aetiologies. We also compared patients with MDR *vs.* non-MDR Pa-ICUAP.
Results: Pseudomonas aeruginosa was the most frequent aetiology (64, 29%); 22 (34%) cases had MDR. Independent predictors for Pa-ICUAP were prior airway colonization by *P. aeruginosa*, previous antibiotic treatment, solid cancer and shock; alcohol abuse and pleural effusion were independently associated to lower risk for Pa-ICUAP. Chronic liver disease independently

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predicted MDR among Pa-ICUAP. The inflammatory biomarkers were similar between all groups. Patients with Pa-ICUAP had lower unadjusted 90-day survival ($p = 0.049$). However, the 90-day survival adjusted for confounding factors using a propensity score did not differ between all groups.

Conclusion: Pseudomonas aeruginosa remains the most frequent aetiology of ICUAP, with high prevalence of MDR. These risk factors should be taken into account to avoid inappropriate empiric antibiotics for Pa-ICUAP. *Pseudomonas aeruginosa*, regardless multidrug resistance, was not associated with different propensity-adjusted survival.

Introduction

Intensive care unit (ICU)-acquired pneumonia (ICUAP), which includes ventilator-associated pneumonia (VAP) and non-ventilator ICUAP, is the leading infection in critically-ill patients and a major cause of morbidity and mortality.[1,2]

Pseudomonas aeruginosa is among the most frequent etiologic agents causing ICUAP, with a high proportion, 23%—46%, of multidrug resistance (MDR).[3—5] Recent studies in patients with *P. aeruginosa* ICUAP (Pa-ICUAP) found that MDR was associated with increased needs for mechanical ventilation[6] and increased mortality,[5] compared to non-MDR Pa-ICUAP. *Pseudomonas aeruginosa*, particularly with MDR, is potentially associated to inappropriate empiric antibiotic treatment, a major determinant of mortality in patients with ICUAP.[7] Then, accurate identification of patients at risk for Pa-ICUAP, with and without MDR, is important and could potentially improve the management and survival of these patients.

A recent epidemiologic study found that patients with VAP caused by *P. aeruginosa* had high rates of prior colonisation by this pathogen.[8] However, this study could not identify any risk factor for this pathogen as aetiology of VAP. This information warrants the need of more studies on the risk factors for *P. aeruginosa* aetiology in patients with ICUAP, and particularly for those cases with MDR. Additionally, there is limited information on the inflammatory response associated to *P. aeruginosa* aetiology of ICUAP.

In view of the renewed interest by pharmacological industries and regulatory agencies to have as soon as possible new anti-pseudomonal antibiotics and preventive strategies such as monoclonal antibodies, an accurate identification of the risk factors for Pa-ICUAP, with and without MDR, is particularly relevant and would help selecting better the target population in future randomized clinical trials.

The aim of this study was to assess the frequency, characteristics, risk factors, systemic inflammatory response and outcomes of Pa-ICUAP, comparing with other aetiologies, with an additional focus on differences between cases due to MDR and non-MDR *P. aeruginosa*.

Methods

Patients

The study was conducted in medical and surgical ICUs with overall 45 beds of an 800-bed university hospital. Data were prospectively collected from January 2007 to June 2013. The investigators made daily rounds in all ICUs. Patients were consecutively included and only the first episode was analysed. We included patients older than 18 years, with clinical suspicion of pneumonia acquired after 48 h of ICU admission. We excluded patients without a positive microbiologic diagnosis, and those cases of polymicrobial Pa-ICUAP with additional pathogens. Patients with severe immunosuppression (neutropenia after chemotherapy or haematopoietic transplant, drug-induced immunosuppression in solid-organ transplant or cytotoxic therapy, and HIV-related disorders) were not registered.

The study was approved by the institution's Internal Review Board (registry number 2009/5427). Written informed consent was obtained from patients or their next-of-kin.

Definition of pneumonia

The clinical suspicion of pneumonia was based on clinical criteria: new or progressive radiological pulmonary infiltrate together with at least two of the following: temperature $>38\ ^\circ C$ or $<36\ ^\circ C$, leucocytosis $>12{,}000/mm^3$ or leukopenia $<4000/mm^3$, and purulent respiratory secretions.[1,9,10] We considered VAP in patients with invasive mechanical ventilation for 48 h or more. Patients were classified as VAP or non-ventilator ICUAP, i.e. cases who do not meet VAP criteria.[2] Early-onset pneumonia was defined as occurring within the first 4 days of hospitalization.[1]

Microbiology and antimicrobial treatment

The microbiologic evaluation was extensively addressed in previous reports.[11,12] Briefly, we collected at least one lower respiratory tract sample (sputum in non-intubated patients or tracheobronchial aspirates (TBAS) in those intubated, and bronchoalveolar lavage (BAL) if possible, within the first 24 h of inclusion). Blood cultures and from pleural fluid if puncture was indicated were also taken. Microbial identification and susceptibility testing were performed by standard methods.[13] Polymicrobial pneumonia was defined as those with more than 1 potentially-pathogenic microorganisms identified.[14] Prior colonization was defined as a previous positive culture of respiratory samples during the current hospital admission without clinical suspicion of pneumonia. During the recruitment period of this study, surveillance cultures of respiratory samples were not systematically performed in patients without clinical suspicion of pneumonia, particularly in those not intubated previously. Patients did not receive selective digestive decontamination.

The initial empiric antimicrobial treatment was administered according to local adaptation of guidelines,[1] based