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Risk factors for *Pseudomonas aeruginosa* pneumonia in the early twenty-first century

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Abbreviations

COPD	Chronic obstructive pulmonary disease
ICU	Intensive care unit
MDR	Multidrug-resistant
OR	Odds ratio
PSA	*Pseudomonas aeruginosa*
RR	Relative risk
VAP	Ventilator-associated pneumonia

Introduction

Along with *Staphylococcus aureus*, *Pseudomonas aeruginosa* (PSA) heads the list of pathogens associated with Hospital-acquired pneumonia [1–3]. Indeed, even in patients with appropriate empiric antibiotic administration [3], the attributable mortality has been estimated to be 13.5 %. In survivors, PSA increases ICU length of stay and use of healthcare resources. In the early twenty-first century, the increase and dissemination of clones with progressive resistance are a cause of concern. In an international study of over 1,200 ICUs in 75 countries, the risk of infections, including those due to *Pseudomonas* species, was found to increase with duration of ICU stay; moreover, infection was also associated with an increased risk of mortality [1]. Therefore, understanding the epidemiology of this pathogen and identifying the risk factors the development of pneumonia should be a priority in research, and has obvious implications for infection control/prevention and therapy.

In 1994, a seminal article published in *Intensive Care Medicine* [4] reported that the risk of ventilator-associated pneumonia (VAP) due to PSA was increased in patients with chronic obstructive pulmonary (COPD) disease [relative risk (RR) 29.9], a mechanical ventilation period longer than 8 days (RR 8.1), and prior use of antibiotics (RR 5.5). The analysis addressed risk factors for PSA versus other types of VAP, but not for PSA VAP incidence per se. Because respiratory tract infections by this organism are associated with high mortality, empiric treatment of VAP episodes in this population must have a strong anti-pseudomonal activity until culture data become available [5]. Seventy-seven articles have referenced this manuscript over the past 20 years (Scopus, 15 May 2013), 32 of them reviews or guidelines. In the light of the current challenges posed by the increasing resistance to antibiotics among pathogens [6], we decided to

reassess the contribution of the *Intensive Care Medicine* study to PSA pneumonia [4].

Pseudomonas aeruginosa and VAP

The analysis by the French national nosocomial pneumonia surveillance group [7] reported an association between PSA and advanced age and length of mechanical ventilation, antibiotics at admission, transfer from a medical unit or ICU, and admission to a ward with a high incidence of patients with *Pseudomonas* infection. PSA was less frequent in trauma patients and in those admitted to a ward with high admission turnover.

The incidence of PSA VAP may differ in patients who are exposed to selective digestive decontamination (SDD) and those who are not [7]. The influence of specific risk factors in both cohorts has not been analyzed. However, the association between prolonged antibiotic exposure and PSA pneumonia is well confirmed [8]. Therefore, reducing the duration of antibiotic use should be promoted if feasible as a stewardship strategy that may reduce the risk of PSA pneumonia.

Pseudomonas aeruginosa has been reported to be one of the top three organisms causing respiratory infection which are resistant to carbapenems [9]. Independent risk factors associated with imipenem-resistance in PSA, *S. aureus*, *Acinetobacter baumannii*, or *Stenotrophomonas* pneumonia are previous use of a fluoroquinolone or aminoglycoside, use of invasive blood pressure monitoring (probably a surrogate for vasopressor use), and bilateral chest X-ray involvement.

Bonten et al. [10] assessed how risk factors for VAP identified in epidemiologic studies have provided a basis for testable interventions in randomized trials. Their study hypothesized that in hospital settings with low baseline levels of antibiotic resistance, approaches to prevent VAP may be different from those in place in settings with high levels of antibiotic resistance. Indeed, a recent report [11] evaluating prescriptions of antibiotics for pneumonia in 27 European ICUs confirmed that baseline incidence of resistance in a specific ICU/ward should be taken into account in the decision-making process for prescribing antibiotics for pneumonia. Moreover, recent studies [12] suggested that even in the absence of classical risk factors, PSA may cause pneumonia, sometimes of early-onset VAP.

A specific group of interest is the subset of patients with mechanical ventilation and concomitant antibiotic exposure. In these patients, PSA was independently associated with an ICU stay of 5 days or longer (RR 3.59), and absence of coma (RR 8.36) [13]. The risk of pathogens other than PSA in early-onset pneumonia associated with coma was estimated to be 87.5 %. This observation emphasizes that the risk factors in patients receiving recent antibiotic treatment caused by PSA or other organisms are not the same, and may have implications for preventive and therapeutic approaches for pneumonia.

Interestingly, Flanagan et al. [14] showed that bacterial diversity decreased following the administration of antibiotics and that communities became dominated by a single pulmonary pathogen. PSA became the dominant species in six of seven patients studied, even though five of these six were treated with antibiotics to which it was sensitive in vitro. These data demonstrate that the loss of bacterial diversity under antibiotic selection is strongly associated with the development of pneumonia in ventilated patients colonized with PSA.

Trouillet et al. [15] sought to determine the epidemiologic characteristics of ICU patients who developed VAP caused by piperacillin-resistant PSA or piperacillin-susceptible PSA. Multivariate analysis identified the following significant independent factors for piperacillin-resistant PSA: presence of an underlying fatal medical condition [odds ratio (OR) 5.6], previous fluoroquinolone use (OR 4.6), and initial disease severity (OR 0.8). This study suggested that restricted fluoroquinolone use was the sole independent risk factor susceptible to intervention.

Summary

Multiple studies have confirmed the association of risk factors for exogenous cross-contamination (>5 days and prior antibiotic exposure) and endogenous colonization (such as COPD) (Table 1). Recently, PSA pneumonia has been identified in patients without these risk factors. Updated information on risk factors has implications for infection management and control, suggesting that the classical paradigm of restricting anti-pseudomonal agents to patients with hospitalization longer than 1 week or prior antibiotic exposure may lead to a substantial delay

Table 1 Summary of risk factors for isolation of multidrug-resistant *Pseudomonas aeruginosa*

Admission to chronic facilities
Prolonged hospitalization
Prolonged ICU stay
Mechanical ventilation
Candida albicans airway colonization
High severity of illness
Invasive blood pressure monitoring
Bilateral chest X-ray involvement
Previous antibiotic exposure
Multiple agents
Broad spectrum agents
Fluoroquinolones: levofloxacin > ciprofloxacin
Aminoglycoside
Cephalosporins: broad-spectrum/anti-pseudomonic
Carbapenems: especially imipenem; except ertapenem

in appropriate therapy in some patients and may compromise outcomes. The emergence of newer multidrug-resistant (MDR) clones with susceptibility only to amikacin and colistin represents a potential challenge that requires further epidemiological, molecular, and experimental research.

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