Prospective Observational Study of Prior Rectal Colonization Status as a Predictor for Subsequent Development of Pseudomonas aeruginosa Clinical Infections

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The potential role of Pseudomonas aeruginosa (PA) intestinal colonization in the subsequent development of infections has not been thoroughly investigated. The aims of this study were to assess the role of PA intestinal colonization as a predictor of subsequent infections and to investigate the risk factors associated with the development of PA infection in patients in the intensive care unit (ICU). For this purpose, a prospective study was conducted that included (i) active surveillance of PA rectal colonization at ICU admission and weekly until ICU discharge, (ii) detection of PA clinical infections, and (iii) genotypic analysis by pulsed-field gel electrophoresis (PFGE). A total of 414 patients were included, of whom 179 (43%) were colonized with PA. Among the 77 patients who developed PA infection, 69 (90%) had prior PA colonization, and 60 (87%) of these showed genotyping concordance between rectal and clinical isolates. The probability of PA infection 14 days after ICU admission was 26% for carriers versus 5% for noncarriers (P < 0.001). Cox regression analysis identified prior PA rectal colonization as the main predictor of PA infection (hazard ratio [HR], 15.23; 95% confidence interval [CI], 6.9 to 33.7; P < 0.001). Prior use of nonantipseudomonal penicillins was also identified as an independent variable associated with PA infection (HR, 2.15; 95% CI, 1.3 to 3.55; P < 0.003). Our study demonstrated that prior PA rectal colonization is a key factor for developing PA infection.

Pseudomonas aeruginosa (PA) is a Gram-negative bacterium that is one of the most common nosocomial pathogens, causing severe infections with significant morbidity and mortality (1). PA has an intrinsic resistance to a wide range of antibiotics and a notable ability to acquire resistance during the course of antibiotic therapy, resulting in the development of multidrug-resistant strains (2). In recent decades, the incidence of infections caused by multidrug-resistant bacteria has continuously increased. This problem is of major concern due to the emergence of strains resistant to almost all of the available antimicrobial drugs (3).

Despite the growing number of antibiotic-resistant infections, the clinical consequences of multidrug resistance are still unclear. Experimental studies suggest a possible association between acquisition of resistance mechanisms and a fitness cost, which decreases the virulence of PA (4–6). Nevertheless, other researchers propose that resistant bacteria may develop additional compensatory mechanisms that can compensate for the fitness cost caused by resistant mutations (7, 8). The current data on the correlation between the resistance pattern of PA and clinical pathogenicity are limited. In an earlier study, our group determined the invasive capacity of PA by analyzing its ability to produce bloodstream infections (9). However, that study had some limitations, such as its retrospective design and the fact that no active surveillance was performed to detect PA colonization.

Intestinal colonization is believed to play an essential role in the pathogenesis of PA infection in patients in the intensive care unit (ICU) (10–14). Although it is widely assumed that colonization precedes the development of infection, little is known about its relative importance in this process. A few descriptive studies have been conducted to assess the issue (14–16); however, the design of these studies did not allow for an assessment of the temporal relationship. Genotype studies are needed to establish a causal link between surveillance strains and clinical samples.

We therefore conducted a prospective active surveillance program in ICU patients to investigate the role of PA rectal colonization as a predictor of subsequent PA infection to determine whether there are differences in the ability to develop infection based on the presence of PA on rectal surveillance cultures. We also investigated the potential influence of other variables on the development of PA infection in order to identify modifying risk factors associated with these infections.

(This paper was presented in part at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 5 to 9 September 2014 [17].)

MATERIALS AND METHODS

Setting. This study was performed in one of the three general ICU units at the Hospital Universitari de Bellvitge, a 700-bed tertiary-care institution for adult patients in Barcelona. The ICU is a 12-bed, private-room ward.
defined clinical when the score was
these antimicrobial agents (24). Pulsed-field gel electrophoresis (PFGE)
CA, USA). CLSI criteria were used to define susceptibility or resistance to
biotic categories.
strains were also included as MDR-PA. Non-multidrug-resistant PA
was defined as a strain nonsusceptible to at least one agent in all but two
antipseudomonal antimicrobial categories. Therefore, XDR-PA
resulting from exposure was very short (1.5 days)
identified with PA. Information describing the study sample was re-
lishment (25). We performed PFGE analysis of 69 pairs of PA strains isolated from the same
patient: 42 samples of non-MDR, 12 pairs of MDR non-XDR, and 15 pairs of XDR. DNA restriction patterns generated by PFGE were interpreted
according to the guidelines (26).

Statistical analysis. Comparative analyses of baseline characteristics of the groups based on results of surveillance culture were performed with the Student t test or the Mann-Whitney U test for continuous variables
and the χ2 or Fisher’s exact test for categorical variables, as appropriate
(Table 1). Continuous variables are expressed as means (standard devia-
tions) or medians (interquartile range), depending on the distribution.
The Kaplan-Meier method was used to investigate the role of PA rectal colonization in subsequent infections. Only single patients were included. PA clinical infection was considered the main event. Time zero was the
date of ICU admission, and patients were censored when they were dis-
charged from the ICU or when they died for reasons other than infection.
The risk to develop clinical infections due to PA is different before and
after a prior rectal colonization. Therefore, positive surveillance culture
was treated as a time-dependent variable to deal with the difference in
risk. The time-dependent covariate was created using the date of the first posi-
tive surveillance culture. Univariate and multivariate analyses of param-
ters predicting PA infection were made with Cox regression analysis
(Table 2). Variables that were associated with infection and had a P value of <0.10 in the crude analyses were included in the adjusted analysis. To
compare the ability to develop infection according to the profile of resis-
tance, we included only the first episode of infection. If colonization was
demonstrated after infection, or if no rectal colonization was identified
during the follow-up, the episode of infection was not analyzed (Fig. 1).

The impact of prior antimicrobial therapy was evaluated when com-
paring the rectal colonization status of the patients (Table 1). To do that,
data on antibiotic exposure were collected from 3 months prior to ICU
admission until the day that surveillance culture become positive in col-
onized patients or the day of discharge or death in noncolonized patients.
In regard to analyses conducted to identify parameters associated with PA
clinical infection (Table 2), antibiotic exposure was measured until the
day of the infection for infected patients and until the day patients were
censored (discharge or death) if infection did not occur. Antibiotic expo-
sure was analyzed as a binary variable and was recorded according to
antibiotic classes. Data were analyzed using SPSS (Statistical Package for
Social Sciences) version 19.0 and R version 3.1.2 software. A P value of
<0.05 indicated statistical significance.

RESULTS
Epidemiological and clinical characteristics. A total of 414 pa-
ients were included in the study, of whom 179 (43%) were colon-
ized with PA. Information describing the study sample was re-
ported elsewhere (27).

During the study, 97 episodes of PA infection occurred in 77
patients: 14 patients presented two episodes of PA infection, and
three patients presented three episodes. The overall incidence of
PA infection in ICU patients during the study was 19% (77/414). Clinical and epidemiological characteristics of the patients in-
cluded in the study are shown in Table 1. Among the 77 first
episodes of infection, 45 (58%) were caused by non-MDR-PA, 12
(16%) by MDR non-XDR strains, and 20 (26%) by XDR-PA. The
source of the infection in non-MDR-PA infections was respiratory in
34 patients (76%), intravascular catheter-related bacteremia in
3 (7%), intra-abdominal in 2 (4%), osteoarticular in 1 (2%), and
other sources in 5 (11%), 1 of whom had bacteremia. The source of
MDR non-XDR infection was respiratory in 10 (84%) patients
(2 with bloodstream infection), intravascular catheter-related
bacteremia in 1 (8%), and intra-abdominal in 1 (8%). The origin

providing care to medical and surgical patients, including those who have undergone solid-organ transplantation.

Study design and data collection. This prospective cohort study in-
cluded all patients admitted to the ICU for >48 h during an 18-month
period (1 January 2012 to 1 July 2013). The study design was approved by
the Clinical Ethics Committee of the Hospital Universitari de Bellvitge,
and patients or family provided written informed consent.

An active surveillance study was performed by obtaining rectal swab
samples on ICU admission and weekly until ICU discharge in order to
identify digestive tract colonization of PA. Patients were followed from
ICU admission to ICU discharge in order to detect invasiveness (defined
as the ability to develop infection in carriers) and to determine patients’
outcomes. Clinical samples were collected as requested by medical staff.

Definitions. Demographic and clinical characteristics of each patient
were collected prospectively. Sex, age, length of hospitalization before
ICU admission, underlying diseases, and the Charlson comorbidity index as an indicator of patient comorbidity were recorded on admission (18).

Patients were considered to have cancer when malignancy was diagnosed
in the last 5 years or if they were receiving oncological therapy. They were
considered to be immunosuppressed if chemotherapy, radiotherapy, cor-
ticosteroids, or other immunosuppressive agents were administered in the
3 months prior to the ICU admission. Prior surgery was defined as the
presence of surgical events within 3 months prior to ICU admission. The
Simplified Acute Physiologic Score (SAPS II) was used to estimate pa-
infectious severity at ICU admission (19). Prior hospital stay was
recorded according to antibiotic family: fluoroquinolones, carbapenems,
aminoglycosides, antipseudomonal, and nonantipseudomonal cephalo-
sporins, and antipseudomonal monobactam.

Exposure to antibiotics was determined as the number of days of an-
tibiotic treatment in the 3 months prior to the ICU admission and was
recorded according to antibiotic family: fluoroquinolones, carbapenems,
aminoglycosides, antipseudomonal, and nonantipseudomonal cephalo-
sporins, and antipseudomonal and nonantipseudomonal penicillins.

Data on other antibiotic families (colistin, glycopeptides, monobactam,
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of XDR-PA infection was respiratory in 12 (60%) patients (1 with bacteremia), intravascular catheter-related bacteremia in 4 (20%), urinary-source bacteremia in 2 (10%), intra-abdominal in 1 (5%), and unknown-source bacteremia in 1 (5%). XDR and other PA phenotype strains differed significantly in regard to the source of infection, with XDR-PA infection presenting a higher percentage with a vascular or urinary catheter focus (6 patients [30%] in XDR-PA versus 4 patients [7%] in non-XDR-PA; \( P = 0.016 \)).

**Phenotypic and genotypic analysis.** Among the 69 pairs of PA strains with subsequent infection, 60 (87%) showed concordance between rectal and clinical isolates: 39/42 (93%) in non-MDR infections, 8/12 (67%) in MDR non-XDR infections, and 13/15 (87%) in XDR infections. The genotypic analysis confirmed a clonal dissemination in XDR-PA strains, which was due to a cluster belonging to the high-risk clone ST175.

**Risk factors for PA infection.** Among the 77 patients who developed PA infection, 69 (90%) presented with prior PA intestinal colonization, while 8 (10%) did not (5 patients with no colonization during admission and 3 with rectal colonization identified after PA infection) (Fig. 1). The proportion of infection was 39% in colonized patients and 3.4% in noncolonized patients (\( P < 0.001 \)).

The unadjusted probabilities of PA infection in PA-colonized patients are shown in Fig. 2. The probability of PA infection at 14 days after ICU admission was 26% for PA-colonized patients versus 5% for noncolonized patients (log rank, \( P = 0.001 \)). Baseline characteristics and variables examined as possible predictors of PA clinical infection are displayed in Table 2. After adjusting for Charlson index, chronic liver disease, prior PA rectal colonization, and prior consumption of fluoroquinolones, antipseudomonal penicillins, and nonantipseudomonal cephalosporins, a Cox regression model showed prior PA intestinal colonization to be the main factor associated with development of PA infection (hazard ratio [HR], 15.23; 95% confidence interval [CI], 6.9 to 33.7; \( P < 0.001 \)).

Sixty first episodes of infection were included (39 non-MDR, 8 MDR non-XDR, and 13 XDR) (Fig. 1). Due to the existence of a

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**TABLE 1 Clinical and epidemiological characteristics of patients based on results of surveillance culture**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of PA* rectal colonized patients (%) (n = 179)</th>
<th>No. of PA noncolonized patients (%) (n = 235)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr, median [interquartile range])</td>
<td>66.8 (56.4–75.3)</td>
<td>64.3 (51.2–73.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex, male</td>
<td>126 (70)</td>
<td>139 (59)</td>
<td>0.013</td>
</tr>
<tr>
<td>Charlson index score (median [interquartile range])</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
<td>0.76</td>
</tr>
<tr>
<td>SAPS II score at ICU admission (median [interquartile range])</td>
<td>44 (36–52)</td>
<td>43 (34–51)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Main underlying disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (24)</td>
<td>65 (28)</td>
<td>0.50</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>47 (26)</td>
<td>47 (20)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>75 (42)</td>
<td>75 (32)</td>
<td>0.04</td>
</tr>
<tr>
<td>End-stage renal failure</td>
<td>24 (13)</td>
<td>30 (13)</td>
<td>0.88</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>24 (13)</td>
<td>30 (13)</td>
<td>0.88</td>
</tr>
<tr>
<td>Vascular/degenerative brain disease</td>
<td>25 (9)</td>
<td>20 (14)</td>
<td>0.08</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>34 (19)</td>
<td>55 (23)</td>
<td>0.34</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>44 (25)</td>
<td>63 (27)</td>
<td>0.73</td>
</tr>
<tr>
<td>Prior hospital stay</td>
<td>132 (73)</td>
<td>96 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>107 (60)</td>
<td>125 (53)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>54 (30)</td>
<td>65 (28)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Prior antibiotic use (days, median [interquartile range])</strong></td>
<td>7 (2–14)</td>
<td>8 (0–16)</td>
<td>0.95</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>35 (20)</td>
<td>41 (17)</td>
<td>0.61</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>46 (26)</td>
<td>60 (26)</td>
<td>1</td>
</tr>
<tr>
<td>Antipseudomonal penicillins</td>
<td>68 (38)</td>
<td>70 (30)</td>
<td>0.07</td>
</tr>
<tr>
<td>Nonantipseudomonal penicillins</td>
<td>65 (36)</td>
<td>57 (24)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Antipseudomonal cephalosporins</td>
<td>16 (8)</td>
<td>16 (7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Nonantipseudomonal cephalosporins</td>
<td>20 (11)</td>
<td>22 (9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>5 (3)</td>
<td>6 (3)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Source of PA clinical infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>71 (92)</td>
<td>6 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAP</td>
<td>53 (69)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>VAT</td>
<td>38 (49)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>15 (20)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Catheter</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>6 (8)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Osteoarticular</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Unknown/endogenous</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>a</strong> PA, <em>Pseudomonas aeruginosa</em>.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>b</strong> VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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of XDR-PA infection was respiratory in 12 (60%) patients (1 with bacteremia), intravascular catheter-related bacteremia in 4 (20%), urinary-source bacteremia in 2 (10%), intra-abdominal in 1 (5%), and unknown-source bacteremia in 1 (5%). XDR and other PA phenotype strains differed significantly in regard to the source of infection, with XDR-PA infection presenting a higher percentage with a vascular or urinary catheter focus (6 patients [30%] in XDR-PA versus 4 patients [7%] in non-XDR-PA; \( P = 0.016 \)).

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Sixty first episodes of infection were included (39 non-MDR, 8 MDR non-XDR, and 13 XDR) (Fig. 1). Due to the existence of a
toward an increased risk of infection in non-MDR-PA intestinal potential confounding factors in a multivariate analysis, a trend prior antibiotic use baseline feature 5216 aac.asm.org September 2015 Volume 59 Number 9 Antimicrobial Agents and Chemotherapy dependent variable within the model. Abbreviations: PA, hospital stay variable as it is nearly predicted by the prior colonization variable. Differential risks for development of prior rectal colonization were accounted for using a time-

DISCUSSION
We designed a prospective study of a 1.5-year cohort of patients admitted to a medical and surgical ICU in order to investigate whether PA intestinal colonization contributes to the development of PA infection acquired in the ICU. Our study demonstrated a significant association between PA-colonized patients and the development of PA infection, as evidenced by the fact that the risk of developing PA clinical infections among PA-colonized patients was 15 times higher than the risk found in noncolonized patients (HR, 15.23; 95% CI, 6.9 to 33.7; P = 0.001).

PA has a remarkable ability to colonize and infect patients. Classic epidemiological analysis suggests that there are two major routes of colonization: endogenous and exogenous (10, 11, 13). Intestinal colonization is considered the most important endogenous source preceding the development of PA infection. In these cases, PA infections are polyclonal and caused by the patient's own flora after PA pathological colonization of endogenous reservoirs (10, 13, 14). Additionally, exogenous routes have been demonstrated to play an essential role in the pathogenesis of PA infection, mainly in outbreak situations (13). In the exogenous colonization, patients may become colonized from contaminated reservoirs or other colonized patients (cross-colonization) (13, 14).

Previous studies of digestive colonization have shown that patients who are colonized are significantly more likely to have episodes of invasive infection than patients who are not. The average rate of infection in colonized patients ranges from 15% to 90%. This discrepancy in the rate of invasive infection in the few studies published may be due in part to the patients’ conditions and the methodology applied (10, 14, 16). The sample size in one of these studies was very small, and the correlation between rectal colonization and development of infection was not definitive, since neither serial intestinal tract cultures nor genotypic studies were performed (14).

Thus, to evaluate the association between colonization and infection, we conducted a weekly active surveillance of intestinal tract PA colonization to establish the temporal relation, and we did a molecular study of the strains to define the genetic relatedness of surveillance and clinical samples. Depending on the presence or absence of prior rectal colonization, differences in the ability to develop PA infection were found. In the multivariate model, previous PA intestinal colonization was the main risk factor for the development of PA infection.

<table>
<thead>
<tr>
<th>Variable*</th>
<th>No. with clinical infection (%) (n = 77)</th>
<th>No. with nonclinical infection (%) (n = 337)</th>
<th>Crude analysis</th>
<th>Adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline feature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 yr</td>
<td>40 (52)</td>
<td>175 (52)</td>
<td>1.02 (0.65–1.62)</td>
<td>0.92</td>
</tr>
<tr>
<td>Male</td>
<td>57 (74)</td>
<td>208 (62)</td>
<td>0.88 (0.68–1.13)</td>
<td>0.31</td>
</tr>
<tr>
<td>Charlson score &gt;2</td>
<td>40 (52)</td>
<td>151 (45)</td>
<td>1.49 (0.95–2.34)</td>
<td>0.08</td>
</tr>
<tr>
<td>SAPS II &gt;40 score at ICU admission</td>
<td>45 (58)</td>
<td>195 (58)</td>
<td>1.01 (0.63–1.59)</td>
<td>0.98</td>
</tr>
<tr>
<td>Main underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (18)</td>
<td>94 (28)</td>
<td>0.85 (0.47–1.52)</td>
<td>0.58</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>17 (22)</td>
<td>77 (23)</td>
<td>1.05 (0.61–1.80)</td>
<td>0.86</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>26 (34)</td>
<td>124 (37)</td>
<td>1.02 (0.63–1.63)</td>
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<td>End-stage renal failure</td>
<td>7 (9)</td>
<td>47 (14)</td>
<td>0.93 (0.43–2.05)</td>
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<td>14 (18)</td>
<td>40 (12)</td>
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<td>0.046</td>
</tr>
<tr>
<td>Vascular/degenerative brain disease</td>
<td>11 (14)</td>
<td>34 (10)</td>
<td>0.95 (0.50–4.82)</td>
<td>0.89</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>17 (22)</td>
<td>72 (21)</td>
<td>0.87 (0.50–1.53)</td>
<td>0.64</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>21 (27)</td>
<td>86 (26)</td>
<td>0.78 (0.56–1.55)</td>
<td>0.78</td>
</tr>
<tr>
<td>Prior hospital stay</td>
<td>72 (94)</td>
<td>156 (46)</td>
<td>10.1 (4.08–25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>49 (64)</td>
<td>182 (54)</td>
<td>1.28 (0.80–2.06)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>26 (34)</td>
<td>93 (28)</td>
<td>1.41 (0.87–2.28)</td>
<td>0.16</td>
</tr>
<tr>
<td>Prior rectal colonization</td>
<td>69 (90)</td>
<td>107 (32)</td>
<td>16.57 (7.53–36.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior antibiotic use &gt;10 days</td>
<td>41 (53)</td>
<td>155 (41)</td>
<td>1.33 (0.80–2.12)</td>
<td>0.27</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>12 (16)</td>
<td>74 (22)</td>
<td>0.42 (0.22–0.78)</td>
<td>0.006</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>25 (32)</td>
<td>96 (28)</td>
<td>0.76 (0.48–1.26)</td>
<td>0.30</td>
</tr>
<tr>
<td>Antipseudomonal penicillins</td>
<td>29 (38)</td>
<td>128 (38)</td>
<td>0.33 (0.20–0.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonantipseudomonal penicillins</td>
<td>34 (44)</td>
<td>88 (26)</td>
<td>1.71 (1.08–2.70)</td>
<td>0.022</td>
</tr>
<tr>
<td>Antipseudomonal cephosphorins</td>
<td>11 (15)</td>
<td>25 (7)</td>
<td>1.35 (0.71–2.57)</td>
<td>0.36</td>
</tr>
<tr>
<td>Nonantipseudomonal cephosphorins</td>
<td>17 (22)</td>
<td>31 (9)</td>
<td>1.88 (1.08–3.27)</td>
<td>0.026</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>3 (4)</td>
<td>8 (2)</td>
<td>1.01 (0.32–3.22)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

* For the multivariate analyses, variables with a P value of <0.10 in the univariate analyses were included. To avoid collinearity problems, the final model does not include the prior hospital stay variable as it is nearly predicted by the prior colonization variable. Differential risks for development of prior rectal colonization were accounted for using a time-dependent variable within the model. Abbreviations: PA, Pseudomonas aeruginosa; HR, hazard ratio; CI, confidence interval.
A retrospective cohort study was done in an ICU where surveillance for detecting Gram-negative bacteria was performed routinely. Researchers found that 74.5% of bacteremia incidences were preceded by colonization, and they were associated with higher rates of appropriate therapy than those occurring in noncolonized patients (12). In line with our findings, a recent retrospective cohort study showed that the presence of carbapenem-resistant *Acinetobacter baumannii* on surveillance cultures was strongly associated with the development of carbapenem-resistant *A. baumannii* infections (28). Our study supports these data, as the genotype study revealed an 87% concordance between surveillance and clinical samples. These molecular data, together with the greater ability to develop infection in patients previously colonized with PA (39%), strongly suggest that PA intestinal colonization is a key requirement for developing PA infection in ICU patients. Moreover, knowledge of PA colonization may help to initiate appropriate empirical therapy and may make it possible to restrict the use of the limited number of drugs available for treating MDR-PA infections (colistin or amikacin) to a select group of patients, thus avoiding the deleterious effect of these drugs in patients not receiving these drugs.

Interestingly, the molecular analysis study of pairs did not coincide in three patients with surveillance and clinical samples presenting non-MDR-PA strains. We cannot dismiss the possibility that multiple genotypes of non-MDR-PA strains were present in rectal samples and were not detected due to the impossibility of isolating all strains with a similar phenotype. This difficulty may also have appeared in the six noncoincident pairs of MDR phenotypes. This underlines the complexity of the clinical epidemiology of PA and the difficulty in drawing conclusions regarding epidemiological causality without molecular studies.

Molecular analysis demonstrated the existence of a clonal dissemination in XDR PA strains, which was responsible for an endemic outbreak in our hospital that was previously described (29). The epidemic nature of the XDR-PA cluster may explain differences in the sources of infection, the most common in XDR-PA infection being the vascular and urinary catheter focused, which are associated with a relatively high rate of manipulation and subsequent horizontal transmission. When we compared the ability of polyclonal non-MDR and polyclonal MDR strains to develop infection, we found a trend toward an increased risk of infection in patients colonized by non-MDR-PA strains, which may suggest that non-MDR strains are more pathogenic. However, these differences are not significant, probably due to the small sample size.
and large future studies are needed to confirm the interplay between antibiotic resistance and pathogenicity in the clinical setting.

Finally, previous studies assessed the influence of antimicrobial use in PA intestinal colonization (27). However, little is known about the role of antibiotic therapy in the development of invasive PA infection. In our study, nonantipseudomonal penicillins were associated with PA infection. PA is a microorganism with inherent resistance to these antibiotic classes, and their consumption in PA-colonized patients may lead to selection of PA, thus causing collateral damage to the endogenous microflora (10, 14, 16). While, overall, antibiotics play a decisive role in selecting intestinal flora, fluoroquinolones and antipseudomonal penicillins can preserve activity against a significant number of PA strains and thus protect against the development of PA infections.

The current study is the largest prospective analysis of the role of PA intestinal colonization in subsequent infection. However, several limitations should be mentioned. Despite being a large cohort, the data set in which we performed our analysis of invasiveness according to the resistance profile of PA was limited by the small number of patients infected by different phenotypes. Moreover, the presence of an epidemic clone with different epidemiological behavior forced us to reduce the sample further. Finally, medical staff were not blinded to the rectal surveillance status.

To our knowledge, this is the first study to focus on the ability of PA to develop infection among PA-colonized patients by means of serial active surveillance and genotypic studies. It demonstrates definitively that PA intestinal colonization is a key requirement for the development of PA infection in ICU patients. Additional epidemiological studies are needed to confirm the implications of resistance in clinical invasiveness and to guide antibiotic policy by allowing a more judicious use of the few antimicrobial options available.

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We declare that we have no conflicts of interest.

REFERENCES


