MAJOR ARTICLE

Acquisition of Multidrug-Resistant *Pseudomonas aeruginosa* in Patients in Intensive Care Units: Role of Antibiotics with Antipseudomonal Activity

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A matched case-control study was performed to identify risk factors for acquiring multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) in intensive care unit (ICU) patients during a 2-year period. MDRPA was defined as *P. aeruginosa* with combined decreased susceptibility to piperacillin, ceftazidime, imipenem, and ciprofloxacin. Thirty-seven patients who were colonized or infected with MDRPA were identified, 34 of whom were matched with 34 control patients who had cultures that showed no growth of *P. aeruginosa*. Matching criteria were severity of illness and length of ICU stay, with each control patient staying in the ICU for at least as long as the time period between the corresponding case patient's admission to the ICU and the acquisition of MDRPA. Baseline demographic and clinical characteristics and the use of invasive procedures were similar for case patients and control patients. Multivariate analysis identified duration of ciprofloxacin treatment as an independent risk factor for MDRPA acquisition, whereas the duration of treatment with imipenem was of borderline significance. These data support a major role for the use of antibiotics with high antipseudomonal activity, particularly ciprofloxacin, in the emergence of MDRPA.

Antibiotic resistance is a major concern of contemporary medicine. The ongoing emergence of resistant strains that cause nosocomial infections contributes substantially to the morbidity and mortality of hospitalized patients [1, 2]. Bacteria from intensive care units (ICUs) have the highest proportion of resistance [3, 4]. During the past decade, infecting strains that are resistant to several (or even most) available antibiotics have emerged, causing major therapeutic problems [2, 5].

Pseudomonas aeruginosa is one of the main organisms responsible for drug-resistant nosocomial infections and is a leading cause of bacteremia and nosocomial pneumonia [6–9]. In addition to being intrinsically resistant to several antimicrobial agents, *P. aeruginosa* often acquires mechanisms of resistance to other antibiotics. Previous treatment with antibiotics that are characterized by high antipseudomonal activity [10–15] and prolonged antibiotic treatment [16] are both recognized risk factors for the emergence of drug-resistant *P. aeruginosa*. Acquisition of strains resistant to ceftazidime, imipenem, piperacillin, or ciprofloxacin is associated with significantly longer hospital stays and an increased rate of secondary bacteremia in patients with *P. aeruginosa* infection [17].

P. aeruginosa strains can acquire resistance to mul-

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tiple (or even all) antibiotics. Multidrug-resistant *P. aeruginosa* (MDRPA) strains were first reported in patients with cystic fibrosis [18]. Outbreaks due to single strains have been reported [19, 20]; however, in other instances, outbreaks have been reported in which the strains varied among patients [21, 22]. The global disease burden associated with *P. aeruginosa* strains that are resistant to all antipseudomonal drugs and the specific risk factors for acquisition of these strains have not been described. Here, we report the results of an epidemiological study of the incidence of and risk factors for infection or colonization with MDRPA strains in 3 ICUs in a large teaching hospital.

PATIENTS AND METHODS

The Bichat–Claude Bernard hospital is a 1100-bed teaching hospital in Paris, France, with >30,000 hospitalizations of >24-h duration each year. There are 5 ICUs in the hospital, including an 18-bed infectious diseases ICU (IDICU), a 17-bed medical ICU (MICU), and a 12-bed surgical ICU (SICU). The total annual number of admissions to these 3 ICUs is ~1300.

Selection of case and control patients. The computerized database of the hospital's bacteriology laboratory was used to identify all cultures obtained from patients hospitalized during 1999 and 2000 that grew strains of multidrug-resistant *P. aeruginosa*. Multidrug resistance was defined as combined resistance or intermediate susceptibility to piperacillin, ceftazidime, imipenem, and ciprofloxacin. Resistance to aminoglycosides was not included in the definition, because these agents are not used as first-line single-drug therapy for *P. aeruginosa* infection, but, rather, in combination with 1 of the 4 antibiotics listed above.

Routine screening for *P. aeruginosa* carriage was not performed during the study period. Thus, all MDRPA strains were isolated from clinical specimens. Immediately after isolation, all MDRPA strains were stored frozen in stock cultures. These cultures were used to confirm identification of the strains by classic identification methods and to test the antibiotic susceptibility of the strains with use of the disk diffusion technique, as recommended by the Antibiotic Susceptibility Testing Committee of the French Society for Microbiology [23]. Susceptibility thresholds for defining resistance were as follows: ≤16 mg/L, for piperacillin; ≤4 mg/L, for ceftazidime; ≤4 mg/L, for imipenem; and ≤1 mg/L, for ciprofloxacin. In comparison, NCCLS susceptibility thresholds for defining resistance are as follows: ≤64 mg/L, for piperacillin; ≤8 mg/L, for ceftazidime; ≤4 mg/L, for imipenem; and ≤1 mg/L, for ciprofloxacin.

A matched case-control study was performed to determine factors associated with MDRPA acquisition. A case patient was defined as a patient hospitalized in 1 of the 3 study ICUs during the study period with a clinical culture that grew a newly identified MDRPA strain >48 h after admission to and <48 h after discharge from the ICU (such patients presumably acquired MDRPA in the ICU). Clinical and microbiological charts of patients with MDRPA were reviewed and patients were classified according to Centers for Disease Control and Prevention (CDC) criteria (slightly modified to account for quantitative microbiological results) as either "infected" or "colonized" [24]. A control patient was defined as a patient who was hospitalized in the same ICU as the corresponding case patient during the study period but whose microbiological cultures for *P. aeruginosa* showed no growth at any time during their ICU stay. For the case patients, the period between admission to the ICU and the first culture positive for MDRPA was defined as the risk exposure time. For each matched control patient, length of stay in the ICU was at least as long as the risk exposure time for the corresponding case patient. In addition, control patients were matched with corresponding case patients on the basis of Simplified Acute Physiology Score II (SAPS II; matched for score ± 2) at ICU admission [25]. If >1 appropriate control patient was available for a particular case patient, the control patient whose ICU admission date was closest to that of the case patient was selected.

Data collection. Age, sex, reason for ICU admission, history of immunosuppression, and severity of underlying disease (as defined by the McCabe and Jackson scales [26] and the chronic health evaluation score [27]) were recorded at ICU admission. Severity of illness at ICU admission and at 4 days before MDRPA acquisition (for the case patients) or the equivalent time point (for control patients) was assessed using the Organ System Failure (OSF) score [28] and the SAPS II.

For all case and control patients, the following were recorded: nature and duration of invasive procedures used during the risk exposure time, nature and duration of use of all antimicrobials given in the ICU for ≥48 h, length of ICU and hospital stays, and mortality. Because of the retrospective design of the study, it was not possible to investigate antibiotics given to a patient before admission to the ICU.

Statistical analysis. Bivariate and multivariate analyses were conducted. In the bivariate analysis, continuous variables were compared using the nonparametric Wilcoxon rank-sum test for paired data. Because the log-linearity assumption was not verified for all durations of antibiotic therapy, these variables were then categorized. For antimicrobials given to <17 patients (25% of the total study population), case and control patients who received each agent were compared with those who did not. For antimicrobials given to >17 patients, the following 3 categories, based on the median percentage of the risk exposure time during which the antimicrobial was given, were created: no therapy with the antimicrobial, duration of therapy less than the median, or duration of therapy greater than the median (calculation of the median percentage of risk

exposure time during which the antimicrobial was given included only patients who received the agent).

Categorical variables were subjected to bivariate analysis using conditional logistic regression (Proc Genmod) to take into account the variations in risk exposure time among pairs. Next, we performed a multivariate analysis on the variables found to be significant in the bivariate analysis ($P < .10$). A forward selection process was used. All tests were 2-tailed, and P values <.05 were considered to be significant. Statistical analyses were performed using EpiInfo, version 6.0 (CDC) and SAS, version 8.0 (SAS Institute). Results are expressed as mean values (±SD), unless otherwise indicated.

RESULTS

During the study period, 2613 patients were hospitalized in the 3 ICUs, and *P. aeruginosa* was recovered from 370 (14.1%) of these patients. Among these 370 patients, prevalence of infection or colonization with strains of *P. aeruginosa* resistant to each of the antibiotics (counting only 1 isolate per patient) was as follows: 21.9% for ceftazidime, 23.5% for imipenem, 30.2% for ciprofloxacin, and 55.9% for piperacillin (administered alone or in combination with tazobactam). Among the patients with *P. aeruginosa*, the prevalence of MDRPA infection or colonization was 10.5% (39 of 370 patients). In 16 (41%) of these 39 patients, the isolates were also resistant to all aminoglycosides (i.e., gentamicin, tobramycin, streptomycin, netilmicin, amikacin, and isepamycin).

Of the 39 MDRPA-positive patients, 2 had cultures positive for MDRPA within the first 2 days after admission to the ICU and were excluded from further analysis. The 37 remaining patients were the case patients for the present study. Eighteen (49%) were in the SICU, 11 (30%) were in the MICU, and 8 (22%) were in the IDICU. Nearly one-half of the patients came from either the cardiac surgery department (24%) or the emergency department (24%) of the hospital. Reasons for admission to the ICU were acute respiratory failure for 13 (35%) of the patients, septic shock or multi-organ failure for 8 (22%), intraabdominal sepsis for 6 (16%); cardiovascular disease for 6 (16%), neurological disease for 2 (5%), and trauma for 2 (5%).

The temporal-spatial epidemiological analysis showed no evidence of patient-to-patient transmission of MDRPA. For 13 (35%) of the MDRPA-positive patients, MDRPA was the first *P. aeruginosa* strain isolated. For 10 other MDRPA-positive patients (27%), a *P. aeruginosa* strain that was fully susceptible to the 4 antibiotics included in the definition of multidrug resistance had been isolated previously during the hospital stay. For the remaining 14 patients, the first *P. aeruginosa* strain isolated in our hospital (before the MDRPA strain was isolated) was susceptible to 3, 2, or 1 of the antibiotics used to define MDRPA (in 3 [8%], 6 [16%], and 5 [14%] of the patients, respectively).

Of these 37 patients, 25 were men and 12 were women, with an age of 57 ± 17 years (median, 63 years). Immunodepression was present in 9 (24%) of the patients. Primary sites from which MDRPA was recovered were the respiratory system (20 patients [54%]), a catheter (7 [19%]), urine samples (6 [16%]), blood samples (4 [11%]), and the abdomen (3 [8%]). Twenty-six (70%) of the MDRPA-positive patients were infected and 11 (30%) were colonized. At admission, the SAPS II was 43 ± 17 (median, 38) and the APACHE II score was 18 ± 8 (median, 16). Time from ICU admission to MDRPA recovery was 29.5 ± 14.3 days (median, 26 days), with a range of 3–140 days. Duration of stay in the ICU was 72 ± 69 days (median, 38 days). The ICU mortality rate was 43%.

For 3 case patients with prolonged ICU stays prior to their first MDRPA-positive culture (stays of 40, 81, and 140 days, respectively), no control patients with similarly long risk exposure times were available. These 3 case patients were excluded from the study. For the 34 case-control pairs left for the study, the duration of risk exposure time was 25.0 ± 15.9 days (median, 26 days; range, 3–63 days). For the case patients, the duration of ICU stay was 57.0 ± 37.3 days (median, 44.5 days), and the ICU mortality rate was 44%.

Baseline demographic and clinical characteristics, underlying disease scores, severity of illness scores at ICU admission and at 4 days before MDRPA acquisition (for the case patients) or at the equivalent time point (for the control patients), use and duration of invasive procedures, and ICU and hospital mortality rates are presented in table 1. No significant differences were found between case patients and control patients, except that hemodiafiltration or hemodialysis was performed significantly more often in the case patient group.

Results of the analysis of the receipt of specific antibiotics are presented in table 2. In the bivariate analysis, receipt of piperacillin (or ticarcillin) or metronidazole for any duration and receipt of imipenem or ciprofloxacin for durations longer than the median were significantly associated with MDRPA acquisition.

The total duration of treatment with antimicrobials that have general activity against gram-negative bacteria (i.e., all β-lactams, fluoroquinolones, trimethoprim-sulfamethoxazole, and aminoglycosides) was not significantly different between the case patients and the control patients (24.3 ± 18.7 days [median, 23.0 days] vs. 20.4 ± 16.0 days [median, 14.5 days], for control patients; $P = .5$). In contrast, case patients received antibiotics with specific antipseudomonal activity (i.e., ceftazidime, imipenem, ciprofloxacin, and broad-spectrum penicillins) for a significantly longer duration than did control patients (mean duration, 16.1 ± 15.8 days [median, 13.0 days] vs. 5.3 ± 9.4 days [median, 2.0 days]; $P = .001$). The control pa-

Table 1. Demographic and clinical characteristics of 34 case patients infected or colonized with multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) and 34 matched control patients hospitalized in intensive care units.

Variable	Case patients (n = 34)	Control patients (n = 34)	P[a]
Age, years	59.0 ± 17.6 (64.6)	61.5 ± 17.3 (61.5)	.48
Male sex	22 (65)	22 (65)	1
Duration of hospitalization prior to ICU admission, days	6.6 ± 11.1 (1)	3.9 ± 7.2 (1)	.43
No hospitalization prior to ICU admission	8 (24)	4 (12)	.21
Presence of immunosuppression	9 (26)	8 (24)	.78
Severity of illness score at ICU admission			
SAPS II score	43.8 ± 17.2 (39.5)	41.2 ± 13.9 (37.5)	.58
APACHE II score	18.6 ± 7.7 (16)	17.4 ± 7.0 (16)	.56
OSF score >1	22 (65)	24 (71)	.60
Ultimately or rapidly fatal disease[b]	25 (74)	19 (56)	.13
Chronic health failure score >2	7 (21)	14 (41)	.08
Severity of illness score 4 days prior to MDRPA acquisition			
SAPS II score	37.3 ± 16.0 (38)	35.4 ± 13.2 (33)	.70
APACHE II score	17.0 ± 13.8 (13)	13.7 ± 6.1 (14)	.66
OSF score >1	17 (50)	16 (47)	.8
Clinical intervention			
Ventilatory support			
Use	33 (97)	33 (97)	1
Duration, days	21.6 ± 16.8 (19)	23.4 ± 16.3 (20.5)	.62
Urinary catheter			
Use	33 (97)	34 (100)	1
Duration, days	23.6 ± 16.1 (23.5)	24.5 ± 15.7 (26)	.83
Central venous catheter			
Use	32 (94)	31 (91)	1
Duration, days	18.5 ± 14.9 (14.5)	17.8 ± 14.2 (14.0)	.86
Arterial catheter			
Use	31 (91)	30 (88)	1
Duration, days	14.4 ± 13.0 (10.5)	14.6 ± 13.1 (10.5)	.92
Hemodiafiltration or hemodialysis			
Use	15 (44)	7 (21)	.04
Duration, days	4.2 ± 9.9 (0)	2.9 ± 7.8 (0)	.19
Pulmonary artery catheter			
Use	6 (18)	12 (35)	.10
Duration, days	0.8 ± 2.9 (0)	0.7 ± 1.4 (0)	.18
Length of ICU stay, days	57.0 ± 37.3 (44.5)	46.9 ± 22.5 (43.5)	.55
Length of hospitalization after ICU discharge, days	11.1 ± 18.6 (0)	5.8 ± 10.4 (0)	.28
ICU mortality	15 (44)	16 (47)	.81
Hospital mortality	16 (47)	17 (50)	.8

NOTE. Data are either no. (%) of patients or mean value ± SD (median). Duration of a procedure was set at 0 if the procedure was absent. APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; OSF, Organ System Failure; SAPS, Simplified Acute Physiology Score.

[a] Bivariate analysis, according to conditional logistic regression, or Wilcoxon rank sum test for paired data, as appropriate.

[b] Severity of underlying disease defined by the McCabe and Jackson scales [26].

Table 2. Receipt of antimicrobial agents in 34 case patients infected or colonized with multidrug-resistant *Pseudomonas aeruginosa* and 34 matched control patients hospitalized in intensive care units.

Antimicrobial agent(s) received	No. (%) of patients, by study group		
	Case (n = 34)	Control (n = 34)	P[a]
Third-generation cephalosporins			
For any duration	12 (35)	15 (44)	.46
For duration longer than the median[b]	5 (15)	10 (29)	.15
Ceftazidime	7 (21)	2 (6)	.15
Piperacillin or ticarcillin	7 (21)	0 (0)	.01
Piperacillin-tazobactam	7 (21)	4 (12)	.32
Imipenem			
For any duration	21 (62)	15 (44)	.14
For duration longer than the median[b]	14 (41)	5 (15)	.02
Ciprofloxacin			
For any duration	13 (38)	8 (24)	.19
For duration longer than the median[b]	10 (29)	1 (3)	.01
Other fluoroquinolones	4 (12)	9 (27)	.12
Aminoglycosides			
For any duration	14 (41)	20 (59)	.15
For duration longer than the median[b]	7 (21)	12 (35)	.18
Glycopeptides			
For any duration	21 (62)	19 (60)	.62
For duration longer than the median[b]	12 (35)	8 (23)	.28
Metronidazoles	11 (32)	4 (12)	.04

[a] Obtained using bivariate analysis, according to the conditional logistic regression analysis.

[b] Median percentage of risk exposure time during which the antimicrobial was given for all patients who received that agent. The median percentage of risk exposure time for those patients receiving third-generation cephalosporins was 27%; for those receiving imipenem, 29%; for those receiving ciprofloxacin, 34%; for those receiving aminoglycoside, 15%; for those receiving glycopeptides, 32%.

tients received antibiotics without antipseudomonal activity more often than did the case patients (28 [82%] vs. 19 [56%]; $P = .018$) and for a longer duration (12.4 ± 11.9 days [median, 8.0 days] vs. 4.9 ± 6.7 days [median, 2.5 days]; $P = .002$). Among case patients, the number of antibiotics active against *P. aeruginosa* that were received during the risk exposure time was as follows: 0, in 8 (24%); 1, in 7 (21%); 2, in 12 (35%); and 3, in 7 (21%). Corresponding figures among the control patients were as follows: 0, in 14 (41%); 1, in 11 (32%); and 2, in 9 (26%); none of the control patients received ⩾3 of these antimicrobials.

Results of the multivariate analysis are reported in table 3. In the final model, only duration of ciprofloxacin therapy was significantly associated with MDRPA acquisition (OR, 11.0; 95% CI, 1.27–32.9; $P = .03$). A trend was observed for duration of imipenem therapy (OR, 3.17; 95% CI, 0.92–10.9; $P = .07$).

DISCUSSION

The prevalence of antimicrobial-resistant *P. aeruginosa* is increasing among ICU patients. Data from the National Nosocomial Infection Surveillance system show that, in 2000, the prevalence of resistant *P. aeruginosa* increased to 17.7% for imipenem, 27.3% for quinolones, and 26.4% for third-generation cephalosporins [4]. In European ICUs, the prevalence of *P. aeruginosa* with decreased susceptibility to imipemen, ceftazidime, piperacillin, and ciprofloxacin ranged from 16%–24% for imipemen, 2%–16% for ceftazidime, 5%–26% for piperacillin, and 8%–37% for ciprofloxacin [29].

Data on MDRPA with decreased susceptibility to all 4 major antipseudomonal antibiotics are scarce, however. Most such data derive from investigations of outbreaks attributable to a single strain originating from the environment [19] and/or transmitted from patient to patient [20]. Among studies that did not investigate outbreaks, a study conducted in a 320-bed referral hospital identified 22 patients with MDRPA over a 3.5-year period [22]. In a study in Brazil, 15 patients had infections due to MDRPA in a 2000-bed hospital over a 5-month period [30]. In a multicenter study, multidrug resistance (defined as combined resistance to piperacillin, ceftazidime, imipenem, and gentamicin) was observed in only 3% of *P. aeruginosa* strains [6]. In another recent study, decreased susceptibility to imipenem was found in 23.8% of *P. aeruginosa* isolates. Of those isolates with decreased susceptibility to imipenem, 40% were not susceptible to ceftazidime, and 72% were not susceptible to ciprofloxacin [31].

We found 39 patients with an MDRPA strain who were hospitalized in the study ICUs during a 2-year period. The large number of patients found in our study, compared with the number of patients in other studies, may be related, in part, to the breakpoints we used to define resistance of *P. aeruginosa* to antipseudomonal drugs. These breakpoints were lower than the NCCLS breakpoints, which were used in most published studies. The long duration of stay in the ICU for our patients (a mean of 9.9–14 days, depending on the ICU and the year) may also have contributed to the high rate of MDRPA acquisition.

As expected, the time to MDRPA acquisition was long, with a mean of 29 days between ICU admission and MDRPA acquisition. This is in accordance with the 23-day mean reported in another study [22]. Furthermore, *P. aeruginosa* strains with greater antibiotic susceptibility than the MDRPA strains were recovered from 65% of our patients before the MDRPA strains were recovered (including 10 patients [27%] from whom fully susceptible strains were recovered). In the present study, susceptible and resistant *P. aeruginosa* strains from a given patient were not compared using molecular techniques. It has been shown, however, that resistance mechanisms can accumulate

Table 3. Multivariate analysis of risk factors associated with infection or colonization with multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) among patients hospitalized in intensive care units.

Variable	OR (95% CI)	
	Initial model	Final model
Receipt of hemodiafiltration or hemodialysis	3.05 (1.03–10.4)	…
Receipt of piperacillin or ticarcillin	4.13 (0.78–21.8)	…
Receipt of imipenem for duration longer than the median[a]	4.05 (1.26–13.1)	3.17 (0.92–10.9)
Receipt of ciprofloxacin for duration longer than the median[a]	53.7 (2.94–114)	11.0 (1.27–32.9)
Receipt of metronidazole	3.56 (1.01–12.7)	…

NOTE. Multivariate analysis was performed using conditional logistic regression with a forward selection process to identify variables independently associated with MDRPA acquisition.

[a] Median percentage of risk exposure time during which the antimicrobial was given for all patients who received that agent. The median percentage of risk exposure time for those patients receiving imipenem was 29%; for those receiving ciprofloxacin, 34%.

gradually in initially susceptible *P. aeruginosa* strains in treated patients [22, 32].

For the risk factor analysis, we paid careful attention to selection of the control patients. First, we selected the potential control patients from among those patients who tested negative for *P. aeruginosa.* It has been established that studies evaluating the role of antimicrobials as risk factors for isolation of a resistant organism should include control patients who do not have cultures positive for antimicrobial-susceptible strains of that organism [33, 34]. Second, we selected control patients whose risk exposure time was at least as long as that of the matched case patient. Although multivariate modeling can adjust for the risk exposure time, other variables, such as use of invasive devices in the ICU, usually show colinearity with the risk exposure time. It is unclear whether adjusting risk exposure time in a multivariate model controls for these other variables [33]. By including the risk exposure time among the matching criteria, we adjusted for one of the most important risk factors for acquisition of multidrug-resistant bacteria [35].

Third, most previous studies investigating the impact of previous antibiotic exposure on the acquisition of resistant *P. aeruginosa* strains included only receipt of antibiotics (usually for >48 h), and few explored the impact of treatment duration [16]. Several studies suggest that not only receipt but also duration of antimicrobial therapy should be taken into consideration [36].

One important finding of our study is that invasive procedures and severity score changes during the ICU stay were not significant risk factors for MDRPA acquisition, in contrast to the findings of other studies [35, 37]. Again, differences in matching criteria probably explain why our findings differ from those of other studies.

The similarities between case and control patients, both in terms of their baseline characteristics and in the use and duration of invasive procedures, strengthen the validity of the differences in antibiotic therapy observed in our study. Overall, there was no difference between case and control patients in receipt of antibiotics, with each group receiving antibiotics active against gram-negative rods for a similar mean duration. When antibiotics with and without activity against wild type strains of *P. aeruginosa* were analyzed separately, major differences were found, including, in control patients, significantly more-common and longer durations of treatment with antibiotics with little antipseudomonal activity and, in case patients, significantly longer durations of treatment with antibiotics with full antipseudomonal activity. This clearly suggests that, if treatment with an antibiotic active against gram-negative bacteria is needed, agents with little antipseudomonal activity should be preferred over those with specific antipseudomonal activity to limit the emergence of MDRPA.

When investigating the role of each antibiotic individually, only the duration of ciprofloxacin therapy and, to a lesser extent, of imipenem therapy were associated with MDRPA acquisition. Another study suggested that receipt of any fluoroquinolone may be a risk factor for acquiring piperacillin-resistant *P. aeruginosa* [37]. In our study, receipt of ciprofloxacin was a critical risk factor, whereas receipt of quinolones without activity against *P. aeruginosa* conferred protection against the emergence of MDRPA. That receipt of imipenem therapy was close to being a statistically significant risk factor for MDRPA acquisition is consistent with the role of imipenem therapy as a risk factor for the emergence of imipenem-resistant *P. aeruginosa,* as reported in at least 3 studies [10, 11, 13]. Given the fairly small number of patients, our study may have lacked statistical power for detecting the risk factor effects of additional antibiotics.

Our study has several limitations. First, active surveillance cultures were not done to screen for *P. aeruginosa.* Had such

cultures been performed, case patients would probably have been identified earlier, some control patients would probably have been identified as case patients, and others would probably have been excluded from the study after having cultures positive for susceptible strains of *P. aeruginosa*. Second, we did not collect data on whether the patients had a history of antibiotic exposure before ICU admission. Third, we cannot exclude the possibility of patient-to-patient transmission of MDRPA strains. However, MDRPA was usually identified after a long stay in the ICU, and we found no evidence of temporal-spatial clustering of cases of MDRPA. Furthermore, if patient-to-patient transmission did occur, this would have weakened the association between MDRPA acquisition and receipt of antibiotics. Finally, we cannot conclude there was a causal association between receipt of ciprofloxacin therapy and acquisition of MDRPA, because of the small set of patients and possible colinearity between exposures to antibiotics.

In conclusion, our data support a major role for antibiotics with specific antipseudomonal activity (most notably, ciprofloxacin) in the emergence of MDRPA. The use and/or duration of treatment with these antibiotics should be restricted as part of efforts to control the emergence of MDRPA in ICUs.

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