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Antibiotics associated with acquisition of carbapenem-resistant *Pseudomonas aeruginosa* in ICUs: a multicentre nested case–case–control study

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Background: Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) strains are involved in severe infections, mostly in ICUs. Exposure to antibiotics other than carbapenems may be associated with isolation of CRPA; therefore, we aimed to identify those antibiotics using the case–case–control study design.

Methods: A case–case–control study was conducted in 2015 in a prospective multicentre cohort that included 1808 adults hospitalized in 2009 in 10 French ICUs. Patients were screened for *P. aeruginosa* at admission to the ICU and then weekly. Cases were patients with CRPA and patients with carbapenem-susceptible *P. aeruginosa* (CSPA) isolation. Controls were patients without *P. aeruginosa* isolation, matched with each case according to centre, length of stay and hospitalization period. Effects of antibiotic exposure were explored, after adjusting for prior treatment with carbapenems and confounding factors comprising colonization pressure with two logistic regression models. The two models were compared to identify specific risk factors for CRPA isolation.

Results: Fifty-nine CRPA, 83 CSPA and 142 controls were compared. In adjusted multivariable analyses, exposure to carbapenems and to antibiotics belonging to the group of β-lactams inactive against *P. aeruginosa* were independent risk factors for CRPA isolation (OR, 1.205; 95% CI, 1.079–1.346 and OR, 1.101; 95% CI, 1.010–1.201, respectively). Conversely, exposure to β-lactams active against *P. aeruginosa* was an independent protective factor for CSPA isolation (OR, 0.868; 95% CI, 0.772–0.976).

Conclusions: Besides carbapenem exposure, exposure to β-lactams inactive against *P. aeruginosa* was a specific risk factor for CRPA isolation. Clinicians should counterweigh the potential benefits of administering these antibiotics against the increased risk of CRPA infection.

Introduction

Pseudomonas aeruginosa is the most common pathogen responsible for healthcare-associated infections in ICUs.[1,2] Infections caused by *P. aeruginosa*, especially ventilator-associated pneumonia or bloodstream infections, are particularly severe and the risk of death increases when this pathogen is MDR.[3] Indeed, carbapenem-resistant *P. aeruginosa* (CRPA) infections have been associated with higher mortality and longer hospital stay.[4–6] Mortality rates greater than 50% have been reported among patients with nosocomial infections caused by *P. aeruginosa* carrying a metallo-β-lactamase.[7] Patients with CRPA bacteraemia have also been identified as being at higher risk of death compared with those with carbapenem-susceptible *P. aeruginosa* (CSPA) bloodstream infections.[8] Carbapenems have excellent clinical utility for the treatment of ventilator-associated pneumonia and other prominent infections in ICUs, therefore the emergence of resistance to carbapenems is challenging owing to the limited number of antimicrobial agents available to treat this type of infection.[9] *P. aeruginosa* is able to develop resistance mechanisms after exposure to carbapenems and other classes of antibiotics. Previous studies identified risk factors for isolation of CRPA, such as previous use of imipenem and also of various other antibiotics such as vancomycin, amoxicillin/clavulanic acid, piperacillin/tazobactam, second-generation cephalosporins and aminoglycosides.[10–15]

However, most of these studies had several methodological limitations: improper design, unclear antibiotic exposure definition, confounding factors (especially colonization pressure) not taken into account and no screening of *P. aeruginosa* among inpatients.[10] As a result, the role of antibiotics other than carbapenems in the isolation of CRPA remains unclear, whereas it could help clinicians when defining probabilistic antibiotic therapy in ICUs. We aimed to identify antibiotics other than carbapenems associated with CRPA isolation in adults in ICUs using the case–case–control study design and taking into account non-antibiotic exposures at the patient level.

Methods

Case–case–control study design

The case–case–control study was designed to overcome limitations of studies exploring risk factors for antimicrobial resistance. It uses two separate case–controls within a single study. The first analysis compares patients from whom a resistant strain of a microorganism of interest was isolated with control patients without the microorganism who are representative of the source population; the second analysis compares patients from whom a susceptible strain of the microorganism was isolated with the same microorganism-free control patients. These two analyses provide two risk models, one for the isolation of the resistant strain and the other one for the isolation of the susceptible strain. Then the two models are qualitatively compared to identify specific risk factors associated with the isolation of the resistant strain.[16]

Since its first description, this study design has been widely used to assess risk factors for antimicrobial resistance.[17–21]

Setting

Population source

We used available data from the multicentre Dynamics of Acquisition of *Pseudomonas aeruginosa* (DYNAPYO) cohort, which was prospectively built in 2009 in 10 ICUs from eight French hospitals (Besançon, Bordeaux, Garches, Lyon, Montpellier, Paris, Lens and Tourcoing) to assess the respective contributions of individual and ICU environmental risk factors for *P. aeruginosa* acquisition.[22,23] Participation was voluntary among ICUs participating in the French ICU nosocomial infections surveillance network REA-RAISIN.[24] The DYNAPYO cohort included 1808 adults hospitalized in an ICU for more than 24 h during the cohort inclusion period. Patients included in the DYNAPYO cohort were screened for *P. aeruginosa* upon admission to the ICU, then weekly and at discharge (oropharyngeal or sputum and rectal swab specimens). Inpatient characteristics collected were: on admission, age, sex, simplified acute physiology score (SAPS II) within 24 h after admission, Charlson comorbidity index for chronic diseases,[25] history of previous hospitalization (<1 year before admission), previous surgery (<30 days before admission) and history of previous *P. aeruginosa* infection or colonization; and during the ICU stay, duration of mechanical ventilation, antibiotic treatment (recorded daily) and the nine equivalents of nursing manpower use score (NEMS).[26] All screening and collection of diagnostic samples performed during the DYNAPYO cohort study were tested. Bacterial colonies growing on selective media were identified to the species level. The susceptibility of *P. aeruginosa* strains to carbapenems (imipenem and meropenem) was determined using the Mueller–Hinton agar disc diffusion method. Inhibition zones were interpreted using the Comité de l'Antibiogramme-Société Française de Microbiologie (www.sfm-microbiologie.org) recommendations.[27]

Cases and control groups

We investigated antibiotics associated with CRPA isolation and with CSPA isolation using the case–case–control study design nested in the DYNAPYO cohort, after adjusting for non-antibiotic exposures and inpatient characteristics. The first case group (CRPA cases) included patients who were negative for *P. aeruginosa* at admission and from whom a CRPA strain was isolated from diagnostic or screening samples after 48 h of ICU stay. The second case group (CSPA cases) included patients who were negative for *P. aeruginosa* at admission and from whom a CSPA strain was isolated from diagnostic or screening samples after 48 h of ICU stay. The source population consisted of patients included in the DYNAPYO cohort from whom a *P. aeruginosa* strain was never isolated from diagnostic or screening samples during their ICU stay. We selected one control per each CSPA and CRPA case from the source population according to the following matching criteria: ICU, length of stay and hospitalization period.

Antibiotic exposures

Individual antibiotic treatments were recorded daily in the DYNAPYO cohort study. For the case–case–control study, antibiotics were first classified according to antibiotic groups and natural *in vitro* susceptibility of WT *P. aeruginosa* (Table 1). Antibiotic group exposures were then expressed as cumulative duration of treatment in number of days and were analysed as continuous variables.

Non-antibiotic exposures

Non-antibiotic exposures were inpatient characteristics, mechanical ventilation expressed as cumulative duration in days, and colonization pressure. Colonization pressure was calculated in patient–days for each included patient, as the cumulative number of patients positive for CRPA in the same unit (colonized or infected patients) from admission to the day prior to *P. aeruginosa* acquisition for cases or from admission to discharge for controls.

Statistical analysis

Univariate and multivariable analyses were performed using logistic regression models. CRPA acquisition and CSPA acquisition were considered separate outcomes. The exposure to each antibiotic group was assessed adjusting for non-antibiotic exposures. ORs and 95% CIs were calculated for all antibiotic groups. Variables (antibiotic group, inpatient characteristics and non-antibiotic exposures) related to outcomes with a conservative threshold of 20% on the Wald test were maintained for multivariable models. Duration of treatment with carbapenems (adjustment variable) was always kept in the models even if not significant. A descendent stepwise approach was used to identify independent associations, and variables were removed manually. A *P* value of 0.05 was considered statistically significant. Effect modification and collinearity were searched, and the validity of two final models was assessed by estimating their goodness-of-fit using the Hosmer–Lemeshow test. Qualitative comparison between the two models was then performed to identify specific risk factors for CRPA acquisition. All analyses were performed using the SAS 9.1 software package (SAS Institute, NC, USA).

Ethics

The DYNAPYO cohort study was approved by the national ethics committee [Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS) et Commission Nationale de l'Informatique et des Libertés (CNIL)] according to the Hospital clinic research programme (PHRC).

Results

Study population

Among 1808 patients included in DYNAPYO cohort, 1314 had no *P. aeruginosa* colonization or infection on admission and were

Table 1. Groups of antibiotics of exposure by family and *P. aeruginosa* WT susceptibility

	P. aeruginosa WT susceptibility	
	susceptible	non-susceptible
β-Lactams	*Carbapenem group* imipenem meropenem	
	Group of β-lactams active against P. aeruginosa piperacillin piperacillin/tazobactam ticarcillin ticarcillin/clavulanic acid	*Group of β-lactams inactive against P. aeruginosa* amoxicillin amoxicillin/clavulanic acid cloxacillin ertapenem first- and second-generation cephalosporins
	Group of 3GCs active against P. aeruginosa ceftazidime cefepime cefpirome aztreonam	*Group of 3GCs inactive against P. aeruginosa* cefotaxime ceftriaxone
Fluoroquinolones	*Fluoroquinolone group* ciprofloxacin levofloxacin ofloxacin	
Aminoglycosides	*Aminoglycoside group* amikacin gentamicin tobramycin	
Glycopeptides		*Glycopeptide group* teicoplanin vancomycin
Nitroimidazoles		*Nitroimidazole group* metronidazole
Others		*Other antibiotics group* macrolides first-generation quinolones tetracyclines colistin fosfomycin fusidic acid sulfamethoxazole/trimethoprim thiamphenicol

eligible for the case–case–control study (Figure 1). Among them, 201 acquired *P. aeruginosa* during their ICU stay; isolates were available from 142 of these 201 patients, of whom 59 were CRPA cases and 83 were CSPA cases. Among the 1113 patients from whom *P. aeruginosa* was never isolated we selected 142 controls according to matching criteria. On admission, no major differences in baseline characteristics between cases and controls were observed; however, cases were more severely ill than controls, with higher SAPS II and longer duration of mechanical ventilation (Table 2).

Case–case–control analyses

CRPA cases versus controls

In univariate analyses, compared with controls, CRPA cases were more severely ill (higher Charlson score, SAPS II and cumulative NEMS) and had a higher colonization pressure, an increased length of invasive mechanical ventilation and a longer exposure to carbapenems (Table 2). In multivariable analyses, after adjustment for confounders and other non-antibiotic exposures, CRPA cases were independently significantly associated with exposure to carbapenems (OR, 1.205; 95% CI, 1.079–1.346), and with exposure to the group of β-lactams inactive against *P. aeruginosa* (OR, 1.101; 95% CI, 1.010–1.201). No statistically significant interaction was found. The Hosmer–Lemeshow goodness-of-fit test indicated that the final CRPA acquisition model reflected the data ($P = 0.12$).

CSPA cases versus controls

Compared with controls, CSPA cases had higher SAPS II, longer duration of invasive mechanical ventilation and longer exposure to the group of β-lactams inactive against *P. aeruginosa* and the group of third-generation cephalosporins (3GCs) inactive against *P. aeruginosa* (Table 2). In multivariable analyses, after adjustment for confounders and other non-antibiotic exposures, CSPA cases were independently associated with exposure to the group of β-lactams active against *P. aeruginosa* (OR, 0.868; 95% CI, 0.772–0.976). No statistically significant interaction was found. The Hosmer–Lemeshow goodness-of-fit test indicated that the final CSPA acquisition model reflected the data ($P = 0.51$).

Comparison of the two models

Among prior antibiotic exposures, only exposure to the group of β-lactams inactive against *P. aeruginosa* was associated with the acquisition of CRPA, whereas there was no association with CSPA acquisition (Table 3).

Discussion

Several studies have demonstrated that case–case–control study design is the most effective and accurate design to assess risk factors for antibiotic resistance in microorganisms because of the simultaneous comparison of factors associated with isolation of resistant strains and of susceptible strains.[16,28–30] This is why we performed a case–case–control study nested in a cohort of inpatients in 10 French ICUs to identify antibiotics other than carbapenems associated with CRPA acquisition.

When the two models were compared, we found that, in ICUs, the risk of CRPA acquisition was associated with carbapenem exposure but also with exposure to β-lactams inactive against *P. aeruginosa* (i.e. amoxicillin, amoxicillin/clavulanic acid, oxacillin, cloxacillin, first- and second-generation cephalosporins and ertapenem). Furthermore, as expected, patients with CRPA fared worse than others. A meta-analysis showed that clinical severity and exposure to medical devices were also the most frequently reported risk factors.[10] Our finding that exposure to carbapenems was

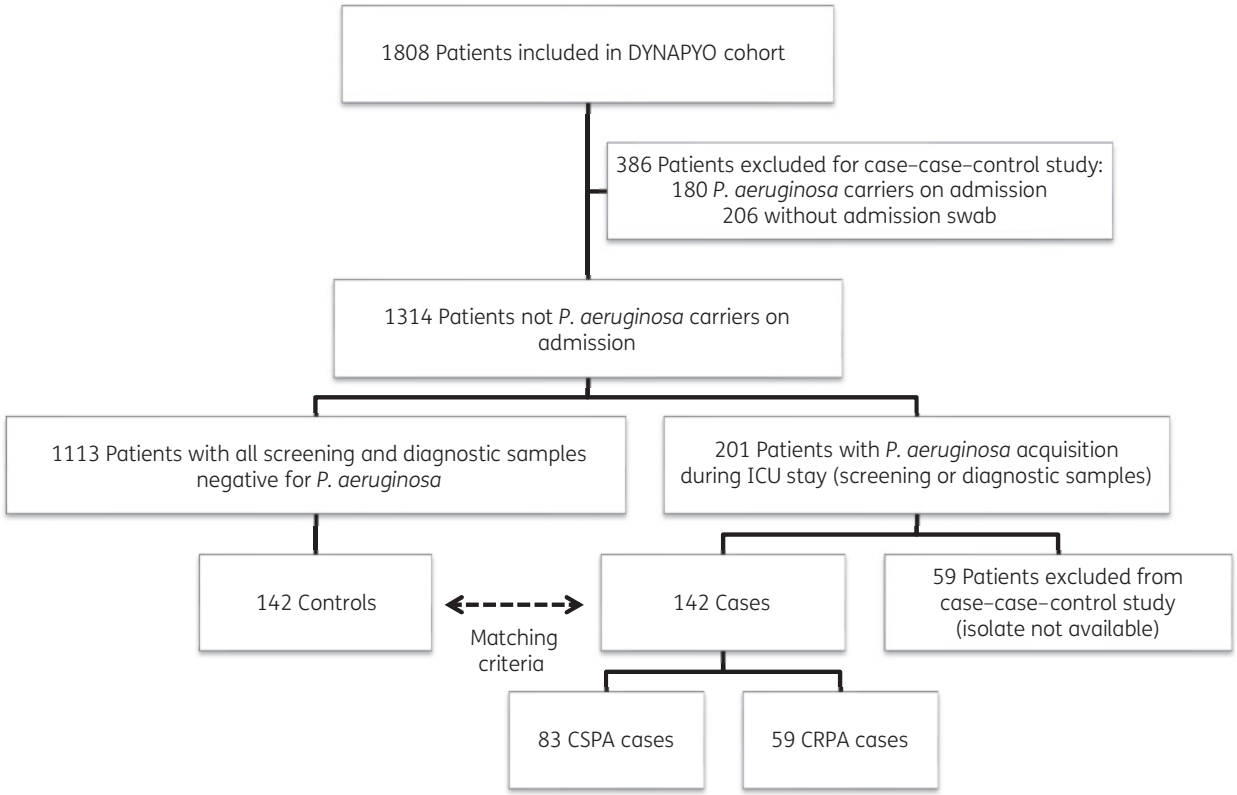

Figure 1. Flow chart of the study population and case–case–control matching.

associated with the acquisition of CRPA strains is consistent with previous studies. Other antibiotics were also identified as a risk factor for CRPA acquisition in those studies, but their results should be interpreted with consideration of the strengths and limitations of their design and data analysis.[31–34]

For instance, exposure to fluoroquinolones has been associated with the acquisition of CRPA in some studies.[35–38] It has been postulated that fluoroquinolones may induce the expression of multidrug efflux pumps, producing an MDR *P. aeruginosa* phenotype.[39,40] We did not identify such an association, possibly because of decreased fluoroquinolone use in France since 2006 or because the design or population of previous studies was different to ours.[41] Previous exposure to aminoglycosides was associated with CRPA acquisition in some studies but not in our study, probably because aminoglycosides are prescribed in association with empirical antibiotic treatment in French ICUs.[13,15,42] Exposure to glycopeptides was identified as a risk factor for CRPA acquisition in case–control studies and surprisingly in case–case–control. We did not identify such an association in our study; this may be explained by misclassification bias because in previous studies controls weren't screened routinely.[13,14,43]

Our study showed that exposure to the group of β-lactams inactive against *P. aeruginosa* frequently used in first-line treatment (especially amoxicillin, amoxicillin/clavulanic acid or ertapenem) or for surgical prophylaxis (first- and second-generation cephalosporins) was a risk factor for CRPA. We hypothesize that this may be due to antibiotic selection pressure, the selection of intestinal flora making the host more susceptible to colonization by resistant strains.

In a prospective observational study not focused on *P. aeruginosa*, the duration of previous piperacillin/tazobactam and aminoglycoside treatment in days was independently associated with carbapenem-resistant Gram-negative bacilli acquisition in ICUs; however, results were not adjusted for colonization pressure.[15] In our study, previous treatment with piperacillin, piperacillin/tazobactam, ticarcillin or ticarcillin/clavulanic acid was a protective factor for CSPA acquisition. Therefore those antibiotics administered to critically ill patients not previously colonized by *P. aeruginosa* may decrease the burden of new acquisition.

Furthermore, part of the discrepancy among studies regarding the role of previous use of antibiotics on *P. aeruginosa* carbapenem resistance may be due to local differences in *P. aeruginosa* mechanisms of resistance. In France, more than 90% of *P. aeruginosa* strains are susceptible to piperacillin/tazobactam and more than 80% are susceptible to ticarcillin.[44] We hypothesized that administration of those antibiotics to ICU inpatients would reduce digestive colonization by *P. aeruginosa*. In our study, almost 90% of CRPA and CSPA strains were susceptible to piperacillin/tazobactam. Treatment with β-lactams inactive against *P. aeruginosa*, particularly amoxicillin/clavulanic acid, can reduce normal flora, which could lead to colonization with *P. aeruginosa*, but also has been thought to foster imipenem resistance by selecting strains with stably derepressed β-lactamase production, which could then be more likely to lose their porin OprD2.[14,45–47] In contrast to other countries, in France the main mechanism for imipenem resistance in *P. aeruginosa* is the repression or inactivation of the OprD gene encoding porin OprD2.[45] For example, in Latin America,

Table 2. Univariate analyses of CRPA and CSPA cases versus controls

Variable	Controls ($n = 142$)	Cases		Univariate analysis			
		CRPA ($n = 59$)	CSPA ($n = 83$)	CRPA cases versus controls		CSPA cases versus controls	
				95% CI	*P* value	95% CI	*P* value
Sociodemographic characteristics							
male gender, %	64.8	71.2	60.2	0.385–1.441	0.38	0.695–2.123	0.49
Age, years (mean ± SD)	57.1±18.3	60.7±17.8	60.6± 19.2	0.994–1.029	0.20	0.995–1.025	0.18
Medical history, %							
hospitalization in the previous year	49.3	43.1	54.3	0.421–1.441	0.43	0.708–2.114	0.47
surgery in the previous month	21.8	12.1	26.5	0.203–1.065	0.07	0.688–2.423	0.42
history of colonization/infection by *P. aeruginosa*	9.1	5.1	6	0.827–12.346	0.09	0.049–4.080	0.48
Clinical data, mean ± SD							
Charlson score	2.0±2.1	2.7±2.5	1.9± 2.3	1.010–1.316	0.03	0.846–1.084	0.49
SAPS II	45.0 ± 19.4	54.8 ± 16.5	48.0 ± 16.6	1.011–1.045	<0.05	1.004–1.034	<0.05
cumulative NEMS	328.1 ± 249.8	473.1 ± 331.6	356.6 ± 208.7	1.001–1.003	<0.05	0.999–1.001	0.92
Non-antibiotic exposures							
colonization pressure, patient days (mean ± SD)	10.3 ± 8.0	15.8 ± 13.6	10.8 ± 6.8	1.002–1.065	<0.05	0.961–1.029	0.76
cumulative duration of invasive mechanical ventilation, days (mean ± SD)	7.6 ± 8.8	14.4 ± 14.9	10.1 ± 6.8	1.022–1.092	<0.05	1.006–1.078	<0.05
Antibiotics, duration of treatment, days, mean (range)							
carbapenem group	7 (3–10)	9 (8–12)	4.3 (2–9)	1.088–1.340	<0.05	0.626–1.045	0.10
group of β-lactams active against *P. aeruginosa*	7 (3–8)	5.5 (3–8.5)	4 (3–5.5)	0.925–1.108	0.79	0.829–1.018	0.10
group of β-lactams inactive against *P. aeruginosa*	6 (3–8)	5 (3–8)	6 (4–8)	0.996–1.175	0.06	1.014–1.191	0.02
group of 3GCs active against *P. aeruginosa*	7 (4–10)	4 (3–4)	3 (2.5–8)	0.801–1.164	0.71	0.806–1.137	0.62
group of 3GCs inactive against *P. aeruginosa*	6 (3–8)	5 (3–7)	5 (3–7)	0.911–1.139	0.75	1.004–1.212	0.04
fluoroquinolone group	4 (3–7)	7 (4–10)	3 (2–8)	0.963–1.143	0.28	0.790–1.019	0.09
aminoglycoside group	3 (2–5)	3 (2–5)	3 (2–5)	0.974–1.240	0.12	0.868–1.225	0.72
glycopeptide group	5 (3–9)	5 (3–7)	4 (2–6)	0.862–1.116	0.77	0.833–1.086	0.46
nitroimidazole group	5.5 (4–9.5)	4 (3–8)	5 (3–8)	0.886–1.079	0.55	0.926–1.104	0.80
other antibiotics group	7 (3–9)	5 (4.5–9)	4.5 (3–8.5)	0.923–1.106	0.82	0.923–1.089	0.95

P. aeruginosa produces metallo-β-lactamase and more than 80% of *P. aeruginosa* strains are resistant to piperacillin/tazobactam.[48,49]

Strengths and limitations

To the best of our knowledge, this is the first case–case–control study exploring antibiotics associated with carbapenem resistance in *P. aeruginosa* taking into account exposure to colonization pressure during inpatients' ICU stay. Colonization pressure, measured at the patient level, was an independent risk factor for the acquisition of *P. aeruginosa* in a critical care setting where most patients were exposed to antibiotics and where the acquisition can be due to cross-transmission.[34,50] Use of the DYNAPYO cohort allowed us to have a valid definition of cases and controls. Indeed, inpatients included in the DYNAPYO cohort were regularly screened (upon admission, weekly and at discharge) to search for the acquisition (or not) of *P. aeruginosa*. In fact, misclassification bias was limited, and we took into account both carriage and infection. Controls were selected in the same wards as cases and with the same index time as cases to reduce selection bias and bias related to non-antibiotic exposures.[51] Moreover, variables influencing *P. aeruginosa* transmission in the ICU, such as colonization pressure, are important confounding factors, but rarely measured in previous studies of CRPA determinants. We were able to take into account colonization pressure as a confounding factor in our study, expressed as the duration of exposure for inpatients with CRPA carriage or infection. That was rarely done in previous studies.[34,52] In our study, antibiotic exposure definition was another strength because we used the cumulative duration of exposure in number of days, providing a more robust characterization of antibiotic exposure; indeed, the risk associated with antibiotic exposure is cumulative.[16,29] Studies expressing antibiotic exposure as a dichotomous variable miss a potential impact of treatment duration, reducing the power to detect associations and resulting in data misinterpretation.[30,53]

Nevertheless, our work presents some limitations. First, in this study, we did not investigate molecular resistance mechanisms of the *P. aeruginosa* strain. In France the main mechanism of carbapenem resistance is loss of the porin OprD2, therefore extrapolation of our findings to other settings with lower prevalence of porin OprD2-induced resistance must be done cautiously. Second, we

Table 3. Multivariable analyses of CRPA cases versus controls and CSPA cases versus controls

	CRPA cases versus controls				CSPA cases versus controls			
	full model		final adjusted model		full model		final adjusted model	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sociodemographic characteristics								
age, years, (mean ± SD)	0.999 (0.978–1.021)	0.93	—	—	1.011 (0.994–1.028)	0.20	—	—
Medical history, %								
surgery in the previous month	0.436 (0.157–1.205)	0.11	—	—	—	—	—	—
history of colonization/infection by *P. aeruginosa*	0.978 (0.920–1.039)	0.47	—	—	—	—	—	—
Clinical data (mean ± SD)								
Charlson score	1.146 (0.978–1.343)	0.09	—	—	—	—	—	—
SAPS II	1.018 (0.997–1.039)	0.10	1.024 (1.006–1.042)	<0.01	1.006 (0.987–1.024)	0.55	—	—
cumulative NEMS	1.000 (0.997–1.002)	0.74	—	—	—	—	—	—
Non-antibiotic exposures								
colonization pressure, patient days (mean ± SD)	0.978 (0.920–1.039)	0.47	—	—	—	—	—	—
cumulative duration of invasive mechanical ventilation, days (mean ± SD)	1.043 (0.970–1.121)	0.25	—	—	1.054 (1.005–1.106)	0.03	1.070 (1.029–1.113)	<0.01
Antibiotics, duration of treatment, days, (mean ± SD)								
carbapenem group	1.218 (1.067–1.391)	<0.05	1.205 (1.079–1.346)	<0.01	0.814 (0.634–1.045)	0.11	0.784 (0.612–1.003)	0.053
group of β-lactams active against *P. aeruginosa*	—	—	—	—	0.916 (0.805–1.042)	0.18	0.868 (0.772–0.976)	0.02
group of β-lactams inactive against *P. aeruginosa*	1.102 (0.995–1.221)	0.06	1.101 (1.010–1.201)	0.03	1.060 (0.958–1.172)	0.26	—	—
group of 3GCs inactive against *P. aeruginosa*	—	—	—	—	1.062 (0.949–1.188)	0.30	—	—
fluoroquinolone group	—	—	—	—	0.887 (0.766–1.027)	0.11	—	—
aminoglycoside group	0.989 (0.853–1.147)	0.89	—	—	—	—	—	—

did not exclude cross-transmission of *P. aeruginosa* between inpatients with molecular typing, even taking into account the colonization pressure. A third limitation was the limited number of cases because some isolates were not available. Fourth, despite the size of the source population, our matching criteria did not allow us to identify more than one control per case; in addition a misclassification bias could result from screening for susceptibility. Furthermore, we didn't take into account the environmental reservoir of *P. aeruginosa*. Last, our definition of antibiotic exposure did not take into account the dose of antibiotics, nor antibiotic combinations that are known to prevent emerging resistance and which are frequently prescribed in the ICU.

Conclusions

Our results must be taken into account to define a probabilistic treatment protocol in the ICU. They provide strong evidence for limiting the use of carbapenems and of β-lactams inactive against *P. aeruginosa* in order to prevent the worrying problem of emerging CRPA while β-lactams with anti-pseudomonal activity protect from CSPA acquisition. Consequences for ICU inpatients will be reduced carriage of *P. aeruginosa* and reduced risk of invasive infection, thanks to the decreased selective antibiotic pressure.

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Transparency declarations

None to declare.

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