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ORIGINAL ARTICLE

Molecular epidemiology of *Pseudomonas aeruginosa* isolated from infected ICU patients: a French multicenter 2012–2013 study

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Abstract

Although *Pseudomonas aeruginosa* has a non-clonal epidemic population structure, recent studies have provided evidence of the existence of epidemic high-risk clones. The aim of this study was to assess the molecular epidemiology of *P. aeruginosa* isolates responsible for infections in French ICUs, regardless of resistance patterns. For a 1-year period, all non-duplicate *P. aeruginosa* isolated from bacteremia and pulmonary infections in ten adult ICUs of six French university hospitals were characterized by antimicrobial susceptibility testing and genotyping (MLST and PFGE). We identified β-lactamases with an extended spectrum phenotypically and by sequencing. The 104 isolates tested were distributed in 46 STs, of which 7 epidemic high-risk (EHR) clones over-represented: ST111, ST175, ST235, ST244, ST253, ST308, and ST395. Multidrug-resistant (MDR) isolates mostly clustered in these EHR clones, which frequently spread within hospitals. Only one ST233 isolate produced the carbapenemase VIM-2. PFGE analysis suggests frequent intra-hospital cross-transmission involving EHR clones. For ST395 and ST308, we also observed the progression from wild-type to MDR resistance pattern within the same PFGE pattern. Molecular epidemiology of *P. aeruginosa* in French ICUs is characterized by high clonal diversity notably among antimicrobial susceptible isolates and the over-representation of EHR clones, particularly within MDR isolates, even though multidrug resistance is not a constant inherent trait of EHR clones.

Keywords *Pseudomonas aeruginosa* · Epidemiology · Infections · Population structure · ICU

Introduction

Pseudomonas aeruginosa is an important opportunistic human pathogen causing infections in patients hospitalized in an intensive care unit (ICU). Its intrinsic resistance to many classes of antibiotics and its capacity to acquire resistance to almost all effective antibiotics during treatment may render infections with this pathogen difficult to treat [1]. Although *P. aeruginosa* has a non-clonal epidemic population structure, recent studies have provided evidence of the existence of widespread multidrug-resistant clones such as ST111, ST235, ST175, and denominated epidemic high-risk (EHR) clones and globally disseminated in hospitals [2, 3]. Although EHR with wild-type susceptibility profiles have been occasionally reported [4, 5], most of the epidemiological studies focused on antibiotic-resistant isolates. Hence, the population structure of *P. aeruginosa* isolates responsible of severe infections, regardless of resistance patterns, remains poorly known. The aim of this study was to characterize consecutive *P. aeruginosa* clinical isolates from ten ICUs located in six

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French university hospitals. We assessed their resistance to antipseudomonal agents and their molecular epidemiology (through their sequence types (STs) and pulsed-field gel electrophoresis (PFGE) patterns) to determine the prevalence and distribution of EHR clones.

Material and methods

Isolate collection

Non-redundant *P. aeruginosa* isolated from bacteremia or pulmonary infections were collected during a 1-year period (2012–2013) from patients hospitalized in ten adult ICUs of six French university hospitals: hospital A (with ICU1 and 2), B (with ICU3), C (with ICU4, 5, and 6), D (with ICU7), E (with ICU8 and 9), and F (with ICU10). Identification of *P. aeruginosa* was performed in each center according to routine bacteriology methods and isolates were sent to the coordinating laboratory in Besançon University Hospital for further investigation.

Susceptibility testing

All isolates were tested for susceptibility against ten antibiotics from four different classes: non-carbapenem β-lactams (cefepime, piperacillin-tazobactam, ticarcillin, ceftazidime), carbapenems (meropenem, imipenem), aminoglycosides (gentamicin, tobramycin, amikacin), and fluoroquinolones (ciprofloxacin) by using the disk diffusion method, as recommended by EUCAST (http://www.eucast.org). Three resistance phenotypes were defined: "wild-type" (susceptible to all the tested antibiotics), "resistant" (non-susceptible to ≥ 1 agent in ≤ 2 antimicrobial classes), and "multidrug-resistant" (non-susceptible to ≥ 1 agent from ≥ 3 classes). Isolates resistant to extended-spectrum cephalosporins were screened for the presence of extended-spectrum β-lactamases (ESBLs), metallo-β-lactamases (MBLs), and extended-spectrum oxacillinases (ES-OXAs) with a phenotypic method described elsewhere [6]. Isolates tested positive with the phenotypic test were subsequently identified by PCR and sequencing with primers targeting ESBL-, MBL-, and ES-OXA-encoding genes [7].

Genotyping

MLST was performed according to the protocol of Curran et al. [8]. The *P. aeruginosa* MLST website (http://pubmlst.org/paeruginosa/) was used for the assignment of allele numbers and ST. The isolates' clonality was also investigated by PFGE with *Dra*I digestion. Pulsotypes (PTs) were defined according to international recommendations as previously described [9]; PFGE was used to assess the clonal diversity within each ST. Isolates which shared similar ST and PT, and recovered from the same ICU or hospital, were thought to be transmitted, directly or indirectly, from a patient to another.

Ethics statement

Approval and written informed consent from all subjects or their legally authorized representatives were obtained before study initiation. The study was approved by the ethical committee "Comité d'Etude Clinique" of the Besançon University Hospital, Besançon, France, references: 2011-A01013-38.

Results

One hundred and four isolates were available for characterization, of which 28 were isolated from blood cultures and 76 from pulmonary infections. Isolates were distributed into the ten ICUs (from 2 to 27 isolates) and the six hospitals (from 8 to 40 isolates). Table 1 details the distribution of resistance phenotypes according to ICUs and hospitals. We classified 39 of 104 isolates (37.5%) as wild-type, 37 (35.6%) as resistant, and 28 (26.9%) as multidrug resistant. The resistance phenotypes were almost equally distributed in hospitals, with the exception of hospitals D and F where no multidrug-resistant (MDR) isolates were recovered. Overall, amikacin, ceftazidime, and cefepime were the most active drugs with 12.5, 13.5, and 15.4% of resistance, respectively. Tobramycin, gentamicin, piperacillin-tazobactam, ticarcillin, and ciprofloxacin were moderately active, with 20.2, 22.1, 30.8, 34.6, and 34.6% of resistance, respectively. The two carbapenems tested were the less active drugs with 35.6 and 41.3% of resistance to imipenem and meropenem, respectively.

The 104 isolates were distributed in 46 STs, of which 7 were over-represented (58 out of 104 isolates, 55.8%). Table 2 shows the distribution of these 7 major STs, which are considered as EHR clones [2]: ST253 (including 11 isolates), ST395 (10 isolates), ST308 (9 isolates), ST235 (8 isolates), ST111 (8 isolates), ST244 (7 isolates), and ST175 (5 isolates). Thirty-nine minor STs were represented by 4 isolates (ST17), 2 isolates (ST170, ST309, ST527, and ST875), and 1 isolate (ST27, ST198, ST207, ST233, ST242, ST260, ST267, ST274, ST277, ST316, ST369, ST385, ST390, ST412, ST446, ST491, ST560, ST625, ST677, ST679, ST708, ST893, ST1125, ST1567, ST2048, ST2128, ST2295, ST2615, ST2683, ST2697, ST2698, ST2700, ST2702, and ST2703). Out of the 28 isolates that displayed a MDR phenotype, 25 belonged to EHR clones. ST111 and ST235 seem to be more frequently associated to MDR than other EHR clones. However, resistance patterns were variable within each clone (Table 2). One isolate of ST233 originating from hospital E produced the VIM-2 metallo-β-lactamase.

Table 1 Distribution of *P. aeruginosa* isolates according to hospitals and ICUs and resistance patterns in 6 French University Hospitals, 2012–2013

Hospital	ICUs	No. of isolates of *P. aeruginosa* (blood/pulmonary)	No. of isolates with wild-type, resistant, multidrug-resistant phenotype
A	Medical ICU: ICU1	12 (3/9)	5/6/1
	Surgical ICU: ICU2	10 (7/3)	4/2/4
B	Surgical ICU: ICU3	9 (3/6)	4/4/1
C	ICUB: ICU4	4 (0/4)	1/1/2
	ICUG: ICU5	4 (2/2)	2/1/1
	ICUR: ICU6	2 (0/2)	0/0/2
D	ICU7	15 (5/10)	7/8/0
E	ICU8	13 (1/12)	3/2/8
	ICU9	27 (2/25)	8/10/9
F	ICU10	8 (5/3)	5/3/0
		104 (28/76)	39/37/28

PFGE analysis suggested in-hospital cross-transmission events involving mainly MDR isolates belonging to EHR clones (Table 2). Isolates of ST308 and ST395 spread within a single ward or hospital: the clone ST308 (represented by 5 isolates with the pulsotype PSL31) spread among hospital E (ICU8 and ICU9), and clone ST395 (represented by 3 isolates with the pulsotype T19) spread in the ICU7 in hospital D (Table 2). Interestingly, their antibiotic resistance pattern spanned from wild-type to R or to MDR. The global PFGE analysis revealed that distant hospitals shared pulsotypes of EHR. Hence, a ST111 strain could have been shared by hospitals A and C since isolates B9 and SE39 have identical pulsotypes. Similarly, ST235 isolates with identical pulsotypes Bo16 and PSL13 were found in the distant hospitals B and E (Table 2).

Discussion

Our results are concordant with the comprehensive review of Oliver et al., who gathered data on population structure of *P. aeruginosa* isolates responsible for nosocomial infections [2]. Indeed, on one hand, we observed a high clonal diversity notably within antimicrobial susceptible isolates and on the other hand, the concentration of MDR isolates among EHR clones. Few studies have explored the *P. aeruginosa* population structure regardless of antimicrobial resistance pattern; Cabot et al. included 15 isolates of each antimicrobial susceptibility pattern and found results in line with ours: over-representation of ST175 and ST111 in MDR and extensive drug-resistant (XDR) isolates, and a clone, in this case ST244, which antimicrobial susceptibility pattern spanned from WT to MDR [4]. We also found that that ESBLs, MBLs, or ES-OXAs were uncommon in MDR isolates and that resistance to β-lactams was mostly due to intrinsic determinants of resistance, in line with previous data [6].

The compilation of data of molecular epidemiology and resistance data of the present *P. aeruginosa* population suggests two types of EHR clones: (*i*) the first type of EHR clones, hereafter called EHR-type I, that mostly display MDR phenotype (ST111, ST175, and ST235) and (*ii*) the second type of EHR clones, hereafter called EHR-type II, with resistance patterns spanning from wild-type to MDR (ST244, ST253, ST308, and ST395). ST235 appeared to be the EHR-type I with the widest distribution. A recent analysis of a large number of whole-genome sequences of ST235 established that this clone emerged in the 1980s, most likely in Europe, and spread via two independent fluoroquinolone-resistant lineages. Thereafter, ST235 isolates acquired locally resistance to other antibiotic classes and were involved in outbreaks, notably in ICUs [5]. Several reports suggest that the global epidemiology of the two other EHR-type I clones (ST111 and ST175) is close to that of ST235, even though such worldwide whole-genome sequence analyses are lacking [10–12].

EHR-type II clones are also responsible for outbreaks, with sometimes isolates displaying a wild-type resistant pattern. This suggests that multidrug resistance is not an inherent trait of theses clones and that drug resistance is not a prerequisite for outbreak [13–15]. The hospital environment has also been frequently incriminated in the hospital spread of EHR-type II clones. For instance, ST395 has been responsible for hospital outbreaks in France [13] and in the UK [15]. In the British outbreak, the authors suggested that *P. aeruginosa* ST395 rapidly colonized the plumbing system of a new hospital, before its commissioning, and was transmitted to burn patients through water bathing. Moreover, a genomic analysis of a collection of independent ST395 isolates identified a genomic island (GI-7) harboring genes involved in copper resistance [16]. Higher survival in copper solution of ST395 isolates was confirmed phenotypically and possibly accounted for their maintenance in the premise plumbing of the hospitals in which outbreaks occurred [16]. ST308 was also responsible for

Table 2 Distribution, origin, diversity of PFGE patterns and antibiotic resistance traits of the 7 major STs of *P. aeruginosa* isolated from infections in 6 French University Hospital, 2012–2013

Sequence Type[a]	Hospital[a]	ICU[a]	PT[a]	Resistance phenotype[a,b]	Remarks
ST111 (8)	A (1)	ICU2 (1)	B9 (1)	MDR (1)	PTs B9 and SE39 shared the same band pattern
	C (1)	ICU4 (1)	SE39	MDR (1)	
	E (6)	ICU9 (6)	PSL12 (1)	WT (1)	
			PSL28 (5)	MDR (5)	
ST175 (5)	A (2)	ICU1 (1)	B18 (1)	MDR (1)	
		ICU2 (1)	B42 (1)	MDR (1)	
	C (1)	ICU5 (1)	SE37 (1)	R (1)	
	E (2)	ICU9 (2)	PSL10 (1)	MDR (1)	
			PSL11 (1)	R (1)	
ST235 (8)	A (2)	ICU1 (1)	B65 (1)	R (1)	PTs Bo16 and PSL13 shared the same band pattern
		ICU2 (1)	B20 (1)	MDR (1)	
	B (1)	ICU3 (1)	Bo16 (1)	MDR (1)	
	C (2)	ICU4 (1)	SE14 (1)	MDR (1)	
		ICU6 (1)	SE14 (1)	MDR (1)	
	E (3)	ICU8 (2)	*PSL13* (2)	MDR (2)	
		ICU9 (1)	PSL15 (1)	MDR (1)	
ST244 (7)	B (1)	ICU3 (1)	Bo11 (1)	WT (1)	
	C (1)	ICU5 (1)	SE25 (1)	WT (1)	
	D (1)	ICU7 (1)	T26 (1)	R (1)	
	E (4)	ICU8 (2)	PSL20 (1)	MDR (1)	
			PSL21 (1)	MDR (1)	
		ICU9 (2)	*PSL22* (2)	R (2)	
ST253 (11)	A (4)	ICU1 (1)	B50 (1)	WT (1)	
		ICU2 (3)	B7 (1)	R (1)	
			B17 (1)	R (1)	
			B26 (1)	WT (1)	
	B (3)	ICU3 (3)	*Bo15 (3)*	R (3)	
	D (1)	ICU7 (1)	T17 (1)	R (1)	
	E (3)	ICU8 (1)	PSL3 (1)	MDR (1)	
		ICU9 (2)	PSL4 (1)	R (1)	
			PSL5 (1)	WT (1)	
ST308 (9)	A (3)	ICU1 (2)	*B48* (2)	R (2)	
		ICU2 (1)	B29 (1)	MDR (1)	
	C (1)	ICU6 (1)	SE19 (1)	MDR (1)	
	E (5)	ICU8 (4)	*PSL31* (3)	WT (1), MDR (2)	
			PSL32 (1)	WT (1)	
		ICU9 (1)	*PSL31* (1)	R (1)	
ST395 (10)	A (1)	ICU2 (1)	B27 (1)	WT (1)	
	C (2)	ICU4 (1)	SE10 (1)	R (1)	
		ICU5 (1)	SE8 (1)	WT (1)	
	D (3)	ICU7 (3)	*T19 (3)*	R (2), WT (1)	

Note: in italics PFGE patterns for which cross-transmission within the ICU or the facility is suspected

[a] Number in parenthesis is the number of isolates

[b] *MDR*, multidrug resistant; *R*, resistant; *WT*, wild type

prolonged hospital outbreaks in France and Germany, for which the environment, particularly water network, played a major role in cross-transmission [3, 17]. In the French ST308 outbreak, the authors suggested that the intraclonal diversity warrants its persistence in the hospital environment. Interestingly, we also found that ST308 was present in remote points of the water network of our hospital and contained the GI-7 involved in copper resistance (D Hocquet, personal data).

The reasons why some particular clones of *P. aeruginosa* are epidemic and prone to cause hospital outbreaks are likely due to their ability to acquire foreign resistance determinants in a setting of high antimicrobial pressure (i.e., ST235) and/or to survive in hospital environment (i.e., ST308 and ST395). These capacities can combine since ST235 outbreaks may be related to environment [14], and ST308 outbreaks may involve metallo-β-lactamase-producing isolates [17]. For other *P. aeruginosa* EHR clones present in our study (i.e., ST244, ST253, and ST233) or in other countries (e.g., ST277 in Brazil, ST292 in China, or ST357 in Central Europe) [18–20], additional research is needed to understand determinants of their success.

Conclusion

P. aeruginosa population structure in French ICUs is characterized by high clonal diversity notably among antimicrobial susceptible isolates and the over-representation of EHR clones, particularly within MDR isolates. Considering the propensity of EHR clones for dissemination, it may be of interest for the infection control team to document the ST of *P. aeruginosa* isolates regardless of antibiotic susceptibility pattern in order to focus interventions. This questions the need for routine detection of EHR by MLST or by a more rapid method [21] to implement targeted isolation precautions for patients carrying EHR isolates or proactive measures reducing the bacterial load in water fittings.

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Authors' contributions CS participated in the design of the study, acquisition of data, coordinated the study and in the article redaction. JR, NvdMM, PB, AMR, and VD participated in the acquisition of data and in the article redaction. PC and MT carried out the bacterial typing. DH coordinated the bacteriology study and participated in the redaction. XB conceived the study, participated in the acquisition of data in its design, and wrote the article.

Compliance with ethical standards

Approval and written informed consent from all subjects or their legally authorized representatives were obtained before study initiation. The study was approved by the ethical committee "Comité d'Etude Clinique" of the Besançon University Hospital, Besançon, France, references: 2011-A01013-38.

Conflict of interest The authors declare that they have no conflicts of interest.

Abbreviations EHR, epidemic high-risk; ESBL, extended-spectrum β-lactamase; ES-OXA, extended-spectrum oxacillinase; ICU, intensive care unit; MBL, metallo-β-lactamase; MDR, multidrug resistant; MLST, multilocus sequence typing; PFGE, pulsed-field gel electrophoresis; PT, pulsotype; ST, sequence type; WT, wild type; XDR, extensive drug resistant

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