

# Study of 109 Achromobacter spp. isolates from 9 French CF centres reveals the circulation of a multiresistant clone of A. xylosoxidans belonging to ST 137

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Lucie Amoureux, Juliette Sauge, Benoit Sarret, Matthieu Lhoumeau, Audrey Bajard, et al.. Study of 109 Achromobacter spp. isolates from 9 French CF centres reveals the circulation of a multiresistant clone of A. xylosoxidans belonging to ST 137. Journal of Cystic Fibrosis, 2019, 18 (6), pp.804-807. 10.1016/j.jcf.2019.04.005 . hal-03372509

# HAL Id: hal-03372509 https://hal.science/hal-03372509v1

Submitted on 21 Jul 2022

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# 1 <u>Title</u>

- 2 Study of 109 Achromobacter spp. isolates from 9 French CF centres reveals the circulation of
- 3 a multiresistant clone of *A. xylosoxidans* belonging to ST 137.
- 4

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- 24
- 25 <u>Keywords</u>: Achromobacter, nrdA, MLST, identification, resistance, cystic fibrosis, ST 137.
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#### 30 Abstract

We previously reported the distribution of Achromobacter spp (species and Sequence Types 31 (ST)) in our French Cystic Fibrosis (CF) centre. In the present study we collected 109 32 Achromobacter isolates (1/patient) from 9 other French CF Centres for species identification, 33 34 antimicrobial susceptibility testings and Multilocus-Sequence-Typing (MLST) analysis. Ten species were detected, A. xylosoxidans being the most predominant one (73.4% of the 35 36 isolates). Piperacillin-tazobactam, ceftazidime, imipenem, meropenem and ciprofloxacin were respectively active against 88, 70, 79, 72 and 23% of the isolates. Among the 79 A. 37 38 xylosoxidans isolates, 46 STs were detected. Interestingly, ST 137, recovered in 4 centres (5 patients), was previously detected in our centre (2 patients). The strains from the 7 patients 39 40 belonged to the same pulsotype (pulsed-field-gel-electrophoresis analysis) and harboured 41 acquired resistance to meropenem, ceftazidime, ciprofloxacin, and except for 2 isolates, to 42 imipenem and piperacillin-tazobactam. This is the first description in France of a circulating multiresistant A. xylosoxidans strain. 43

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#### 45 Manuscript

46 Achromobacter spp. are increasingly isolated from cystic fibrosis (CF) patients respiratory 47 samples (1-4). In France the prevalence of Achromobacter spp. in CF patients raised from 2.7 48 % in 2001 to 6.3% in 2016 (Registre Français de la Mucoviscidose, www.vaincrelamuco.org). 49 The pathogenicity of these bacteria is not well established yet, but chronic colonization has 50 recently been associated with more greater rates of mortality and transplantation among CF patients (5). To date 18 species have been described within the genus (6). However it is not 51 52 known yet, whether particular species or Sequence Types (STs) are linked with more pathogenicity or chronic colonisation. Therefore it is important to describe the distribution of 53 54 the species and STs identified among CF patients.

Biochemical systems (API 20 NE) or mass spectrometry (MALDI-TOF-MS) are reliable in
identifying the isolates to the genus level. However the identification to the species-level
requires specific techniques that are not commonly performed by routine diagnostic
laboratories. These techniques are based on housekeeping genes sequencing: *nrdA* (765 bp
fragment) (7) or Multilocus Sequence Typing (7 genes sequencing) (8).

Few studies have described the distribution of *Achromobacter* species among CF patients (14, 7, 9-11) but the distribution of STs within CF centres has only been reported in a Spanish
centre, two Brazilian centres, in a British multicentric study and in our centre (University
Hospital of Dijon, France) (4, 9-11).

64 The present study is the first French multicentric study to report identification, resistance and
65 MLST typing of *Achromobacter* detected from CF patients sputum.

66

In 2014, a total of 109 isolates of *Achromobacter* spp. were collected among 9 French CF
centres belonging to the French group MucoMicrobes (Besançon, Caen, Lyon, Nantes, ParisTrousseau, Paris-Necker, Roscoff, Suresnes and Toulouse) (Figure 1). We included the first
isolate of 2014 for each patient that previously presented at least one positive culture.

Identification was performed by *nrdA* sequencing, and genotyping of the isolates belonging to *A. xylosoxidans* was performed by MLST, as described previously (7, 8). The results are
presented in Table 1. Antimicrobial susceptibilities to piperacillin-tazobactam, ceftazidime,
imipenem, meropenem, ciprofloxacin and aminoglycosides (AG) (tobramycin, amikacin,
gentamicin) were determined in accordance with the methodological recommendations of
CA-SFM-EUCAST (2014).

77 Among these 109 isolates, a total of 10 species were identified. As reported previously, A. 78 xylosoxidans was the most predominant species in the study and in each centre with 73.4 % 79 (n=80 /109) of the isolates. The other species included A. insuavis (9.2 %; n=10), A. dolens 80 (3.7 %; n=4), A. mucicolens (3.7 %, n=4), A. marplatensis (2.8 %, n=3), A. aegrifaciens (2.8 %, n=3), A. insolitus (1.8 %; n=2), A. pulmonis (0.9 %; n=1), A. deleyi (0.9 %; n=1) and A. 81 82 genogroup 3 (0.9 %; n=1). Interestingly and as reported previously in our centre (9), we did 83 not detect any isolate belonging to A. ruhlandii in this study although this species is 84 widespread in Denmark, in the US, (3, 7) and in a Brazilian centre (4).

85

As expected, a large majority of the isolates were resistant to AG (92%). This resistance is
linked to the production of the constitutive AxyXY-OprZ efflux system expressed by the
species A. xylosoxidans, A. insuavis, A. dolens, A. insolitus, A. aegrifaciens, A. deleyi, A. *pulmonis* and A. genogroup 3 (12, 13).

90

91 Piperacillin-tazobactam was the most active antibiotic (88% of susceptibility). Acquired 92 resistance to this beta-lactam was only observed for the species *A. xylosoxidans*. Meropenem 93 was less active than imipenem (respectively 72 versus 79% of susceptibility). It is noteworthy 94 that 12 isolates were resistant to meropenem but not to imipenem. This phenotype had already 95 been noticed in our centre. This resistance could be mediated by over-expression of efflux 96 system (14). Resistance to ceftazidime was observed for 30% of the strains, which is 97 consistent with data from CF studies (10, 15). Resistance to ciprofloxacin was high (77%), as

- 98 often described among CF, non CF and environmental isolates (16). It was observed for 94 %
- 99 of *A. xylosoxidans* isolates but only for 39 % of the isolates belonging to the other species.
- 100

101 MLST analysis was performed for 79 isolates identified as A. xylosoxidans. They were 102 classified into 46 STs. Twenty-five STs were already referenced in the PubMLST database 103 181 ST on the 18<sup>th</sup> (Table 2) which contained January 2019 104 (https://pubmlst.org/achromobacter/). Twenty-one were new undescribed STs (29 isolates) 105 that we submitted to the PubMLST database for number assignments (ST 433 to 453).

106

Despite this diversity, 21 STs (52 isolates) were detected at least twice in the study, and surprisingly, in most of the cases, the isolates originated from patients not attending the same centre. Pulsed field gel electrophoresis analysis (PFGE) was performed on the 52 isolates as already described (14) (Table 1). Restriction patterns were interpreted according to Tenover's

- **111** criteria (17).
- 112 Some STs included isolates that all shared « indistinguishable » or « closely related » profiles.

113 This suggested a circulation of some clonal strains in France. For example, ST 153 was 114 detected from 5 patients of the study originating from 3 distinct centres and previously from 115 one patient of our centre. This ST had already been reported from a chronically colonized 116 patient in Spain (10).

ST 2 was detected in the present study from 4 patients (4 centres), but also in our hospital from 1 CF, 2 non CF patients and environmental samples (16). In PubMLST database, this ST is recorded for isolates from CF patients in the US, in France, and from non CF patients in Belgium. The 4 isolates were categorized as "possibly related" by PFGE analysis, suggesting

- 121 that the isolates derived from a common parent.
- Interestingly for 3 patients originating from Caen, Suresnes and Roscoff, the isolates belonged
  to ST 290, already detected from a patient of our centre that was colonized for 19 years with
  the same strain before and after lung transplant.
- 125

Finally, the major finding of our study is the detection of ST 137 from 5 patients originating from 4 centres (Besançon, Roscoff, Nantes and Suresnes). Two chronically colonized patients from our CF centre harboured isolates belonging to this ST. PFGE profiles of the 7 isolates were indistinguishable, which suggests an epidemic strain. Moreover, all the isolates were multiresistant: all isolates acquired resistance to meropenem, ceftazidime and ciprofloxacin, and 5/7 to piperacillin-tazobactam and imipenem. A common source of contamination or 132 cross-contamination are unlikely, as the 5 centres are geographically distant. Strains 133 belonging to ST 137 have also been recorded in Belgium among CF patients 134 (http://pubmlst/achromobacter) and in Montpellier (France) but their resistance phenotypes 135 are not reported. One might wonder whether the strains belonging to this ST are presenting 136 more virulence factors, or a selective advantage.

137

In conclusion, this first multicentric study confirmed the diversity of Achromobacter species 138 recovered from CF patients sputum in France, and the predominance of A. xylosoxidans as 139 140 reported previously. We also observed a large variety of STs, but MLST and PFGE analysis 141 indicated the circulation of several clones among CF centres. Particular attention should be 142 paid to ST 137 that is linked with multiresistance to antibiotics, seems to have an 143 epidemiogenic potential, and might be linked with chronic colonization, as already described 144 with the mutiresistant Danish Epidemic Strain (3). More epidemiological data are needed to 145 help determine which strains might be of clinical importance, to guide the virulence studies, 146 and to propose guidelines for therapeutic or prophylaxis management of the patients.

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- 148

#### 149 Acknowledgments

150 The authors gratefully acknowledge Theodore Spilker for his contribution in *nrdA* sequences

- 151 analysis and ST assignments.
- 152

#### **153** Conflict of interest statement

- 154 The authors have no conflict of interest related to this work.
- 155
- 156 Funding sources

157 This work has been partly supported by Vaincre la mucoviscidose Grant number158 RF20150501371.

- 159
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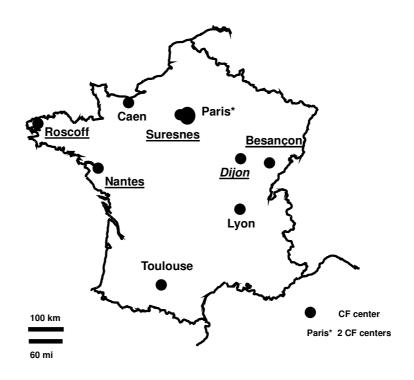
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## Figure 1 : Location of the 9 French CF centres of the study and Dijon.

Paris\* : 2 CF centers (Paris-Trousseau and Paris-Necker) Underlined : CF centers where ST 137 was detected.



Isolate	CF center	Species	ST	PFGE	Antimicrobial acquired resistance
116b	Lyon	A. xylosoxidans	1	/	IPM, MEM, CIP
102b	Toulouse	A. xylosoxidans	2	A1	CIP
44b	Paris-Trousseau	A. xylosoxidans	2	A2	CIP
28b	Roscoff	A. xylosoxidans	2	A3	CIP
83b	Nantes	A. xylosoxidans	2	A1	CIP
15b	Roscoff	A. xylosoxidans	15	В	PTZ, CAZ, IPM, MEM, CIP
90b	Nantes	A. xylosoxidans	15	В	PTZ, CAZ, MEM, CIP
3b	Roscoff	A. xylosoxidans	15	В	PTZ, CAZ, MEM, CIP
48b	Suresnes	A. xylosoxidans	19	/	CAZ, MEM, CIP
14b	Roscoff	A. xylosoxidans	22	/	CAZ, IPM, MEM, CIP
37b	Caen	A. xylosoxidans	27	С	CIP, IPM
52b	Suresnes	A. xylosoxidans	27	С	IPM, MEM, CIP
56b	Suresnes	A. xylosoxidans	28	D1	CIP, IPM
79b	Nantes	A. xylosoxidans	28	D2	PTZ, CAZ, IPM, MEM, CIP
5b	Besançon	A. xylosoxidans	137	E	CAZ, IPM, MEM, CIP
	Roscoff	A. xylosoxidans	137	E	PTZ, CAZ, IPM, MEM, CIP
	Suresnes	A. xylosoxidans	137	E	PTZ, CAZ, IPM, MEM, CIP
	Suresnes	A. xylosoxidans	137	E	PTZ, CAZ, MEM, CIP
	Nantes	A. xylosoxidans	137	E	PTZ, CAZ, IPM, MEM, CIP
	Suresnes	A. xylosoxidans	153	F	CIP
	Toulouse	A. xylosoxidans	153	F	CIP
	Toulouse	A. xylosoxidans	153	F	CIP
	Lyon	A. xylosoxidans	153	F	CIP
	Lyon	A. xylosoxidans	153	F	CIP
	Paris-Trousseau	A. xylosoxidans	175	/	CIP
	Necker	A. xylosoxidans	176	/	CAZ, CIP
	Suresnes	A. xylosoxidans	179	G1	PTZ, CAZ, MEM, CIP
	Suresnes	A. xylosoxidans	179	G2	PTZ, CAZ, CIP
	Suresnes	A. xylosoxidans	179	G3	CIP
	Lyon	A. xylosoxidans	180	/	CIP
	Lyon	A. xylosoxidans	184	/	None
	Nantes	A. xylosoxidans	202	/	CIP
	Toulouse	A. xylosoxidans	211	/	CAZ, CIP
	Roscoff	A. xylosoxidans	226	Н	PTZ, CAZ, IPM, MEM
13b	Roscoff	A. xylosoxidans	226	Н	CAZ, CIP
32b	Roscoff	A. xylosoxidans	226	Н	PTZ, CAZ, IPM, MEM, CIP
117b	Lyon	A. xylosoxidans	234	I	CIP
65b	Paris-Necker	A. xylosoxidans	234	I	CIP
81b	Nantes	A. xylosoxidans	248	Un.	PTZ, CAZ, IPM, MEM, CIP
	Nantes	A. xylosoxidans	248	Un.	CIP
	Toulouse	A. xylosoxidans	273	J	CAZ, CIP
	Toulouse	A. xylosoxidans	273	J	CIP
	Roscoff	A. xylosoxidans	290	K1	CIP
	Caen	A. xylosoxidans	290	K2	MEM, CIP
	Suresnes	A. xylosoxidans	290	K1	CIP
58b	Suresnes	A. xylosoxidans	292	/	CAZ, MEM, CIP

	- "				
	Roscoff	A. xylosoxidans	314	Un.	CAZ, IPM, MEM, CIP
	Suresnes	A. xylosoxidans	314	Un.	CAZ, IPM, MEM, CIP
	Lyon	A. xylosoxidans	315	1	CAZ, CIP
	Toulouse	A. xylosoxidans	424	/	CIP
	Roscoff	A. xylosoxidans	433	L	IPM, CIP
18b	Roscoff	A. xylosoxidans	433	L	CIP
11b	Roscoff	A. xylosoxidans	434	/	IPM, CIP
12b	Roscoff	A. xylosoxidans	435	Μ	CIP
84b	Nantes	A. xylosoxidans	435	М	CIP
25b	Roscoff	A. xylosoxidans	436	/	None
45b	Suresnes	A. xylosoxidans	437	/	CIP
61b	Suresnes	A. xylosoxidans	438	N1	CIP
95b	Toulouse	A. xylosoxidans	438	N2	MEM, CIP
62b	Suresnes	A. xylosoxidans	439	/	CAZ, MEM, CIP
63b	Paris-Necker	A. xylosoxidans	440	/	CIP
77b	Nantes	A. xylosoxidans	441	/	CIP
93b	Toulouse	A. xylosoxidans	442	/	CIP
23b	Roscoff	A. xylosoxidans	443	/	IPM
67b	Paris-Necker	A. xylosoxidans	444	0	CAZ
39b	Paris-Trousseau	A. xylosoxidans	444	0	CAZ
51b	Suresnes	A. xylosoxidans	445	Р	IPM, CIP
72b	Paris-Necker	A. xylosoxidans	445	Р	IPM, MEM, CIP
66b	Paris-Necker	A. xylosoxidans	446	/	CIP
70b	Paris-Necker	A. xylosoxidans	447	/	CIP
	Nantes	A. xylosoxidans	448	Q	CIP
	Nantes	A. xylosoxidans	448	Q	CIP
	Nantes	A. xylosoxidans	449	/	CAZ, CIP
	Lyon	A. xylosoxidans	450	R	None
	Lyon	A. xylosoxidans	450	R	CIP
	Lyon	A. xylosoxidans	451	S	MEM, CIP
	Lyon	A. xylosoxidans	451	S	MEM, CIP
	Nantes	A. xylosoxidans	452	/	CAZ, CIP
	Lyon	A. xylosoxidans	453	/	CIP
	Paris-Trousseau	A. xylosoxidans	/	/	CIP, IPM
	Suresnes	A. pulmonis	/	/	CAZ, MEM, CIP
	Paris-Necker	A. mucicolens	/	/	
	Toulouse	A. mucicolens	/	/	
		A. mucicolens	,	/	
	Lyon	A. mucicolens	/	/	
	Lyon	A. marplatensis		/	
	Roscoff		/	/	CIP
	Roscoff	A. marplatensis	/	/	
	Toulouse	A. marplatensis A. insuavis	/	/	
	Roscoff		/	/	MEM
4b	Roscoff	A. insuavis	/	/	CIP
	Roscoff	A. insuavis	/	/	
41b	Paris-Trousseau	A. insuavis	/	/	CIP
	Suresnes	A. insuavis	/	/	CIP
78b	Nantes	A. insuavis	/	/	

92b	Toulouse	A. insuavis	/	/	
101b	Toulouse	A. insuavis	/	/	CIP
107b	Toulouse	A. insuavis	/	/	
118b	Lyon	A. insuavis	/	/	CIP
36b	Caen	A. insolitus	/	/	
68b	Paris-Necker	A. insolitus	/	/	
103b	Toulouse	A. genogroup 3	/	/	
7b	Roscoff	A. dolens	/	/	CAZ, CIP
85b	Nantes	A. dolens	/	/	
106b	Toulouse	A. dolens	/	/	CIP
110b	Lyon	A. dolens	/	/	
97b	Toulouse	A. deleyi	/	/	MEM, CIP
16b	Besançon	A. aegrifaciens	/	/	
69b	Paris-Necker	A. aegrifaciens	/	/	
75b	Nantes	A. aegrifaciens	/	/	CAZ, IPM, MEM, CIP

# <u>Table 1</u> : Origin, species identification, ST , PFGE results and antimicrobial acquired resistance for the 109 *Achromobacter* spp. isolates.

CAZ : ceftazidime ; PTZ : piperacillin/ tazobactam ; IPM : imipenem ; MEM : meropenem ; CIP : ciprofloxacin ST in bold were already detected in our CF center in previous studies.

\*PFGE profiles were interpreted according to Tenover's criteria (16)

Isolates categorized as « indistinguishable or « closely related » were assigned the same letter and number. i.e. : isolates 102 and 83 (pulsotype A1).

For isolates categorized as « possibly related » (profiles differing by four to six fragments) a number was added to the letter. i.e. : isolates 102, 44, 28, 83 (pulsotypes A1, A2, A3, A4).

« Un. » refers to unique profiles

ST	This study no. of patients (no. of centers)	PubMLST database (outside France)	Previous studies in our CF center (Dijon, France)
1	1 patient (1)	USA (CF)	-
2	4 patients (4)	Belgium (non CF patients), USA (CF patients)	1 CF patient, 2 non CF patients, hospital environment
15	3 patients (2)	USA (CF)	-
19	1 patient (1)	USA, Spain (non CF), Belgium (CF)	-
22	1 patient (1)	Sweden, Italy, Belgium (CF)	-
27	2 patients (2)	USA, Spain (CC*), Thailand (non CF)	1 CF patient, hospital environment
28	2 patients (2)	UK, USA (non CF)	-
137	5 patients (4)	Belgium (CF)	2 CF patients (CC**)
153	5 patients (3)	Spain (CF, CC*)	1 CF patient
175	1 patient (1)	UK, Belgium (CF) UK (non CF)	3 CF patients , hospital and river
176	1 patient (1)	UK (non CF)	-
179	3 patients (1)	UK, India (non CF)	-
180	1 patient (1)	UK (CF), UK, Belgium, Thailand (non CF)	-
184	1 patient (1)	Belgium (CF), Thailand (non CF)	hospital environment
202	1 patient (1)	Brazil (CF)	-
211	1 patient (1)	Belgium, Russia (CF)	-
226	3 patients (1)	Belgium (CF)	-
234	2 patients (2)	Belgium (CF)	-
248	2 patients (1)	Belgium (CF)	-
273	2 patients (1)	Belgium (CF)	-
290	3 patients (3)	-	1 CF patient (CC**), river
292	1 patient (1)	-	1 CF patient (CC**), domestic environment
314	2 patients (2)	China (non CF)	-
315	1 patient (1)	China (non CF)	-
424	1 patient (1)	Belgium	-

## <u>Table 2</u> : ST detected in the 9 CF centers already recorded in the pubMLST database (<u>http://pubmlst/achromobacter</u>).

CF : cystic fibrosis patient

CC : chronic colonization

- \* Amoureux *et al.,* 2016 (10)
- \*\*Barrado et al., 2013 (9)