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Stenotrophomonas maltophilia healthcare-associated infections: identification of two main pathogenic genetic backgrounds

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SUMMARY

Background: *Stenotrophomonas maltophilia* is an opportunistic multi-drug-resistant bacterium responsible for healthcare-associated infections. Strategies for in-hospital infection control and management of carriers and environmental reservoirs remain controversial.

Aim: To determine the population structure of *S. maltophilia* strains in hospitalized infected patients and to identify putative highly pathogenic subpopulations that require upgraded infection control measures.

Methods: Eighty-three diverse human strains of various clinical origins from 18 geographically distant hospitals were characterized phenotypically and genotypically using a multi-locus sequence typing (MLST) approach.

Findings: Neither a predominant nor emerging sequence type (ST) was identified. Among the 80 typeable strains, only 29% corresponded to described STs, especially ST5 ($N = 6$) and ST4/26/31 ($N = 2$). The ST distribution and the phylogenetic tree based on the concatenated MLST genes did not account for geographical, clinical origin or antimicrobial susceptibility clustering. A phylogenetic tree that included 173 ST profiles from the MLST database and the 80 typeable strains confirmed the high genetic diversity of *S. maltophilia*, the previously reported genogroup organization and the predominance of genogroup 6, as it represented 41% (33/80) of the strains. Unexpectedly, genogroup 2 was the second most prevalent genogroup and included 16% (13/80) of the strains. These genogroups represented 57% (20/35) of the strains in respiratory patients and 75% (9/12) of the strains in patients with cystic fibrosis.

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Conclusion: Beyond MLST, the over-representation of some genogroups among strains responsible for healthcare-associated infections was confirmed. Genogrouping affiliation is recommended to implement infection control measures selectively for the most pathogenic strains isolated from patient or environmental reservoirs.

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Introduction

Stenotrophomonas maltophilia is a non-fermenting Gram-negative bacillus found in a variety of environments, such as diverse water sources, soils and rhizospheres.¹ In humans, *S. maltophilia* is an emerging opportunistic pathogen responsible for acute healthcare-associated infections (HCAIs) in immunocompromised patients, and is known for chronic colonization in patients with cystic fibrosis (CF).^{1–4} Its low intrinsic virulence is balanced by its natural resistance to a wide range of antibiotics, including broad-spectrum antibiotics such as carbapenems. In humans, the spectrum of HCAIs includes respiratory tract, bloodstream, catheter-associated, and skin and soft tissue infections.¹ With respect to the pathophysiology of these infections, several basic issues are still unresolved, notably the putative adaptation of some *S. maltophilia* strains to specific niches, such as human environments, tracts, microbiota or diseases. This adaptive mechanism has been reported for other environmental bacteria such as *Agrobacterium radiobacter*.⁵ A specific *S. maltophilia* CF phenotype and/or genotype has been proposed previously but still requires further characterization.^{6,7} In healthcare facilities, *S. maltophilia* originates from colonized/infected patients or from environmental reservoirs such as the water system or scopes.^{4,8} Infection control strategies rely on monitoring these sources; however, the practical management of human carriers and environmental reservoirs is still debated.^{9,10} Additionally, information regarding the putative pathogenicity of particular *S. maltophilia* strains is required. The genetic backgrounds of *S. maltophilia* strains have been explored previously using various molecular methods, including multi-locus sequence typing (MLST), which has demonstrated a high level of genetic diversity.^{11,12} This study explored the genetic population structure of *S. maltophilia* strains using a large sample of strains responsible for HCAIs. By combining these data with disease, host and antimicrobial susceptibility characteristics, the study aimed to identify specific genetic backgrounds of strains with high human pathogenicity.

Materials and methods

Strain collection

A specific collection study was performed through the Collège de Bactériologie–Virologie–Hygiène des Hôpitaux de France study group, which is a well-established network representative of the geographic diversity of French hospitals, and two additional centres located in Tunisia and Spain.¹³ Among the 16 participating centres in France, five hospitals belonged to the national network of specialized CF care centres, the comprehensive list of which is edited periodically by the French Ministry of Health. During two three-month periods (mid-June to mid-September 2013 and mid-February to mid-

May 2014), all of the clinical *S. maltophilia* strains responsible for infection were included successively and exhaustively by all departments regardless of their clinical origin; they were centralized at the University Hospital Henri Mondor (Créteil, France). Only strains responsible for nosocomial infections (i.e. infections occurring at least three days after hospital admission) or HCAIs as defined by French guidelines (criteria correspond with the original publication of Friedman *et al.*) were included.^{14,15} Only one strain per patient was included. Patients were informed about participation in the study locally, and only anonymized metadata were collected for analysis, including age, sex, respiratory tract chronic illness, immunodeficiency and nature (if any), ward and clinical specimen origin.

Strain selection and characterization

In order to constitute the widest possible sample of strains according to their geographical and clinical origins for subsequent phenotypic and genotypic investigation, the first strain from each clinical origin and from each department was selected. All strains were identified using MALDI-TOF mass spectrometry (Andromas, Beckmann Coulter, Villepinte, France). Antimicrobial susceptibilities were tested and interpreted using the disc diffusion method according to the guidelines of the Antimicrobial Committee of the French Society of Microbiology (<http://www.sfm-microbiologie.org>). Ticarcillin–clavulanate, ceftazidime, ciprofloxacin and cotrimoxazole (trimethoprim–sulfamethoxazole combination) were tested. The minimum inhibitory concentration of colistin was determined using the Etest (BioMérieux, Marcy l’Etoile, France) method according to the manufacturer’s recommendations. After DNA extraction using the QIAAsymphony DSP Mini Kit (Qiagen, Courtaboeuf, France) on a dedicated platform, the MLST profile was determined using the Kaiser scheme.¹² Briefly, seven housekeeping genes were amplified and sequenced according to the PubMLST website recommendations (<http://pubmlst.org/smaltophilia/>): *atpD*; *gapA*; *guaA*; *mutM*; *nuoD*; *ppsA* and *recA*. In the case of new allele identification, sequencing was controlled with a new DNA extract. MLST assignments were obtained online. For each strain, the seven allelic sequences of the seven housekeeping genes (final length: 3591 nt) were concatenated and aligned using Seaview 4.0 (<http://doua.prabi.fr/software/seaview>). A phylogenetic tree was reconstructed using PhyML 3.0 based on the maximum-likelihood principle (<http://www.atgc-montpellier.fr/phyml/>), and a 100-repetition bootstrap analysis was performed. The phylogeny tree was obtained using FigTree v1.4 and rooted on corresponding *Stenotrophomonas rhizophila* sequences (DSM14405, RefSeq SAMN02727981). Statistical analysis was performed using χ^2 test, and $P \leq 0.05$ was considered to indicate statistical significance. An additional comprehensive phylogeny tree was constructed using all

available 173 MLST types in the PubMLST website on 1st October 2016 that included the 64 *S. maltophilia* strains from the original work of Kaiser et al. (*S. africana*, *S. nitritireducens* and *S. acidaminiphila* were excluded).¹² These 173 strains originated from Europe ($N=125$), Asia ($N=25$), Australia ($N=14$) and North America ($N=9$), and they were collected from human ($N=126$), environmental ($N=32$) and unknown ($N=15$) sources. Furthermore, 121 different sequence types (ST, a specific combination of seven alleles) were represented; the five main genogroups were genogroup 6 ($N=79$), 2 ($N=31$), 3 ($N=12$), 1 ($N=9$) and D ($N=9$). This tree was rooted on the corresponding *S. rhizophila* allelic sequences. Finally, the 14 genogroups described by Kaiser et al. were reported according to their original affiliation.¹²

Results

The geographical distribution of the 18 participating centres, including the French metropolitan ($N=14$) and non-metropolitan ($N=2$) centres and the extranational ($N=2$) centres, is reported in Figure 1. Among the 83 included strains, 42% (35/83) originated from the respiratory tract (sputum, $N=16$; tracheal aspiration, $N=10$; protected distal specimen, $N=7$; bronchoalveolar lavage, $N=2$); 34% (12/35) of the corresponding patients had CF. The other specimen types included blood (21%, 18/83), urine (11%, 9/83), suppuration (10%, 8/83), central arterial/venous catheter (5%, 4/83) and others (11%, 9/83, bile, eyes, sinus, amniotic fluid, cutaneous biopsy, joint fluid, deep collection). The sex ratio was 1.44 (49 males vs 34 females), and the median age was 53 years (ranging from 2 to 93 years). The hospitalization ward specialties included medicine (57%, 47/83), intensive care (34%, 28/83), surgery (7%, 6/83) and others (2%, 2/83). Chronic respiratory disease was identified in 33/83 (40%) patients, while a severe

immunocompromised condition was present in 24/83 (29%) patients (solid cancer, haematological malignancy and organ transplant). The antimicrobial susceptibility rates are reported in Table I according to CF status; intermediate and resistant strains were further grouped together into a non-susceptible category.

Due to the lack of *recA* (one strain) or *mutM* (two strains) amplification, an ST profile could not be assigned to three of the 83 strains. A known ST was identified in a minority of strains (29%, 23/80) (Table A, see online supplementary material). The previously identified STs were ranked as follows: ST 5 ($N=6$), ST4/26/31 ($N=2$ for each ST) and ST8/14/29/39/77/78/92/93/94/122/152 ($N=1$ for each ST). The characteristics of the strains exhibiting a new ST (i.e. a new combination of known alleles or a combination including at least one new allele) were reported according to allele assignment, or to the closest

Table I

Antimicrobial susceptibility rates of the 83 strains according to cystic fibrosis (CF) status (intermediate and resistant strains were grouped into a non-susceptible category)

Antibiotic	Susceptibility rate (%)			P^a
	Global ($N=83$)	Non-CF patients ($N=71$)	CF patients ($N=12$)	
Ticarcillin–clavulanate	43	48	17	0.06
Ceftazidime	30	35	0	0.01
Ciprofloxacin	83	86	67	0.11
Cotrimoxazole	95	96	92	0.47
Colistin	70	73	50	0.17

^a Statistical comparison of susceptibility rates between CF and non-CF patients.

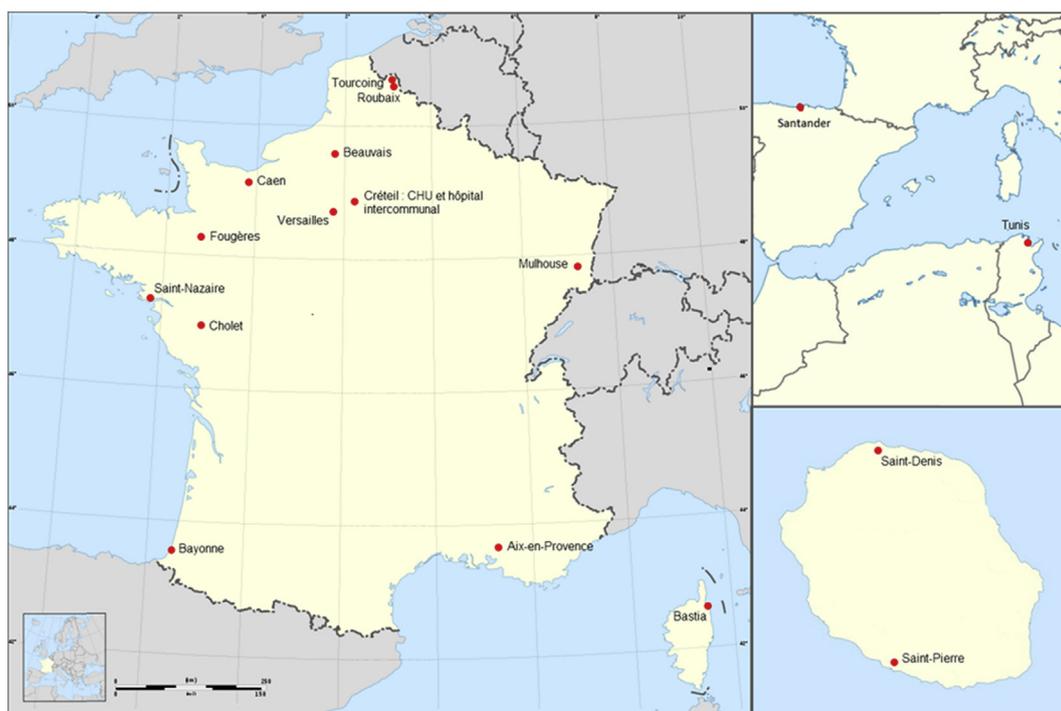


Figure 1. Geographical distribution of the 18 hospitals, including the two non-metropolitan and two extranational centres.

alleles if new mutations were identified (Table B, see online supplementary material).

The phylogenetic tree of the 80 MLST-type strains is reported in Figures A–E (see online supplementary material). Except for three small groups of strains with the same geographical origins (Figure A, see online supplementary material; SM30/32/35, SM225/226, SM29/31 and SM74/151), no other clustering of strains was observed according to their geographical (Figure A, see online supplementary material), respiratory and/or CF origin (Figure B, see online supplementary material), or their antimicrobial non-susceptibility to ticarcillin–clavulanate (Figure C, see online supplementary material), ciprofloxacin (Figure D, see online supplementary material) or colistin (Figure E, see online supplementary material). The very low number of cotrimoxazole-resistant strains ($N=4$) did not permit a similar assessment for this antimicrobial compound.

All five specialized CF care centres provided isolates from patients with CF; none of the 12 CF strains presented an identical ST or an identical nearest combination of alleles (Tables A and B, see online supplementary material). Finally, the comprehensive phylogenetic tree that includes all 173 available STs on the MLST website at the time of analysis (including the 63 strains from the original study of Kaiser *et al.*), the 80 typeable strains from the present study and genogroup subtyping is reported in Figure 2.¹² Genogroups 6

and 2 represent 41% (33/80) and 16% (13/80) of the strains, respectively; these two genogroups contained the majority of the respiratory (57%, 20/35) and CF (75%, 9/12) strains.

Discussion

S. maltophilia is an environmental opportunistic pathogen that demonstrates a natural multi-drug-resistant phenotype. Moreover, some strains have acquired additional resistance traits that limit antimicrobial therapeutic options.¹⁶ The putative emergence of strains with particular genetic backgrounds that exhibit enhanced human pathogenicity is an ongoing issue that could significantly impact strategies for controlling and preventing these infections. The detection of emerging clones with specific genotypic or phenotypic characteristics is of interest. Such opportunistic ‘superbugs’ have been reported previously for other environmental bacteria such as *Pseudomonas aeruginosa*.^{5,17} This study has provided genetic data from a substantial multi-centric sample of various clinical strains using an MLST method. By selecting unique hospital/ward/clinical origin strains, the risk of strain redundancy by cross-transmission or, more likely, by exposure to the same environmental reservoir has been reduced. Indeed, in the present study only three small clusters of two or three strains

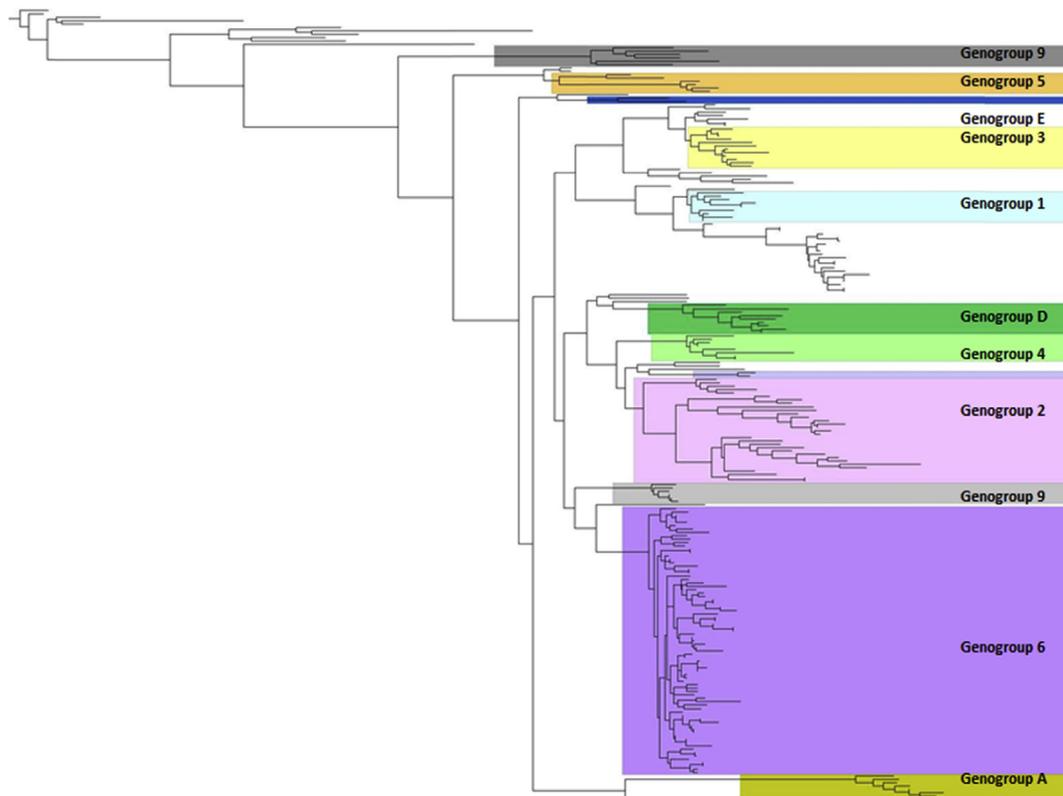


Figure 2. Maximum-likelihood tree based on the concatenated sequences of the seven housekeeping gene fragments (3591 nt). The tree shows the structure of the studied *Stenotrophomonas maltophilia* population that includes: (i) the 80 typeable strains of the present study; and (ii) all 173 sequence types available on the multi-locus sequence typing (MLST) website at the time of analysis, which included the 64 *S. maltophilia* strains from the original work of Kaiser *et al.*¹² The horizontal lines represent the genetic distance, with the scale bar indicating the number of substitutions per nucleotide position. The tree was rooted with a sequence from *Stenotrophomonas rhizophila*. The numbers at the nodes indicate support values estimated using 100 bootstrap replicates. The genogroup affiliation according to MLST in the original study is indicated by coloured frames.¹²

could be genetically linked owing to a shared origin. The over-representation of a strain responsible for a local outbreak could corrupt the original aim of the study, namely to decipher the population structure of the *S. maltophilia* strains responsible for human infections. Beyond local flaws in infection control practices, it is assumed that a particular genetic background well adapted to humans will be identified in different patients from different healthcare facilities. Currently, the French Society of Infection Control does not recommend isolation of patients infected with or carrying a *S. maltophilia* strain.¹⁸ Nevertheless, it is not known with certainty that none of the 83 patients were isolated for *S. maltophilia* or for carriage of other multi-drug-resistant bacteria.

Beyond outbreak investigations, very few studies have explored the genetic diversity of *S. maltophilia* at national level using an MLST approach. To the best of the authors' knowledge, this study is the first contribution since the founding article was published by Kaiser *et al.* in 2009.¹² This study also reports the largest panel of clinical origins for a collection of *S. maltophilia* strains that infect humans. The identification of a large panel of different STs and previously unrecognized allelic combinations supports the high diversity of the study sample. At the MLST level, no specific associations were identified between the genetic background and either the clinical origin or the acquired resistance traits. Among known STs, the most common was ST5, which was identified in different French cities and in the Tunisian centre. This ST had been reported previously in different countries, including Germany, Austria and Korea.^{12,19} Nevertheless, the putative successful genetic background of ST5 should be confirmed by a larger study; only six representatives of this ST were identified in the present study. A predominance of CF strains of this ST, as reported by Kaiser *et al.*,¹² was not seen in the present study. This finding underlines the need to confirm all of the epidemiological trends using different strain samples. This study failed to identify a clear predominance of any particular ST in the 12 patients with CF; the same observation was made regarding respiratory tract infection strains. As reported previously, strains isolated from patients with CF appear to be more resistant than strains from non-CF patients.¹ This study identified *S. maltophilia* strains exhibiting different antimicrobial phenotypes within the same ST. The MLST type represents the genetic background of a strain; some different acquired resistance genes or some different levels of resistance gene expression could be present in strains from the same genetic backbone. This has been well described for other species, such as the ST-131 *E. coli* strains.²⁰

In the late 1990s, the characterization of genogroups by Hauben *et al.* using the amplified fragment length polymorphism approach highlighted a putative genetic association between genetic background and human pathogenicity.^{11,21} At that time, some genogroups harboured environmental strains exclusively, such as genogroups 4, 9 and 10, while others included mainly clinical strains (genogroups 1, 7, A and C). Moreover, respiratory and CF isolates were clustered in a specific genogroup (genogroup 6). Interestingly, this finding was confirmed by another molecular approach, MLST. Kaiser *et al.* confirmed the existence of the nine previously described genogroups, and completed the description of this pattern by adding five genogroups.¹² The present study found a predominance of genogroup 6 among samples, and identified a second

predominant genogroup, genogroup 2, that included the majority of clinical and respiratory strains. Regarding the 12 CF strains, nine of 12 isolates belonged to genogroup 2 or 6; they were genetically distant and originated from the five specialized CF care centre. Although these findings must be confirmed using a larger sample of specimens and centres, it is reasonable to exclude the local spread of a clonal strain in a limited number of centres. These findings support the legitimacy of genogroup subtyping rather than other molecular methods, and highlight the clinical relevance of these two genogroups. The ST- and genogroup-based conclusions are not contradictory but illustrate the discrepancies between these two approaches in term of viewpoints.²² The primary aim of this study was to identify the subgroups of *S. maltophilia* strains that demonstrate a putative enhanced pathogenic potency, and that require more aggressive preventive measures. Clearly these two genogroups should be monitored carefully in clinical or environmental reservoirs. The population structure of these two major groups suggests microbial adaptations to the human niche and/or pathogenic behaviours in humans other than patients with CF.

This study has several limitations, including the fact that the number of strains should be increased along with the diversity of their geographical origin. However, the inclusion of strains from overseas or foreign areas likely reduced the recruitment bias. The authors planned two periods of inclusion to prevent seasonal bias. Strains from the same ward and from the same clinical origin were excluded from the molecular analysis, missing putatively highly pathogenic strains. From the authors' perspective, the over-representation of a strain resulting from a local outbreak could corrupt the original aim of the study (i.e. deciphering the population structure of the *S. maltophilia* strains responsible for human infections). Beyond local flaws in infection control practices, it is assumed that a particular genetic background well adapted to humans will be identified in different patients from different healthcare facilities. Therefore, the authors focused on the diversity of the sample of selected strains for molecular characterization. No data about putative ongoing *S. maltophilia* outbreaks in each participating centre during the collecting periods were recorded; this could constitute a bias but the high diversity of *S. maltophilia* strains challenged this hypothesis. Furthermore, the inclusion of a large sample of environmental and animal strains in the phylogenetic analysis constitutes the next step in the analysis. Hospital environmental strains should be included with caution due to their putative direct relationship with human hospital-acquired counterparts. In terms of the quality of sampling, this effort should also benefit from the emergence of the next-generation-sequencing technologies, as this work supports more investigations with the genogroup scheme using core MLST.²³ Additionally, being able to examine all of the genetic characteristics of each strain could constitute an exciting opportunity to investigate the relationships between gene content, clinical origin and virulence potency.²⁴

In conclusion, this study: supports the absence of emerging STs among *S. maltophilia* isolated from hospitalized patients; confirms the previously proposed genogroup organization for the *S. maltophilia* population and the over-representation of genogroup 6 among strains responsible for HCAs; and reports, for the first time, the emergence of genogroup 2 strains. These are important for larger additional whole-genome-sequencing

based studies. In the meantime, efforts should be focused on controlling environmental contamination and/or cross-transmission to prevent infection by these human-predominant and, putatively, most pathogenic genogroups.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jhin.2017.02.003>.

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