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1 **Molecular basis of macrolide-lincosamide-streptogramin (MLS) resistance**
2 **in *Finegoldia magna* clinical isolates**

3

4 Running title: MLS resistance in *F. magna*

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28

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30

31 **ABSTRACT**

32 Of 69 clinical isolates of *Fingoldia magna* tested, 36% presented high-level MICs of
33 erythromycin (>256 µg/ml), harboring *erm(A)* (n=20) or *erm(B)* (n=5). Of nine isolates
34 exhibiting an inducible resistance phenotype to macrolides-lincosamides-streptogramins B,
35 four (44%) were susceptible with a potential risk of treatment failure due to emergence of
36 resistant mutants.

37 Clinically-relevant Gram-positive anaerobic cocci (GPAC) comprise several main genera
38 including *Finegoldia*, *Peptostreptococcus*, *Peptoniphilus*, *Anaerococcus* and *Parvimonas*
39 [1,2]. *Finegoldia magna* (formerly *Peptostreptococcus magnus*), the unique species of the
40 genus, is a commensal bacteria recovered from different human microbiotas (i.e., mouth,
41 gastrointestinal and genitourinary tract, and skin) [3,4].

42 This species as other GPAC can become opportunistic pathogens and they can be isolated
43 from diverse clinical specimens [5]. Indeed, *F. magna* has been reported as responsible for
44 different types of infections, mostly skin and soft tissue and prosthetic joint infections (PJIs)
45 and less frequently mediastinitis, endocarditis and necrotizing pneumonia [6-9].

46 *F. magna* is usually highly susceptible to penicillins and metronidazole but alternative
47 therapies can be useful in case of allergy/intolerance, acquired resistance or infections (as
48 PJIs) for which antibiotic diffusion is limited [10-12]. Although levels of resistance to
49 clindamycin can be as high as 40%, little is known about the genetic basis of resistance to
50 macrolides-lincosamides-streptogramins (MLS) in GPAC [12-14]. Bacterial resistance to
51 MLS can be associated to four main mechanisms: target modification by methylation of
52 rRNA (*erm* genes), ribosomal protection, active efflux and enzymatic inactivation [15]. Up to
53 now, only one study has investigated MLS resistance determinants in *Peptostreptococcus* spp.
54 (including only 8 *F. magna* clinical isolates), *erm*(A) subclass *erm*(TR) being the unique gene
55 detected [16].

56 The aim of the study was then to assess *in vitro* activity of MLS against a collection of 69 *F.*
57 *magna* clinical isolates recovered from patients in seven hospitals and to decipher the genetic
58 basis of MLS resistance.

59 From 2013 to 2014, 69 epidemiologically-unrelated *F. magna* clinical isolates were collected
60 from seven healthcare facilities, including six hospitals in France (Limoges, Tours, Clermont-
61 Ferrand, Paris, Lille and Caen) and another in Switzerland (La Chaux-de-Fonds). The type

62 strain *F. magna* ATCC 15794^T (bought at the DSMZ collection) was also included in the
63 study. The following clinical data were obtained for each patient: site of isolation, gender and
64 age. Microbiological findings (abundance in culture and concomitant organisms) were also
65 recorded. The vast majority of clinical isolates were recovered from deep infections (n=60,
66 87%) strains while some were responsible for PJI (n=4, 6%) or bacteremia (n=5, 7%). There
67 was a large predominance of male patients (sex ratio M/F = 4) and the median age of patients
68 was 61 years (range, 24-95 years). Microbiologically, all specimens yielded an important
69 number (>50) of colonies of *F. magna* with a large majority (80%) of mixed cultures.
70 For microbiological investigation, strains were grown on 5% horse blood agar plates
71 (bioMérieux, Marcy-l'Etoile, France) incubated at 35°C for at least 48 h in anaerobic jars
72 using the Anoxomat Anaerobic Cultivation System (Mart Microbiology, Drachten, The
73 Netherlands). Phenotypic identification at the species level was performed using the MALDI-
74 TOF mass spectrometry technology (Microflex; Bruker Daltonics, Wissembourg, France) in
75 accordance with the manufacturer's instructions.

76 MICs were determined by the broth microdilution (BMD) method using Brucella broth
77 supplemented with 5% lysed horse blood, 5 µg/mL hemin and 1 µg/mL vitamin K1 according
78 to CLSI recommendations [17]. Microplates were incubated at 35°C for 48 hours
79 anaerobically using jars and an Anoxomat system (Mart Microbiology BV, Lichtenvoorde,
80 The Netherlands). The eight following antibiotics were tested: erythromycin (ERY),
81 azithromycin (AZI), spiramycin (SPI), telithromycin (TEL), clindamycin (CLI), lincomycin
82 (LIN), pristinamycin (PRI) and quinupristin–dalfopristin (SYN). Interpretation of results was
83 made according to 2020 CLSI clinical breakpoints for CLI whereas no cutoffs were
84 recommended for other molecules [17]. *Streptococcus pneumoniae* ATCC 49619 served as
85 quality control strain for each tested batch.

86 A double-disc diffusion test (D-test) was performed to distinguish between phenotypes of
87 cross-resistance to MLS_B antibiotics according to CLSI guidelines [17]. Briefly, ERY and
88 CLI discs were applied 12–16 mm apart (edge-to-edge) on a Brucella blood agar (BBA)
89 containing 5% lysed horse blood, 5 $\mu\text{g}/\text{mL}$ hemin and 1 $\mu\text{g}/\text{mL}$ Vitamin K1 (BBA)
90 (bioMérieux, France). Blunting of the zone of inhibition around the CLI disc was considered
91 positive for the inducible MLS_B ($iMLS_B$) resistance phenotype, whereas a constitutive MLS_B
92 ($cMLS_B$) resistance phenotype was defined in the absence of D-shaped zone.

93 Bacterial genomic DNA of MLS-resistant isolates was extracted using the QIAamp DNA
94 Mini Kit (Qiagen, Courtaboeuf, France) as recommended by the manufacturer. Detection of
95 *erm*(A) [including subclass *erm*(TR)], *erm*(B), *erm*(C), *erm*(F), *erm*(T), *erm*(X), *msr*(A),
96 *msr*(D), *mef*(A) and *mef*(E) genes was performed as previously described [18-20]. Mutations
97 in the 23S rRNA (*rrl*) gene were also screened using the following primers: 23S-FM-F
98 (5'AGCAACGAACTTAAGCCCCA-3') and 23S-FM-R
99 (5'TCGTCTCTGCTCGACCTGTA-3'). All PCR-amplified products were sequenced in both
100 directions by the Sanger method using the same primers.

101 For some strains for which a mechanism of efflux was suspected, MICs of ERY and CLI were
102 determined on BBA by the agar dilution method (tested range, from 0.06 to 256 $\mu\text{g}/\text{ml}$) with
103 or without an efflux pump inhibitor (reserpine, 10 $\mu\text{g}/\text{ml}$).

104 The distributions of the MLS MICs as well as calculated MIC_{50} and MIC_{90} values are
105 represented in Figure 1. Two groups were clearly identified depending on their susceptibility
106 to ERY: a first group of 44 isolates with low-level MICs (1-8 $\mu\text{g}/\text{ml}$) and a second group of
107 25 isolates highly resistant to ERY (MICs >256 $\mu\text{g}/\text{ml}$). Among these ERY-resistant isolates,
108 16 (64%) and 9 (36%) presented a $cMLS_B$ and $iMLS_B$ phenotype, respectively. These bimodal
109 MIC distributions were similar for AZI and SPI whereas that of TEL was not. For the 44
110 isolates exhibiting low-level MICs for ERY, MICs of LIN and CLI were lower, ranging from

111 0.25 to 4 $\mu\text{g/ml}$ and ≤ 0.016 to 2 $\mu\text{g/ml}$, respectively. Out of the 25 isolates with high-level
112 ERY MICs, 21 (84%) were resistant to CLI (MICs >4 $\mu\text{g/ml}$), including the 16 isolates with a
113 cMLS_B phenotype. Out of the nine isolates exhibiting an iMLS_B phenotype, four were
114 categorized as susceptible. By contrast, MIC distributions of both streptogramins (i.e., PRI
115 and SYN) were homogeneous and unimodal whatever the phenotype, with MICs comprised
116 between 0.03-1 $\mu\text{g/ml}$ and 0.03-2 $\mu\text{g/ml}$, respectively.

117 All ERY-resistant isolates (25/69, 36%) harbored either an *erm(A)* subclass *erm(TR)* gene
118 (n=20) or an *erm(B)* gene (n=5). Nor *erm(C)*, *erm(F)*, *erm(T)*, *erm(X)*, *mef(A)*, *mef(E)*,
119 *msr(A)* and *msr(D)* genes were detected, neither mutations in 23S rRNA. The detection of
120 efflux pump-encoding genes (i.e., *mef(A)*, *mef(E)*, *msr(A)*, and *msr(D)*) was negative, which
121 was consistent with the absence of difference in MICs determined with or without reserpine.
122 Note that the type strain ATCC 15794^T was susceptible to all MLS and harbored no resistance
123 gene.

124 *F. magna* has become an opportunistic pathogen due to the increase of invasive procedures
125 and immunocompromising therapies, being now the most frequently GPAC isolated from
126 human infections [21,22]. Although almost all clinical isolates of *F. magna* remain
127 susceptible to penicillins and metronidazole, CLI constitutes an interesting therapeutic
128 alternative (especially in PJI treatment) despite a resistance rate that can vary between 0 and
129 40% [10-14].

130 Whereas studies of MLS resistance in *Peptostreptococcus* spp. were performed at least two
131 decades ago with no recent clinical isolates, this study provides updated data on *F. magna*
132 with an accurate method of identification (i.e., MALDI-TOF mass spectrometry) for GPAC.

133 Herein, we detected only two genes (*erm(A)* subclass *erm(TR)* and *erm(B)*) involved in MLS
134 resistance, both coding rRNA methylases. Although *erm(A)* subclass *erm(TR)* has been
135 already reported in ERY-resistant *Peptostreptococcus* spp. [16], this is the first description of

136 *erm(B)* in *F. magna*. As in aerobic Gram-positive bacteria (i.e., staphylococci, streptococci
137 and enterococci), the expression of both *erm(A)* and *erm(B)* can also be inducible (in the
138 presence of ERY) or constitutive [23]. Whereas being quite frequently identified in anaerobes,
139 no *erm(F)*, no *erm(X)* and no mutations in 23S rRNA were found in *F. magna* [24].

140 Whereas ERY is a good marker for the detection of all MLS_B phenotypes, it is not
141 recommended to be tested. Indeed, it could be a useful surrogate marker for the detection of
142 an iMLS_B phenotype, as done for aerobic Gram-positive bacteria. Although, some *F. magna*
143 clinical isolates with an iMLS_B phenotype were categorized as susceptible to CLI, there is a
144 potential risk of clinical failure due to the emergence of CLI-resistant mutants. This
145 acquisition of resistance, well described in aerobic Gram-positives [23], would result from
146 structural alterations in the upstream regulatory region that lead to a constitutive expression of
147 *erm(A)* or *erm(B)*. Note that the evidence of an iMLS_B phenotype in *Peptostreptococcus* spp.
148 was initially shown in the early 1990s and that the authors already recommended
149 susceptibility testing towards both ERY and CLI, in order to detect the CLI-susceptible
150 isolates presenting ERY resistance and that may harbor a MLS resistance mechanism [25].

151 Finally, *F. magna*, as a commensal of the normal oropharyngeal microbiota, may also act as
152 an underestimated reservoir of MLS resistance genes in humans [6]. Therefore, there is a
153 putative risk of in vivo transfer of *erm* genes to major pathogens, as previously demonstrated
154 in vitro with *Streptococcus pyogenes* [15].

155 For the first time, we have evaluated in vitro antimicrobial activity of MLS against a large
156 collection of invasive *F. magna* clinical isolates. Note that the rate of resistance to MLS
157 (36%) by acquisition of an *erm* gene is substantial and therefore it would be important to
158 evaluate the susceptibility to both CLI and ERY before its use in therapy.

159

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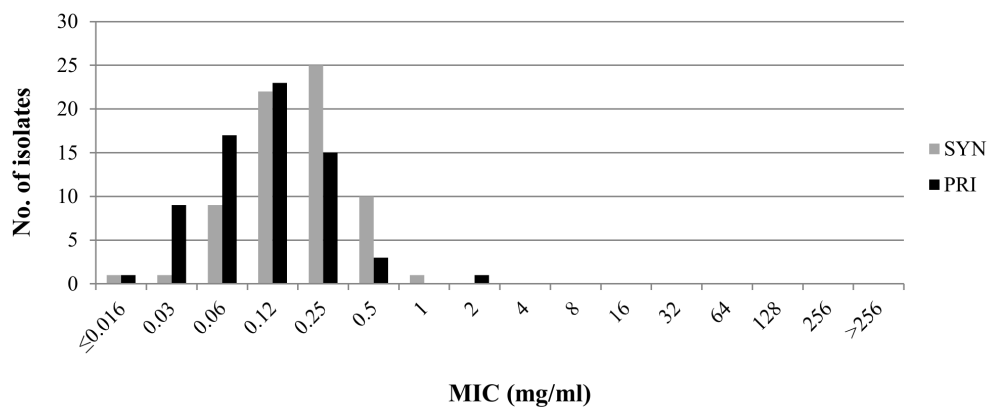
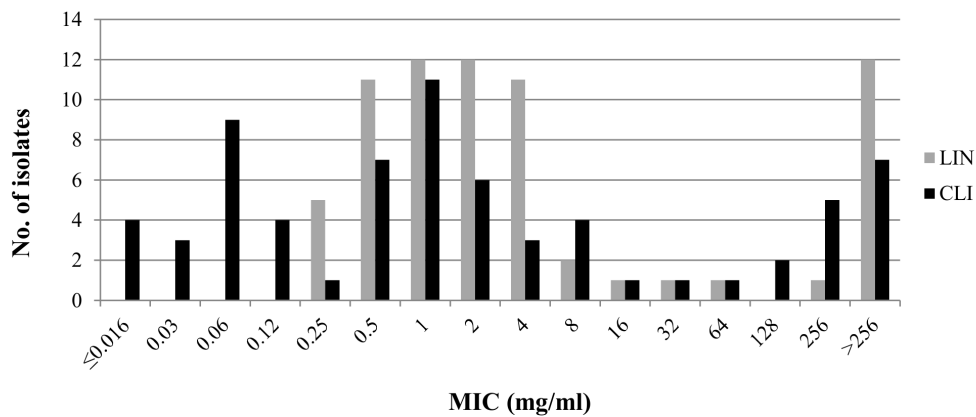
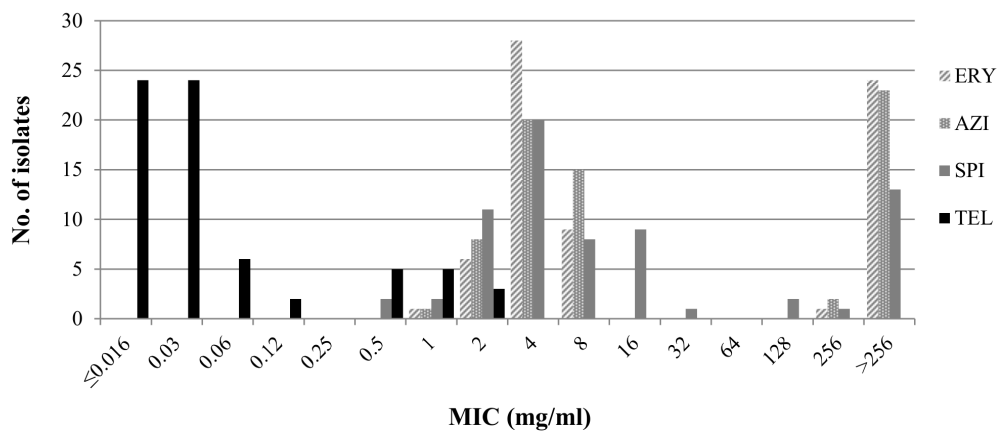
222 **Legend of the figure**

223 **Figure 1.** MIC distributions (in $\mu\text{g/ml}$) of macrolides, lincosamides and streptogramins for the
224 69 *F. magna* clinical isolates. AZI, azithromycin; CLI, clindamycin; ERY, erythromycin;
225 LIN, lincomycin; PRI, pristinamycin; SPI, spiramycin; SYN, quinupristin-dalfopristin; TEL,
226 telithromycin.

Table 1MLS susceptibility profiles for the 69 clinical isolates of *F. magna* according to their genotypes and MLS_B phenotypes

Genotypes ^a	No. of strains	MIC (µg/ml)															
		Erythromycin		Azithromycin		Spiramycin		Telithromycin		Lincomycin		Clindamycin		Pristinamycin		Quinupristin-Dalfopristin	
		MIC ₅₀ / MIC ₉₀	Range	MIC ₅₀ / MIC ₉₀	Range	MIC ₅₀ / MIC ₉₀	Range	MIC ₅₀ / MIC ₉₀	Range	MIC ₅₀ / MIC ₉₀	Range	MIC ₅₀ / MIC ₉₀	Range	MIC ₅₀ / MIC ₉₀	Range	MIC ₅₀ / MIC ₉₀	Range
All	69	4/>256	1->256	8/>256	0.25->256	4/>256	0.5->256	0.03/0.25	≤0.016-2	2/>256	0.25->256	1/>256	≤0.016->256	0.12/0.25	0.03-2	0.25/0.5	0.03-1
Wild-type	44	4/8	1-8	4/8	0.25-8	4/16	0.5-16	0.03/0.03	≤0.016-0.06	1/4	0.25-4	0.5/2	≤0.016-2	0.12/0.25	0.03-0.06	0.12/0.25	0.06-0.25
All <i>erm</i> (A)	20	>256/>256	>256	>256/>256	>256	>256/>256	1->256	0.12/2	0.03-2	32/>256	1->256	128/>256	0.25->256	0.12/0.5	0.03-0.5	0.25/0.5	0.06-0.5
iMLS _B	8	-	>256	-	>256	-	1-256	-	≤0.016-0.12	-	1-32	-	0.25-16	-	0.03-0.5	-	0.06-0.5
cMLS _B	12	>256/>256	>256	>256/>256	>256	>256/>256	4->256	1/2	0.03-2	>256/>256	4->256	>256/>256	64->256	0.12/0.25	0.06-0.5	0.25/0.5	0.06-0.5
All <i>erm</i> (B)	5	-	>256	-	>256	-	128->256	-	0.06-2	-	4->256	-	8->256	-	0.03-2	-	0.03-1
iMLS _B	1	-	>256	-	>256	-	>256	-	0.06	-	4	-	8	-	0.03-2	-	0.12
cMLS _B	4	-	>256	-	>256	-	>256	-	0.5-2	-	>256	-	128->256	-	0.06	-	0.03-1

^acMLS_B, constitutive MLS_B phenotype ; iMLS_B, inducible MLS_B phenotype.



Highlights

- Twenty-five (36%) isolates of *F. magna* were highly resistant to erythromycin
- All harbored an *erm(A)* subclass *erm(TR)* gene (80%) or an *erm(B)* gene (20%)
- They exhibited a constitutive (64%) or an inducible MLS_B phenotype (36%)
- Clindamycin resistance was found in 84% of erythromycin-resistant isolates
- For isolates with an inducible MLS_B phenotype, 44% were susceptible to clindamycin

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All the authors declare that they have no conflict of interest regarding the publication of this article.

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