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1 **Impact of colonisation pressure on acquisition of extended-spectrum β -lactamase-producing**
2 ***Enterobacteriaceae* and meticillin-resistant *Staphylococcus aureus* in two intensive care units: a**
3 **19-year retrospective surveillance**

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19 **Running title** Colonisation pressure on MDRO incidence

20 **Declarations of interest:** none

21 **Summary**

22 **Background,** Colonisation pressure is a risk factor for intensive care unit (ICU)-acquired multidrug-
23 resistant organisms (MDROs).

24 **Aim,** To measure the long-term respective impact of colonisation pressure on ICU-acquired extended-
25 spectrum β -lactamase-producing *Enterobacteriaceae* (ESBL-PE) and meticillin
26 resistant *Staphylococcus aureus* (MRSA).

27 **Methods,** All patients admitted between 01/1997 and 12/2015 to two ICUs (medical and surgical)
28 were included in this retrospective observational study. Rectal and nasal surveillance cultures were
29 obtained at admission and weekly thereafter. Contact precautions were applied for colonised or
30 infected patients. Colonisation pressure was defined as the percentage of patient-days (PDs) with an
31 MDRO to the number of PDs. Single-level negative binomial regression models were used to evaluate
32 the incidence of weekly MDRO acquisition.

33 **Findings,** Among the 23 423 patients included, 2 327 (10.0%) and 1 422 (6.1%) were ESBL-PE and
34 MRSA colonised, respectively, including 660 (2.8%) and 351 (1.5%) acquisitions. ESBL-PE
35 acquisition increased from 0.51/1 000 patient-exposed days (PED) in 1997 to 6.06/1 000 PED in 2015
36 ($P<0.001$). In contrast, MRSA acquisition steadily decreased from 3.75 to 0.08/1 000 PED ($P<0.001$).
37 Controlling for period-level covariates, colonisation pressure in the previous week was associated with
38 MDRO acquisition for ESBL-PE ($P<0.001$ and $P=0.04$ for medical and surgical ICU), but not for
39 MRSA ($P=0.34$ and $P=0.37$ for medical and surgical ICU). The increase of colonisation pressure was
40 significant above 100/1 000 PDs for ESBL-PE.

41 **Conclusion,** Colonisation pressure contributed to the increasing incidence of ESBL-PE but not
42 MRSA. This study suggests that preventive control measures should be customized to MDROs.

43

44 **Keywords:** Meticillin-Resistant *Staphylococcus aureus*; extended-spectrum β -lactamase-
45 producing *Enterobacteriaceae*; Colonisation pressure; Incidence; Intensive Care Units; Observational
46 study

47

48 **Introduction**

49

50 Over the last five decades, multidrug-resistant organisms (MDROs) have spread in hospitals
51 worldwide, becoming endemic in most countries. The two most frequent MDROs in developed
52 countries are meticillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β -lactamase–
53 producing *Enterobacteriaceae* (ESBL-PE). MRSA outbreaks are characterised by an emergence
54 during the 1970s, with a proportion of *S. aureus* isolates resistant to meticillin as high as 60% in
55 hospital-acquired infections [1]. The more recent decreasing rates noted in many countries [2,3] are
56 mostly due to improved compliance with hand hygiene [4,5]. ESBL-PE emerged in the 1980s, with
57 rapidly increasing rates of ESBL among *Escherichia coli* and *Klebsiella pneumoniae*. Despite some
58 success in controlling ESBL-PE spread, few studies have reported long-term control. This difficult
59 control is ascribable to the dissemination of ESBL *E. coli* in the community, with prevalence in the
60 population ranging from 5-10% in high-income countries to more than 60% in middle- and low-
61 income countries [6,7]. ESBL *K. pneumoniae* spreads more easily than ESBL *E. coli* [8]. However,
62 the spread of ESBL-PE contrasts with the progressive control of MRSA in the hospital setting, despite
63 the implementation of similar control measures for both MDROs [2].

64

65 The concept of colonisation pressure has been developed to account for the presence of patients
66 carrying MDRO and serving as a reservoir for transmission to non-colonised patients. Patients can be
67 colonised at admission, with the addition of acquired cases serving as a reservoir for secondary
68 transmission. Previous studies have shown that colonisation pressure is a risk factor for MDRO
69 acquisition for vancomycin-resistant enterococci [9], MRSA [10,11], *Clostridium difficile* [12,13] and
70 ESBL-PE [14,15].

71

72 Intensive care units (ICUs) are the hotspot of cross-transmission of MDROs, due to high antibiotic
73 selective pressure, high colonisation pressure and high care dependency with multiple opportunities
74 for cross-transmission by the hands of healthcare workers. Screening for MDRO colonisation at ICU
75 admission and during the ICU stay is therefore frequently advocated to identify the MDRO reservoir

76 and implement contact precautions for colonised patients. Yet active surveillance cultures and contact
77 precautions for colonised patients remain a matter of intense debate [16–18].

78

79 The long-term impact of colonisation pressure according to local MDRO epidemiology and control
80 measures has rarely been studied [12], and mostly investigated for only one MDRO [12] or all MDROs
81 [19]. We assessed the long-term impact of colonisation pressure on MDRO dynamics in two ICUs.

82

83 **Methods,**

84

85 *Setting and design*

86 The Bichat-Claude Bernard hospital is a 900- to 1100-bed teaching hospital in Paris, France, serving
87 as both a primary and a tertiary referral centre. There are five ICUs, including a 20-bed medical ICU
88 (MICU) and a 12-bed surgical ICU (SICU). Both ICUs have only single-bed rooms.

89 We performed a retrospective observational study of MDRO epidemiology in these two ICUs, based
90 on prospectively collected data, from January 1997 to December 2015.

91

92 *Data collection and definition*

93 The following data were collected: basic demographic characteristics, date of ICU admission and
94 discharge, type of ICU admission (direct or transfer), date of MRSA or ESBL-PE identification and
95 site of colonisation or possible infection.

96 Throughout the 19-year study period, routine rectal (ESBL-PE) and nasal (MRSA) premoistened
97 swabs were performed at admission and weekly from all patients in both ICUs.

98 We used the following definitions: *case*, a patient in whom MDRO was recovered from any site;

99 *colonised*, a patient who had MDRO-positive screening samples before a positive clinical sample;

100 *possible infection*, a positive clinical sample or a non-surveillance isolate. Cases were categorized as

101 *imported* to the ICU when either of the following criteria were met: MDRO identified in the previous

102 6 months or MDRO recovered from any site within 48 hours after admission. *Acquired* cases were

103 defined as MDRO-positive at least 48 hours after ICU admission from surveillance or clinical samples
104 or 48 hours after ICU discharge.

105

106 *Infection control program*

107 Contact precautions were used in all MDRO cases throughout the study period. These measures
108 consisted in flagging microbiological reports, charts, and doors of rooms of MDRO-positive patients;
109 wearing gloves when entering the room; wearing gowns when caring for the patient; hand hygiene
110 with antiseptic soap before July 2000 and alcohol hand rub thereafter. Decontamination of nasal
111 colonised MRSA with mupirocin, selective digestive decontamination and daily chlorhexidine bathing
112 were not used during the study period. The nurse-to-patient and nurse assistant-to-patient ratios were
113 1:2.5 to 1:2.7 and 1:4 to 1:5, respectively, and did not change over the study period.

114

115 *Microbiological techniques*

116 Nasal swabs were plated on Chapman agar (1997-2011) then on a chromogenic selective media (2011-
117 2015) and incubated for 48 hours at 37 °C. *S. aureus* was identified using the coagulase test with
118 rabbit plasma and the DNase (1997–2002) or slidex agglutination test (2003–2010).

119

120 Rectal swabs were cultured on selective media: Drigalski agar (Bio-Rad, Marnes-la-Coquette, France)
121 supplemented with cefotaxime (0.5 mg/L) from 1997-2004, BLSE Agar (AES Chemunex, Ivry sur
122 Seine, France) from 2005-2007, and ChromID ESBL Agar, (bioMérieux, Marcy-l'Etoile, France) from
123 2008-2015. *Enterobacteriaceae* species were identified using the API 20E ID system (bioMérieux,
124 Marcy-l'Etoile, France) (2006-2010).

125 From 2011 to 2015, strains were identified using mass spectrometry (Maldi Biotyper, Bruker,
126 Wissenbourg, France).

127 Clinical specimens were isolated on conventional media used for infection diagnosis.

128

129 Susceptibility to antibiotics was tested using the disk diffusion method on Mueller-Hinton media (Bio-
130 Rad, Marne-la-Coquette, France) and interpreted as recommended by the French Society for

131 Microbiology (<http://www.sfm-microbiologie.org/>). Double-disk diffusion testing of screening or
132 clinical specimens detected production of ESBL by a synergistic effect between clavulanic
133 acid/amoxicillin and cefotaxime, ceftazidime, or aztreonam.

134

135 *Statistical analysis*

136 Data were described using the median and interquartile ranges for continuous variables and
137 proportions (%) for categorical variables.

138

139 The outcome of interest was MDRO (MRSA or ESBL-PE) acquisition in exposed patients. Exposed
140 patients had no previous MDRO-positive sample, either MRSA or ESBL-PE. The incidence was
141 calculated as the ratio of the number of acquisitions to the number of patient-exposed days (PED).

142

143 Prevalence at admission was calculated as the ratio of the number of imported cases to the number of
144 ICU admissions. Colonisation pressure was computed per week for each ICU as the ratio of the
145 number of MDRO-positive patient-days (PDs) of each MDRO to the total number of PDs. Imported
146 cases were considered to have had MDRO colonisation throughout their ICU stay. Acquired cases
147 were considered to be MDRO colonised from the date of the positive sample until discharge from the
148 ICU.

149

150 Temporal annual trends of incidence of MDRO acquisition in exposed patients and MDRO prevalence
151 were estimated using negative binomial regression. Single-level negative binomial regression models
152 were used to evaluate the incidence of weekly MDRO acquisition within two distinct periods (<2005,
153 ≥ 2005), because of the epidemiology of MDRO; this approach allowed us to consider a nested
154 hierarchical structure of the data.

155

156 Univariate analyses were performed per ICU to assess the association between MDRO acquisition in
157 the week (Week+1) after colonisation pressure was measured. Univariate analysis was assessed by
158 calculating incidence rate ratio (IRR) and 95% confidence interval (CI). Continuous variables were

159 converted into categorical variables with same categorization for MRSA and ESBL-PE and median
160 was used as cut-off. Two-sided $P < 0.05$ defined significance.

161

162 In order to account for falsely negative screening at admission with secondary detection of MDRO
163 under the selective pressure of antibiotics, we performed a sensitivity analysis with MDRO acquisition
164 defined as an acquisition at least 7 days after ICU admission. This restricted definition of MDRO
165 acquisition also allowed us to restrict the analysis to patients with at least one weekly screening
166 sample in addition to an admission sample.

167

168 Statistical analysis was performed using Stata® software, v15.1 (StataCorp, College Station, Texas,
169 USA).

170

171 **Results**

172 During the 988-week study period, 23 423 patients were admitted to the ICUs. In total, 2 327 (10.0%)
173 were ESBL-PE cases, including 1 667 (7.1%) imported cases and 660 (2.8%) acquisitions. For MRSA,
174 1 422 (6.1%) were cases, including 1 071 (4.6%) imported cases, and 351 (1.5%) acquisitions (Figure
175 1).

176 Patient characteristics are summarized in Table I. The average PDs increased over time ($P < 0.001$).

177 Conversely, the average length of ICU stay did not increase over time ($P = 0.78$).

178

179 The prevalence of ESBL-PE imported cases increased from 0.7% in 1997 to 14.4% in 2015 ($P <$
180 0.001) and decreased from 4.1% to 2.3% ($P = 0.11$) for MRSA, (Figure 2). There were 213 409 PDs in
181 total, 186 850 and 194 452 of which were ESBL-PE and MRSA patient-exposed days (PED),
182 respectively. ESBL-PE acquisition increased from 0.51/1 000 PED in 1997 to 6.06/1 000 PED in 2015
183 ($P < 0.001$). The increase was abrupt from 2005 and stabilized between 2010 and 2015 ($P = 0.30$). In
184 contrast, MRSA acquisition steadily decreased from 3.75 to 0.08/1 000 PED ($P < 0.001$) during the
185 study period (Figure 2).

186

187 Colonisation pressure varied greatly between MDRO, ICU and periods (< 2005 and ≥ 2005). ESBL-
188 PE and MRSA colonisation pressure per week ranged from 0 to 516/1 000 PDs for MICU and from 0
189 to 578/1 000 PDs for SICU, and from 0 to 554/1 000 PDs for MICU and from 0 to 467/1 000 PDs for
190 SICU, respectively, over the study period (Supplementary Table I).

191
192 After controlling for period-level covariates by single-level negative binomial regression models,
193 colonisation pressure during the previous week was associated with MDRO acquisition for ESBL-PE
194 ($P < 0.001$ and $P = 0.04$ for MICU and SICU, respectively), but not for MRSA ($P = 0.34$ and $P = 0.37$
195 for MICU and SICU) (Figure 3; Supplementary Table II). The relationship between colonisation
196 pressure and MDRO acquisition was observed above 100/1 000 PDs for ESBL-PE. Similar results
197 were obtained in the sensitivity analysis when considering only MDRO acquisition after 7 days in the
198 ICU (Supplementary Table III). The thresholds of ESBL-PE acquisition were above 75 and 125/1 000
199 PDs of colonisation pressure in the MICU and SICU, respectively, and above 200/1 000 PDs for
200 MRSA (Supplementary Figure 1).

201

202 **Discussion**

203

204 This observational study showed opposite trends in the incidence and prevalence of MRSA
205 (decreasing) and of ESBL-PE (increasing) during the 19-year study period. These results are
206 consistent with those of the French networks participating in the European Antimicrobial Resistance
207 Surveillance Network [2,20,21]. Moreover, the incidence and prevalence of MRSA and ESBL-PE
208 were similar to previous findings [22,23]. The increase of ESBL-PE was abrupt from 2005, probably
209 due the emergence of ESBL-PE – notably, CTX-M-producing *E coli*, with rapid dissemination in the
210 community. We observed a simultaneous increase of both ESBL-PE prevalence and incidence. This
211 increase was coincident with the introduction of commercially prepared selective media. However,
212 accuracy and sensitivity were similar between commercially prepared selective media and in-house-
213 made media [24].

214

215 The other finding of this study was that colonisation pressure contributed to an increase in incidence of
216 ESBL-PE the next week but not that of MRSA. Graphical representation of colonisation pressure
217 suggested that thresholds were different across MDROs and ICUs, with higher thresholds for MRSA
218 than for ESBL-PE. Colonisation pressure is considered as a risk factor for MDRO acquisition based on
219 the principle that it increases the probability of transmission through contacts between healthcare
220 workers, patients and environment, due to a higher density of colonised patients. For ESBL-PE, these
221 results are consistent with previous findings [14,15]. Similar results were obtained in the sensitivity
222 analysis when considering only acquisition occurring 7 days after admission, in order to exclude
223 imported cases not detected at admission.

224

225 During the study period, the same control measures were implemented for MRSA and ESBL-PE,
226 including single-bed rooms, universal screening at admission and weekly thereafter, and contact
227 precautions for known MDRO-colonised or infected patients, according to national guidelines [25],
228 similar to other recommendations [26,27]. However, colonisation pressure impacted differently on
229 MRSA and ESBL-PE acquisition. This difference might be mostly explained by the bacterial
230 epidemiology of both pathogens. Indeed, ESBL-PE mainly colonises the digestive tract, with high
231 digestive concentrations, up to 10^8 ESBL-PE per gram of faeces, particularly in patients exposed to
232 antibiotics [28]; MRSA colonises the skin and nose, with a much lower burden of colonisation. Thus,
233 barrier precautions for MRSA may be more effective for prevention of transmission. In contrast,
234 ESBL-PE acquisition increased with high colonisation pressure. In addition to the digestive burden of
235 ESBL-PE and transmission through the hands of healthcare workers during direct care, environmental
236 contamination by ESBL-PE and transmission through the handling of contaminated faeces could be
237 other routes of transmission [29,30]. Moreover, management of excreta and control of faecal matter
238 was not explicitly included in contact precautions, which may contribute to the different transmission
239 rates between MRSA and ESBL-PE [31]. Thus, classic control measures may be effective in
240 preventing transmission of MRSA but not of ESBL-PE when colonisation pressure exceeds 100/1 000
241 PDs. However, the incidence of ESBL-PE has stabilized since 2010, despite the increased rate of
242 imported cases.

243

244 In a systematic review of the role of colonisation pressure [12], most studies demonstrate that
245 colonisation pressure is strongly and independently associated with MRSA acquisition [10,11,32].
246 These studies, however, were performed in the 1990s, before the introduction of alcohol handrub for
247 hand hygiene, which led to greater microbiological efficacy and compliance. Recently, a multicentre
248 interventional study in 14 ICUs suggested that higher compliance with hand hygiene and
249 chlorhexidine bathing resulted in a decrease of MRSA acquisition, but was ineffective in controlling
250 the spread of highly resistant *Enterobacteriaceae*, mainly ESBL-PE [33]. Our data are in line with this
251 study, suggesting that improved compliance with barrier precautions is more effective for controlling
252 MRSA dissemination than ESBL-PE.

253

254 The dynamics of MDRO spread differed between the two ICUs. This difference could be explained by
255 patient characteristics, degree of dependency of care and the number of opportunities for cross-
256 transmission, antibiotic selection pressure, and the level of compliance with hand hygiene and contact
257 precautions.

258

259 Our study has several strengths, including the very long study period, the large number of included
260 patients, the same screening strategy and control measures for MRSA and ESBL-PE over nearly 20
261 years, and the thorough weekly computing of colonisation pressure in both ICUs. Moreover,
262 colonisation pressure and incidence rate were calculated using both clinical and screening samples.

263

264 Although the present study covers a long study period, it has several limitations. First, our analysis did
265 not include all potential risk factors for MDRO acquisition, especially antibiotic use, severity of
266 illness, nurses' workload and compliance with hand hygiene and contact precautions [34,35]. Second,
267 the possible absence of universal screening obtained at admission could have biased the results if
268 missed screenings did not occur at random. Third, culture of screening samples may suffer from weak
269 sensitivity [36]. Fourth, as patients were screened weekly, and discharge screening was not performed,
270 positive patients could have been identified with a delay or missed. Fifth, only the first ESBL-PE

271 species identified was selected for case classification. Sixthly, as a single-centre study its
272 generalisability is limited. Finally, molecular typing was not performed to confirm acquisition.

273

274 **Conclusions**

275

276 In conclusion, our study suggests that different strategies for controlling cross-transmission should be
277 implemented for ESBL-PE as compared to MRSA, including the potential worth of contact
278 precautions in reducing ESBL-PE cross-transmission in ICUs with high colonisation pressure.

279 Moreover, colonisation pressure impacts MDRO acquisition, likely according to variable compliance
280 with standard and contact precautions.

281

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283 **Declarations of interest:** none

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285 commercial, or not-for-profit sectors.

286

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413

414 **Table I.** Characteristics of the patients admitted to the intensive care units over the 19-year study
 415 period

Variables	MICU (n=14 210)	SICU (n=9 213)	Total (n=23 423)
Male gender	9 014 (63.4)	5 955 (64.6)	14 969 (63.9)
Age (year)	58.9 (44.1-71.3)	60.2 (44.9-72.8)	59.4 (44.4-72.0)
Type of ICU admission			
direct (from the emergency room)	7 627 (53.7)	3 876 (42.1)	11 503 (49.0)
transfer (from wards)	6 583 (46.3)	5 337 (57.9)	11 920 (51.0)
Length of ICU stay (days)	3.5 (1.4-8.8)	3.1 (1.2-8.8)	3.3 (1.2-8.8)
ICU mortality	2 737 (19.3)	1 942 (21.0)	4 679 (20.0)
ESBL-PE			
Imported and acquired cases	1 609 (11.3)	718 (7.8)	2 327 (10.0)
Imported cases	1 191 (8.4)	476 (5.2)	1 667 (7.1)
Acquired cases	418 (2.9)	242 (2.6)	660 (2.8)
Possible infection	97 (0.7)	48 (0.5)	145 (0.6)
Colonisation only	321 (2.3)	194 (2.1)	515 (2.2)
Time to acquisition (days)	8 (5-12)	8 (5-14)	8 (5-13)
MRSA			
Imported and acquired cases	897 (6.3)	525 (5.7)	1 422 (6.1)
Imported cases	689 (4.8)	382 (4.1)	1 071 (4.6)
Acquired cases	208 (1.5)	143 (1.6)	351 (1.5)
Possible infection	83 (0.6)	56 (0.6)	139 (0.6)
Colonisation only	125 (0.9)	87 (1.0)	212 (0.9)
Time to acquisition (days)	9.5 (5.5-18)	8 (5-19)	9 (5-18)

416

417 Data are n (%) or median (IQR)

418 Abbreviations: ESBL-PE, extended-spectrum β -lactamase-producing *Enterobacteriaceae*; ICU,
419 intensive care unit; IQR, interquartile range; MICU, medical intensive care unit; MRSA, meticillin-
420 resistant *Staphylococcus aureus*; SICU, surgical intensive care unit
421

422 **Figure legends**

423

424 **Figure 1.** Flow chart

425 Abbreviations: ESBL-PE, extended-spectrum β -lactamase-producing *Enterobacteriaceae*; ICU,
426 intensive care unit; MRSA, meticillin-resistant *Staphylococcus aureus*; SICU, surgical intensive care
427 unit

428

429 **Figure 2.** Quarterly prevalence and incidence of ESBL-PE (a, c) and MRSA (b, d), 1997-2015

430 MICU (dashed line), SICU (solid line)

431 Abbreviations: ESBL-PE, extended-spectrum β -lactamase-producing *Enterobacteriaceae*; MICU,
432 medical intensive care unit; MRSA, meticillin-resistant *Staphylococcus aureus*; SICU, surgical
433 intensive care unit

434

435 **Figure 3.** Single-level negative binomial regression models of ESBL-PE and MRSA acquisition in the

436 MICU and SICU

437 Abbreviations: ESBL-PE; extended-spectrum β -lactamase-producing *Enterobacteriaceae*, IRR;
438 incidence rate ratio, MICU; medical intensive care unit, MRSA; meticillin-resistant *Staphylococcus*
439 *aureus*, PDs; patient-days, SICU; surgical intensive care





