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1 **Risk Factors for, and Clinical Relevance of, Faecal Extended-Spectrum β -**
2 **Lactamase producing *Escherichia coli* (ESBL-EC) Carriage in Neutropenic**
3 **Patients with Haematological Malignancies.**

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15

16 **Keywords:** ESBL-*Escherichia coli*, neutropenia, faecal carriage, risk factors,
17 outcome

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46 **ABSTRACT**

47 **Purpose:** To assess the risk factors for, and the clinical relevance of faecal carriage
48 by extended-spectrum β -lactamase producing *Escherichia coli* (ESBL-EC) in
49 neutropenic cancer patients (NCP).

50 **Methods:** An observational prospective multicentre cohort study was conducted
51 during two years at two teaching hospitals. Patients with acute leukaemia or
52 undergoing stem cell transplantation were included during neutropenia episodes.
53 Rectal swabs were obtained at hospital admission and weekly thereafter until
54 discharge or death. ESBL-EC colonized episodes were compared with non-colonized
55 episodes. ESBL-EC strains were studied by PCR and isoelectric focusing, and
56 molecular typing was performed by PFGE.

57 **Results:** Among 217 episodes of neutropenia, the prevalence of ESBL-EC faecal
58 carriage was 29%, 14% at hospital admission. Multivariate analysis identified
59 previous antibiotics as the only independent risk factor for ESBL-EC faecal
60 colonization (OR: 5.38; 95% CI: 2.79-10.39). Analysis of ESBL-EC isolates revealed
61 a polyclonal distribution with CTX-M predominance (81.3%). *E. coli* bacteraemia
62 was mainly caused by non-ESBL producing strains and its rate was similar in both
63 groups (13% vs 11%). We found no association between ESBL-EC carriage and an
64 increased risk of ESBL-EC bacteremia or a negative influence on other clinical
65 outcomes, including length of hospitalisation, early and overall mortality rates.

66 **Conclusions:** ESBL-EC faecal colonization is frequent in NCP but difficult to
67 identify by epidemiological or clinical features on presentation. Prior antibiotic
68 therapy is the major associated risk factor. In this setting colonization does not appear

69 to have a significant clinical relevance. Thus, routine testing for ESBL-EC faecal
70 carriage does not seem to be beneficial.

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86 **INTRODUCTION**

87 Infectious complications remain a major cause of morbidity and mortality in
88 neutropenic cancer patients (NCP). *Escherichia coli* is one of the commonest causes
89 of bacteraemia in this patient population, and so the development of antimicrobial
90 resistance in *E. coli* is a cause of special concern in NCP. In the last decade, there has
91 been a marked increase in colonization and infection due to quinolone-resistant *E.*
92 *coli*, probably as a consequence of the widespread use of fluoroquinolone prophylaxis
93 for febrile neutropenic episodes [1-4]. More recently, other resistance mechanisms in
94 *E. coli*, such as extended-spectrum β -lactamase (ESBL) production, have been
95 described in a range of epidemiological scenarios worldwide [5-9]. Recently we
96 reported a high prevalence of ESBL-EC faecal colonization among neutropenic
97 patients with haematological malignancies [10]. However, no prospective studies
98 have investigated the associated risk factors and the clinical relevance of this carriage
99 in these patients.

100

101 **METHODS**

102 **Setting, patients, and study design**

103 An observational prospective multicentre cohort study was conducted between 1 May
104 2006 and 31 December 2007 in Barcelona, Spain, at two teaching hospitals: Hospital
105 Duran i Reynals (hospital A) and Hospital Germans Trias i Pujol (hospital B).

106 The study population comprised consecutive adult patients with acute leukaemia or
107 undergoing haematopoietic stem cell transplantation, and who received chemotherapy
108 and developed grade IV neutropenia. The same patient could be included more than

109 once for different neutropenia episodes, provided there was an interval of two months
110 in between and no history of previous colonization or infection by ESBL-*E coli*.
111 Information regarding baseline characteristics, clinical data, rectal swabs, empirical
112 antibiotic therapy and outcomes was carefully recorded in a computerized database.
113 Rectal swabs were obtained at hospital admission and weekly thereafter until
114 discharge or death. To assess risk factors for intestinal colonization by ESBL-EC, we
115 compared baseline and demographic characteristics of colonized and non-colonized
116 episodes. We also compared these two groups in order to assess the clinical relevance
117 of faecal colonization. Following our institutional guidelines, most febrile neutropenic
118 episodes were empirically treated with the combination of a broad-spectrum
119 cephalosporin or a carbapenem, plus an aminoglycoside for the first 48 hours. The
120 initial empirical antibiotic treatment was not modified according to the results of the
121 rectal swabs. No antibacterial prophylaxis was administered during the study period.
122 This study was approved by the ethics committee of our institution.

123

124 **Definitions**

125 Grade IV neutropenia was defined as an absolute neutrophil count $<500/\text{mm}^3$. Prior
126 antibiotic therapy was defined as the receipt of any systemic antibiotic within one
127 month before colonization, or one month before admission in non-colonized patients.
128 Early mortality was defined as death for any cause within 7 days of admission and
129 overall mortality as death by any cause during hospitalisation.

130

131 **Microbiological studies**

132 Rectal swabs were cultured on three plates: MacConkey agar alone and supplemented
133 with cefotaxime (2µg/ml) and ceftazidime (4µg/ml) [11]. *E. coli* ATCC 25922 (non-
134 ESBL strain) and *K. pneumoniae* ATCC 700603 (ESBL-strains) were used as
135 controls. Identification of *E. coli* strains and their antibiotic susceptibility testing were
136 performed using commercial panels from Microscan® system (SIEMENS).
137 Susceptibility or resistance to antimicrobial agents was defined according to CLSI
138 criteria, and ESBL production screening was detected by double-disk synergy test
139 [12]. The genetic relatedness of *E. coli* strains was tested by pulsed field gel
140 electrophoresis (PFGE). The whole DNA was digested with *XbaI*. Strains that
141 differed in three or fewer bands were considered as belonging to the same cluster [13].
142 ESBLs were characterized by a multiplex PCR [14]. One strain per neutropenia
143 episode was studied.

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145 **Statistical analysis**

146 The prevalence of intestinal colonization by ESBL-EC was calculated as the
147 percentage of carriers among the total number of episodes included. Colonized and
148 non-colonized episodes were compared using univariate analysis with the chi-square
149 test for categorical variables and Student's t-test or the Mann-Whitney U-test, as
150 appropriate, for continuous variables, and multivariate logistic regression analysis was
151 performed to determine the independent risk factors related to intestinal colonization.
152 Multivariable conditional logistic-regression analysis of factors potentially associated
153 with ESBL-EC acquisition and mortality included all statistically significant variables
154 in univariate analysis, gender and age, and all clinically important variables, whether

155 they were statistically significant or not [15]. The analysis was performed with the
156 stepwise logistic-regression model of the SPSS software package (SPSS).

157

158 **RESULTS**

159 During the study period, 217 episodes of neutropenia (130 hospital A and 87 hospital
160 B) from 162 patients were studied (78 hospital A and 84 hospital B). The median
161 number of episodes per patient was 1.3 (1-5). The mean number of stool samples
162 obtained from each group (colonized and non-colonized episodes) was similar ($4.55 \pm$
163 1.73 vs. 4.62 ± 1.91 samples). Overall, ESBL-EC strains were isolated from faeces of
164 63 (29%) of the 217 episodes studied, 29 (13%) of them on hospital admission. Table
165 1 shows the main baseline and demographic characteristics of all episodes compared
166 by groups. No significant differences were found regarding the majority of
167 characteristics analysed. Univariate analysis identified prior antibiotics (62% in the
168 colonized group vs. 25% in the non-colonized group; $p < 0.001$) as the only factor
169 associated with ESBL-EC colonization. An unconditional logistic regression model
170 with ESBL-EC colonization as the dependent variable and adjusted for age, gender,
171 presence of central venous catheter (CVC) and previous antibiotic therapy, also
172 identified previous antibiotic therapy as an independent risk-factor (OR: 5.38; 95%
173 CI: 2.79-10.39; $p < 0.001$) (Table 2).

174 Sixty of the 63 ESBL-EC strains were available for typing and ESBL
175 characterization. The ESBLs identified among the 60 available strains in order of
176 frequency were: CTX-M-9 group (55%, 33/60), CTX-M-1 (26.7%, 16/60), SHV
177 (15%, 9/60), and TEM (3.3%, 2/60). Four isolates carried simultaneously an ESBL
178 enzyme and an OXA type β -lactamase [(3 strains harboured simultaneously a CTX-

179 M-1 ESBL and OXA, and 1 strain harboured a TEM ESBL and OXA). Fifty-three
180 different PFGE patterns were found among the 60 neutropenia episodes. Five patients
181 had two different neutropenia episodes, and only two of them were colonized by an
182 ESBL-EC strain of the same cluster in the two episodes. The remaining three patients
183 with two different neutropenia episodes were colonized by ESBL-EC strains of
184 different PFGE patterns. The spread of three clones (EC1, EC2 and EC3) carrying
185 *bla*_{CTX-M14} ESBL was detected among six patients of hospital B: EC1 in four patients,
186 EC2 in two patients and EC3 in two patients (Figure 1). Resistance rates to non- β -
187 lactam antibiotics were as follows: quinolones 75%, trimethoprim-sulfamethoxazole
188 66.7%, gentamicin 30%, and tobramycin 33.3%. All strains remained fully
189 susceptible to amikacin and carbapenems. The 16.7% of the strains were resistant to
190 amoxicillin-clavulanic and 3.4% to piperacillin-tazobactam. Table 3 shows the
191 antibiotic resistance rates, the resistance patterns, and PFGE patterns of the 60
192 available ESBL-EC strains, according to ESBL type.

193 Outcomes of the study population according to the ESBL-EC faecal carriage are
194 shown in Table 4. Out of the 217 episodes of neutropenia, 67 and 123 episodes of
195 infection were documented in group 1 and group 2 respectively, either clinically or
196 microbiologically, with no differences between groups. Among the microbiologically
197 documented infections, non-ESBL-EC strains accounted for 15 infections in group 1
198 and 15 infections in group 2, of which 8 and 13 were bacteraemias and 7 and 2 were
199 urinary tract infections respectively. ESBL-EC strains caused one infection
200 (bacteraemia) in group 1 and two infections (bacteraemia and urinary tract infection)
201 in group 2. One of the 2 patients with ESBL-EC bacteraemia received cefepime as the
202 initial empirical antibiotic therapy, which was switched to imipenem 48 hours later;
203 the patient died 4 days after the onset of bacteraemia due to cerebral haemorrhage.

204 The second patient was empirically treated with imipenem from the beginning,
205 presenting a good clinical response. There were no statistical differences between
206 groups regarding other outcomes during admission, including early and overall
207 mortality.

208

209 **DISCUSSION**

210 In recent years, a significant increase in the incidence of ESBL-EC faecal carriage has
211 been detected in a variety of settings, including hospitalised patients, outpatients and
212 healthy individuals [16-20]. We recently reported a high prevalence of ESBL-EC
213 colonization in NCP [10]. This figure, reaching a rate of 31.8%, was higher than that
214 found by other investigators in non-neutropenic populations [20-22]. It would be
215 interesting to know the corresponding data from other cancer centres.

216 Patients analysed in the present study can be considered representative of a
217 homogeneous population of adults with haematological malignancies and
218 neutropenia. There were no significant differences in their baseline characteristics or
219 clinical features, between patients who presented ESBL-EC faecal carriage and those
220 who did not. The only variable found to be an independent risk factor for ESBL-EC
221 colonization was previous antibiotic exposure, which has been widely recognized as a
222 risk factor for different ESBL-EC infections, especially bacteraemia and urinary tract
223 infections, by several authors in non-neutropenic populations [5,7,9,23,24]. The use of
224 prophylactic antibiotics, mostly quinolones, to prevent infection in febrile neutropenia
225 is a controversial issue in the literature [25]. Taking into account that antibiotic
226 exposure is a well defined risk factor for ESBL-EC colonization, it is reasonable to
227 speculate that if our patients had received routine antibiotic prophylaxis with

228 quinolones for febrile neutropenic episodes, the subsequent ESBL-EC colonization
229 rate would have been much higher. In our study, the presence of a CVC at admission
230 was more frequently found in the colonised group. Nevertheless, we could not find a
231 reasonable explanation for this finding, thus, we considered it irrelevant.

232 Molecular typing and characterization of the ESBL-EC strains showed a high clonal
233 diversity among the isolates, with a clear predominance (81%) of ESBL type CTX-M.
234 This finding is in good agreement with previous reports performed in the same
235 geographic area and also in several parts of the world [19,24,26]. Antibiotic resistance
236 by ESBL-EC strains to non β -lactam antibiotics was high, as previously reported
237 [23,24].

238 As expected, infections caused by *E. coli* were frequent in our study, but we did not
239 find a correlation between the detection of ESBL-EC faecal colonization and the risk
240 of developing an ESBL-EC infection. In fact, the rate of non ESBL-EC bacteraemia
241 was around 10% in both groups, whereas the rate of ESBL-EC bacteraemia was less
242 than 2%. This may indicate that, in spite of the presence of ESBL-EC colonies in the
243 selective plates, non ESBL-EC strains constitute the predominant *E. coli* population in
244 the faecal flora. Moreover, the occurrence of two episodes of ESBL-EC infection (one
245 episode of bacteraemia and one urinary tract infection) among the group of non-
246 colonised patients is remarkable. One possible explanation is the potential lack of
247 sensitivity of the screening test in the selective plates. Accordingly, our findings
248 suggest that testing faecal carriage for the presence of ESBL-EC strains may not be
249 cost effective.

250 On the other hand, as the number of persons colonized by ESBL-EC strains appears to
251 be expanding in the community, one would expect clinical infections caused by these

252 strains to increase, albeit slowly. The therapeutic options for ESBL-EC infections are
253 limited, since these strains are considered to be resistant to all oxyiminobetalactams
254 and frequently present associated resistance to other antimicrobial families such as
255 aminoglycosides and quinolones [27]. This limitation is of special concern in NCP
256 and may lead to universal use of carbapenems as empirical therapy for the febrile
257 episodes. However, in view of our current knowledge, this practice should be
258 undertaken with caution and assessed in controlled trials.

259 Despite a number of strengths (prospective and multicentre study) our study has some
260 limitations that should be acknowledged. First, the study was conducted in a small
261 geographical area, which may not reflect the situation in different epidemiological
262 settings. And second, the small number of patients with ESBL-EC infections may
263 have not allowed us to find differences in outcomes between both groups.

264 In conclusion, in our study we found that ESBL-EC faecal colonization is frequent in
265 NCP but difficult to identify by epidemiological or clinical features on presentation.
266 Prior antibiotic therapy and is the major associated risk factor. Although *E. coli*
267 remains a frequent cause of infection in NCP, ESBL-EC bacteraemia is still rare.
268 Overall, the clinical relevance of this colonization appears to be low, and it does not
269 have a significant negative influence on the outcomes. In this setting, routine testing
270 for ESBL-EC faecal carriage does not seem to be beneficial.

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282 have any relationship that may constitute a dual or conflicting interest.

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396 Table 1. Baseline characteristics of the study population according to the extended-
 397 spectrum β -lactamase *E. coli* faecal carriage.

Characteristics	Total	ESBL-EC carriage	ESBL-EC non-carriage	<i>p</i>
No. of episodes	217	63	154	-
Sex (M/F)	132 / 85	35 / 28	97 / 57	0.3
Mean age (yr, range)	51.39± 12.29	50.95± 11.92	51.57± 12.47	0.7
Underlying disease				
Acute leukaemia	141 (65%)	36 (57%)	105 (68%)	-
Malignant Lymphoma	31 (14%)	13 (21%)	18 (12%)	-
Multiple myeloma	34 (15%)	11 (17%)	23 (15%)	-
Myelodysplastic Syndrome	7 (3%)	3 (5%)	4 (3%)	-
Myeloproliferative disease	4 (3%)	0	4 (3%)	-
Haematopoietic stem cell transplant	99 (46%)	31 (49%)	68 (44%)	0.5
Previous chemotherapy (6 months)	148 (68%)	42 (67%)	106 (69%)	0.7
Health-care contact	172 (79%)	47 (75%)	125 (81%)	0.3
Central venous catheter at admission	99 (45%)	22 (35%)	76 (50%)	0.048
Urinary catheter at admission	5 (2%)	2 (3%)	3 (2%)	0.6
Previous antibiotic therapy	77 (36%)	39 (62%)	38 (25%)	< 0.001

398 NOTE: ESBL-EC: extended-spectrum β -lactamase *E. coli*

399

400 Table 2. Independent risk factors for faecal extended-spectrum β -lactamase-producing
401 *E. coli* carriage.

Risk-factor	Adjusted OR (95% CI)	<i>p</i>
Age (years, mean)	0.99 (0.97-1.02)	0.73
Gender (female)	1.39 (0.72-2.67)	0.32
Central venous catheter	0.43 (0.22-0.85)	0.015
Previous antibiotic therapy	5.38 (2.79-10.39)	< 0.001

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413 Table 3. Antibiotic resistance, PFGE patterns and resistance patterns of 60 extended-
 414 spectrum β -lactamase (ESBL) producing *E. coli* strains according to ESBL type.

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Antibiotic	CTX-M9 (n=33)	CTX-M1 (n=16)	SHV (n=9)	TEM (n=2)
	No of resistant strains			
Amoxicillin-clavulanic acid	2	4	3	1
Piperacillin-tazobactam	0	0	2	0
Ciprofloxacin	26	11	8	0
Gentamicin	14	4	0	0
Tobramycin	13	6	0	1
Amikacin	0	0	0	0
Cotrimoxazole	25	10	5	0
N° different PFGE patterns	27	15	9	2
Resistance patterns (N° of strains)	Cip, Gen , Tob, SxT (11) Cip, SxT (11) Cip (4) SxT (3) Cip, Gen, Tob (2) Cip, Gen (1) S (1)	Cip, SxT (3) Cip (3) Cip, Gen, Tob, SxT (2) Cip, Tob, SxT (2) SxT (2) Gen, Tob, SxT (1) Cip, Gen, Tob (1) S (2)	Cip (4) Cip, SxT (4) SxT (1)	Tob (1) S (1)

416 NOTE: ESBL-EC: extended-spectrum β -lactamase *E. coli*

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418 Table 4. Outcomes of the study population according to the extended-spectrum β -
 419 lactamase faecal carriage.

Characteristics	ESBL-EC carriage N=63 (%)	ESBL-EC non- carriage N=154 (%)	<i>p</i>
One or more febrile episodes	61 (97)	145 (94)	0.3
Infections per episode (mean \pm SD)	1.57 \pm 0.99	1.41 \pm 0.72	0.3
Episodes of infection	67	123	-
Clinically documented	6 (9)	7 (6)	0.4
Microbiologically documented	61 (91)	116(94)	0.4
Non-ESBL-EC infections	15 (22)	15 (12)	0.07
Bacteraemia	8 (13)	13 (11)	0.7
Urinary tract infection	7 (10.4)	3 (2.4)	0.018
ESBL-EC infections	1 (1.5)	2 (1.6)	0.9
Bacteraemia	1 (1.5)	1 (1)	0.7
Urinary tract infection	0	1 (1)	0.5
Days of hospitalization (mean \pm SD)	30.15 \pm 13.70	29.05 \pm 12.11	0.6
Days of antibiotic therapy (mean \pm SD)	19.03 \pm 12.34	19.39 \pm 13.55	0.9
Early mortality during hospitalization (7 days)	1 (1.6)	0	0.1
Overall mortality during hospitalization	6 (10)	17 (11)	0.74

420 NOTE: ESBL-EC: extended-spectrum β -lactamase *E. coli*

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