

1 **Clinical outcome of extended-spectrum beta-lactamase-producing *Escherichia coli***  
2 **bacteremia in an area with high endemicity**

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4 Kelvin K. W. To<sup>1,2,3</sup>, Wai-U Lo<sup>3</sup>, Jasper F. W. Chan<sup>3</sup>, Herman Tse<sup>1,2,3</sup>, Vincent C. C. Cheng<sup>3</sup>,  
5 Pak-Leung Ho<sup>1,2,3</sup>

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7 <sup>1</sup>Research Centre of Infection and Immunology,

8 <sup>2</sup>State Key Laboratory for Emerging Infectious Diseases,

9 <sup>3</sup>Department of Microbiology, The University of Hong Kong; Pokfulam Road, Pokfulam,  
10 Hong Kong Special Administrative Region, China

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14 Reprints or correspondence: Pak-Leung Ho, Carol Yu Centre for Infection and Division of  
15 Infectious Diseases, Department of Microbiology, The University of Hong Kong, Queen  
16 Mary Hospital, Pokfulam Road, Pokfulam, Hong Kong Special Administrative Region, China  
17 (e-mail: plho@hkucc.hku.hk).

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19

20 **Abstract**

21 **Objectives**

22 This study assessed the impact of discordant empirical antibiotic therapy (ET) on the  
23 outcome of bacteremia caused by extended-spectrum beta-lactamase-producing *Escherichia*  
24 *coli* (ESBL-EC).

25 **Methods**

26 The clinical features and outcome for a cohort of patients hospitalized with ESBL-EC  
27 bacteremia between 2007 and 2008 were retrospectively reviewed. The effect of different  
28 antimicrobial regimens on patient outcomes was analyzed.

29 **Results**

30 ESBL-EC accounted for 24.2% (207/857) of *E. coli* bacteremia cases. Urinary tract  
31 (43.6%) was the most common source of infection, followed by the hepatobiliary tract  
32 (23.0%). Discordant ET was given to 51.9% patients. Admission to the intensive care unit  
33 was associated with the use of carbapenem as ET ( $p < 0.001$ ). Univariate analysis revealed no  
34 significant differences in the 30-day mortality rates between patients receiving concordant  
35 and discordant ET (21.9% vs 19.8%,  $p = 0.732$ ); carbapenem and non-carbapenem ET (29.8%  
36 vs 19.1%,  $p = 0.118$ ); beta-lactam-beta-lactam-inhibitor combinations (BLBLIs) and non-  
37 BLBLIs ET (20.3% vs 22.3%,  $p = 0.734$ ); and cephalosporin and non-cephalosporin ET  
38 (18.6% vs 23.1%,  $p = 0.639$ ). The findings were confirmed by multivariate analysis.

39 **Conclusions**

40 Despite a high proportion of discordant ET, ESBL production had little effect on 30-  
41 day mortality. Whether the observation would be applied to different ESBL types is unknown  
42 and warrants further study.

43

44

45 **Introduction**

46 In the last five to ten years, the incidence of infections caused by *Enterobacteriaceae*  
47 producing extended-spectrum  $\beta$ -lactamase (ESBL) has increased rapidly and was mainly  
48 attributed to the successful distribution of CTX-M enzymes among *Escherichia coli* causing  
49 urinary tract and bacteremic infections <sup>1-3</sup>. A particularly challenging issue is that CTX-M-  
50 producers are increasingly recovered from patients with community-onset infections,  
51 especially those with minimal or absent healthcare risks <sup>4</sup>. In Hong Kong, China, we have  
52 previously shown that the CTX-M enzymes are emerging <sup>5-7</sup>. Among female outpatients with  
53 urinary tract infections, the ESBL prevalence was 6.6% in 2004 and 10% in 2005 <sup>6</sup>. All  
54 ESBL-producers were found to carry CTX-M type  $\beta$ -lactamases <sup>6</sup>. For bacteremia, the ESBL  
55 rate for both community onset and hospital onset episodes had increased from 8.9% and  
56 20.3% in 2000 to 25.5% and 43.5% in 2010, respectively <sup>8</sup>. Consequently, there is a need to  
57 assess how antimicrobial strategies should be modified to minimize the impact of  
58 antimicrobial resistance on patient care.

59

60 As the majority of ESBL-producing *E. coli* (ESBL-EC) remains susceptible to the  
61 carbapenems, this class of antibiotics is widely accepted as the agents of choice in treating  
62 patients with serious or bacteremic infections caused by such organisms. However, whether  
63 or not other *in vitro* active agents such as amoxicillin-clavulanate, piperacillin-tazobactam  
64 and fluoroquinolones can be administered for treating bacteremia remains controversial <sup>9,10</sup>.  
65 Furthermore, there is debate on whether the third generation cephalosporins are effective  
66 against low-MIC ESBL-producers <sup>11</sup>. While some studies have demonstrated that  
67 inappropriate initial therapy is associated with excess mortality in infections caused by  
68 ESBL-EC <sup>12,13</sup>, others have not found such an association, especially in low risk bacteremia  
69 and when therapy involves agents with some *in vitro* activity against the infecting ESBL-

70 producers<sup>14</sup>. Therefore, the present study was conducted to describe the impact of ESBL  
71 production and inappropriate empirical therapy on bacteremia caused by ESBL-producing *E.*  
72 *coli*.

73

74 **Methods**

75 *Setting and patient description*

76 This study was performed in Queen Mary Hospital, which is a university-affiliated  
77 teaching hospital consisting of 1650 beds. As a general recommendation in our hospital,  
78 cefuroxime or amoxicillin-clauvanate are given to patients with mild bacterial infections,  
79 while piperacillin-tazobactam or carbapenem are reserved for patients with moderate or  
80 severe infections as empirical treatment <sup>15</sup>. Adult patients aged 18 years or above with  
81 bacteremia due to *E. coli* bacteremia from January 2007 to December 2008 were identified  
82 with the laboratory information system. Each patient was recruited only once. For patients  
83 with more than one episodes of bacteremia, the first episodes were used in the analysis.  
84 Clinical information of patients infected with ESBL-producing strains was retrieved from the  
85 Clinical Management System. Patients were excluded if clinical records were not accessible  
86 for review or antibiotics were not given before death. This study has been approved by the  
87 Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong  
88 West Cluster.

89

90 *Bacterial identification and antimicrobial susceptibility testing*

91 The BACTEC 9240 blood culture system (Becton Dickinson, MD, USA) was used for  
92 processing of blood specimens. Bacterial isolates were identified using the VITEK GNI  
93 system (bioMérieux Vitek Inc., Hazelwood, MO, USA). Antibiotics susceptibility testing was  
94 performed using the Kirby–Bauer disk diffusion method and interpreted according the  
95 Clinical and Laboratory Standards Institute interpretative criteria <sup>16</sup>.

96

97 *Definitions*

98 Healthcare risk factors included hospital onset (first positive blood culture collected  
99 on  $\geq 2$  days after admission), prior hospitalization within 1 year before the positive blood  
100 culture and residency in residential care home for the elderly (RCHE). Community-associated  
101 infection was defined as infection in a patient who did not have any healthcare risk factors,  
102 while hospital-associated infection was infection in those who had any healthcare risk factors.  
103 Charlson comorbidity index was used in measuring comorbidity using ICD-9 coding and  
104 verified by review of records<sup>17</sup>. Empirical antibiotic therapy (ET) was defined as antibiotics  
105 given before the culture result was reported, whereas known pathogen therapy (KPT) was  
106 defined as antibiotics given after culture result was reported. Concordant therapy was defined  
107 by the use of carbapenems, beta-lactam-beta-lactam-inhibitor combinations (BLBLIs) or  
108 fluoroquinolones to which the isolated strain was susceptible. Discordant therapy was defined  
109 by *in-vitro* resistance to the given antibiotics. The use of third-generation cephalosporins was  
110 considered to be discordant irrespective of *in vitro* results<sup>11</sup>.

111

#### 112 *Statistical analysis*

113 Statistical analysis was performed using SPSS software, version 17.0 for Windows  
114 (SPSS).  $\chi^2$  test was used for comparison of categorical variables. Univariate and multivariate  
115 analyses were used to assess factors that affect patient outcome. The following parameters  
116 were included in the multivariate analysis: age, sex, comorbidities, source of infection and ET.  
117 For the calculation of the length of stay, patients in which length of stay cannot be  
118 determined were excluded. A *P*-value of  $<0.05$  was considered to be statistically significant.

119

120

121 **Results**

122           During the 24-month study period, there were a total of 857 adult patients with a  
123 positive blood culture for *E. coli*. Of these, 207 (24.2%) patients had ESBL-EC bacteremia.  
124 Two patients were excluded because the clinical records were not available for review and  
125 one patient was excluded because antimicrobial was not given before death. Therefore, 204  
126 patients were included in this study (Table 1). Overall, 8.3% (17/204) and 91.7% (187/204)  
127 of the patients were classified as having community-associated and hospital-associated  
128 infections respectively. Among the hospital-associated infections, 32.1% (60/187) were  
129 classified as hospital onset, 38.5% (72/187) were RCHE residents and 89.8% (168/187) had  
130 prior hospitalization within 1 year. More than two-thirds of the patients were aged 65 years or  
131 above. At the time of blood culture collection, more than 50% of patients were located in the  
132 medical ward. Urinary tract (43.6%) was the most common source of infection, followed by  
133 the hepatobiliary tract (23.0%).

134

135           Table 2 shows the result of the susceptibility testing. All strains were susceptible to  
136 imipenem. Over 90% of the strains were susceptible to piperacillin-tazobactam or amikacin.

137

138           The use of antibiotics is illustrated in Figure 1. There was no significant difference in  
139 the Charlson comorbidity score between patients with different ET regimens. Patients who  
140 required admission to the intensive care unit were more likely to receive carbapenem than  
141 those who did not (70.0% [14/20] vs 17.9% [33/184],  $p < 0.001$ ). Concordant ET was given to  
142 98 (48%) patients, including 22 patients who were concurrently treated with more than one *in*  
143 *vitro* active antibiotics. Discordant ET was given to 106 (51.9%) patients. The mean duration  
144 of discordant therapy was 2.5 days (standard deviation: 0.9 days). Nineteen patients (9.3%,  
145 including 10 patients on concordant and 9 patients on discordant therapy) died before

146 antibiotic susceptibility results were reported. Out of the 185 patients with KPT, 154 (83.2%)  
147 patients received concordant KPT. Among patients who did not receive carbapenem as ET,  
148 91 (63.6%) received carbapenem as KPT. For the 52 patients who did not receive  
149 carbapenem as KPT, 21 received BLBLIs (11 amoxicillin-clavulanate, 8 piperacillin-  
150 tazobactam, 1 ticarcillin-clavulanate), 19 received cefuroxime, 6 received fluoroquinolones,  
151 and 3 received other antibiotics (2 nitrofurantoin, 1 cotrimoxazole).

152

153 Overall, the median length of stay was 17 days (interquartile range 9-33 days). The  
154 length of stay could not be determined for a patient who had been transferred to another  
155 hospital, and another patient who has not been discharged from the hospital at the time of  
156 writing. Twenty (9.8%) patients required admission to the intensive care unit, in whom 14  
157 (70%) received carbapenem ET. Forty-four (21.6%) patients died within 30 days of blood  
158 culture collection. Patients without healthcare risk factors had a significantly lower 30-day  
159 mortality rate than those with healthcare risk factors (0% [0/17] vs 23.5% [44/187],  $p=0.024$ ).  
160 There was no statistically significant differences in the 30-day mortality rate between  
161 different ET regimens: concordant vs discordant (23.5% [23/98] vs 19.8% [21/106],  
162  $p=0.526$ ); carbapenem (Group 1) vs non-carbapenem (Group 2) (29.8% [14/47] vs 19.1%  
163 [30/157],  $p=0.118$ ) (Figure 1); BLBLIs vs non-BLBLIs (20.3% [15/74] vs 22.3% [29/130],  
164  $p=0.734$ ); cephalosporin vs non-cephalosporin (18.6% [14/71] vs 22.6% [30/133],  $p=0.639$ );  
165 fluoroquinolone (group 2b) vs non-fluoroquinolone (8.3% [1/12] vs 22.4% [43/192],  
166  $p=0.251$ ). When susceptibility results for the BLBLIs were interpreted as found, the 30 day  
167 mortality rates for patients who received concordant and discordant BLBLI were 19.1%  
168 (9/47) and 22.2% (6/27), respectively ( $p=0.752$ ). When all BLBLIs were considered to be  
169 discordant irrespective of the in vitro result, the mortality rate for concordant and discordant  
170 ET became 27.5% (14/51) and 19.6% (30/153), respectively ( $p=0.238$ ). There was no



171 statistically significant difference in the length of stay between different ET regimens.  
172 Discordant ET was not associated with higher 30-day mortality or longer length of stay in the  
173 multivariate analysis. Among patients who did not receive carbapenem as ET (group 2), the  
174 30-day mortality rates were not significantly different between patients who received  
175 carbapenem as KPT and those who did not (11.0% [10/91] vs 11.5% [6/52],  $p=1.000$ );  
176 between patients receiving BLBLIs and non-BLBLIs (14.3% [3/21] vs 10.7% [13/122],  
177  $p=0.626$ ); and between patients who received cephalosporins and those who received other  
178 antibiotics (15.8% [3/19] vs 10.5% [13/124],  $p=0.494$ ). Taken together, there was no clear  
179 association between the choice of antimicrobial and outcome.

180

181

182 **Discussion**

183 Our study showed that a high proportion of patients with ESBL-EC bacteremia  
184 received initial therapy which was considered to be inappropriate because many of them  
185 involved agents with little *in-vitro* activity or uncertain efficacy against the infecting  
186 organisms. In most patients, such “inappropriate” (i.e. discordant) therapy lasted two to three  
187 days. Our findings showed that this had little effect on patient mortality and the length of stay  
188 in hospital. In addition to the relatively short duration of inappropriate therapy, there were  
189 other possible explanations for our findings. Firstly, the “inappropriate” antibiotics might  
190 have some activity *in vivo*. Cephalosporins have been associated with treatment failure, but  
191 they might be effective for infections caused by organisms with low-MIC ESBL-producers<sup>18</sup>.  
192 BLBLIs, particularly piperacillin-tazobactam, have been shown to be non-inferior to  
193 carbapenems in a recent post-hoc analysis of 6 prospective cohorts of ESBL-EC bacteremia<sup>9</sup>.  
194 Secondly, the site of infection is an important determinant of patients’ outcome. Almost half  
195 of the patients in our cohort had urinary tract infection. Bacteremia due to urinary tract  
196 infection has been considered to be of low risk<sup>19</sup>. The second most common source was the  
197 hepatobiliary tract. Many of our patients had cholangitis which required biliary drainage. In  
198 these situations, early drainage is more important than antibiotics in determining patients’  
199 outcome<sup>20, 21</sup>. Thirdly, the severity of disease can affect outcome. In general, patients with  
200 severe disease are more likely to receive antibiotics with wider spectrum or combinations of  
201 antibiotics, thereby more likely to be *in vitro* active. In our cohort, 70% of patients in  
202 intensive care unit received carbapenem as ET. Finally, the type of ESBL enzyme may affect  
203 outcome. In the present study, CTX-M-9 group enzymes predominated among the ESBL-EC  
204 isolates which are often susceptible to BLBLI and ceftazidime *in vitro*<sup>3</sup>. By comparison,  
205 ESBL-EC producers in the UK were often found to have both CTX-M-15 and OXA-type  
206 enzymes and were resistant to BLBLIs and ceftazidime<sup>22</sup>.

207

208           The prevalence of ESBL-EC strains among *E. coli* bacteremia (24.2%) in our study  
209 was higher than those reported in other studies conducted during the same period<sup>22,23</sup>. In our  
210 previous study, the incidence density of ESBL-EC bacteremia has increased from 8.6 per  
211 100,000 patient-days in year 2000-2005 to 16.9 per 100,000 patient-days in year 2006-2010<sup>8</sup>.  
212 Previously identified risk factors for ESBL-producers included healthcare associations such  
213 as RCHE residency and hospital onset bacteremia, recent use of antibiotics, comorbidities,  
214 presence of gastrostomy tubes or urinary catheters, and urinary tract infections<sup>24-26</sup>. The  
215 baseline characteristics of our study cohort concur with these known risk factors. We have  
216 also found that 8.3% of patients with ESBL-EC bacteremia were community associated. The  
217 prevalence of community-acquired infections has been increasing, and one study in India  
218 showed that up to 46% of *Enterobacteriaceae* strains from outpatients were ESBL-producer  
219<sup>27</sup>. The increase in community-acquired ESBL-EC infection parallels with the increasing  
220 carriage of ESBL-EC in the community. In Hong Kong, stool carriage of ESBL-producing  
221 organisms was found in 43.5% in the children who were admitted for respiratory tract  
222 infection and their household members<sup>28</sup>. The rate of ESBL-producers in urine collected  
223 from women in the community now exceeds >5%<sup>6,29</sup>. It has been postulated that an increase  
224 in ESBL-EC in the community is due to the high rate of antibiotic resistance in food animals  
225<sup>30</sup>. In our locality, there is a high fecal carriage rate of ESBL-EC in food animals, exceeding  
226 60% in live pigs and chickens<sup>5</sup>. Since ESBL-EC bacteremia results in high mortality as  
227 shown in the current study (21.6%), controlling the incidence and spread of ESBL-EC in the  
228 community would be very important.

229

230           Over 90% of our isolates were susceptible to piperacillin-tazobactam. The  
231 piperacillin-tazobactam susceptible rate in our cohort was higher than that reported in other

232 studies<sup>31, 32</sup>. To a certain extent, such variations in susceptibility reflect differences in the  
233 major clonal types and ESBL enzymes. In Hong Kong, the CTX-M-9 group and CTX-M-14  
234 allele were the predominant ESBL type<sup>3</sup>. Among the patients in the present study, the  
235 sequence type (ST) was determined for the isolates from 116 randomly selected patients,  
236 among which 30 patients (25.9%) had infection by *E. coli* belonging to ST131. The  
237 remaining isolates included 5 ST69, 3 ST12, 3 ST68 and 75 singletons<sup>3</sup>. In our study, we  
238 have also found a low susceptibility rate to levofloxacin. This is of particular concern, as  
239 patients with contraindications to receiving beta-lactams, such as allergic reactions, are often  
240 given fluoroquinolone as ET. Our results stressed the importance of adding amikacin as ET if  
241 patients are suffering from severe infections.

242

243         There are several limitations in this study. Firstly, retrospective analysis of factors  
244 affecting patients' outcome is often affected by confounding factors. Previous studies have  
245 used case-control studies to adjust for confounding factors, but adjustment for disease  
246 severity is difficult. Secondly, as the attending clinicians adjusted the antimicrobial regimen  
247 according to their clinical judgment, a patient could have received several classes of  
248 antibiotics as empirical therapy. Therefore, a prospective randomized controlled study would  
249 be needed to assess the effect of different therapies. Thirdly, we were not able to analyze the  
250 effect of third generation cephalosporin as only 4% of the patients received them as ET.

251

252         The result of this study highlights the therapeutic challenges faced by clinicians in  
253 areas where ESBL is highly prevalent. We submit that prudent choice of antimicrobial agents  
254 according to patient characteristics and disease severity should continue to be practiced<sup>15</sup>.  
255 Rapid determination of the identity and antibiotics susceptibility of the organisms is crucial  
256 for early optimization of antibiotics, especially for patients with severe infections. Currently

257 available methods for rapid detection of resistant organisms include direct antibiotics  
258 susceptibility testing <sup>33</sup>, molecular techniques detecting resistance genes <sup>34</sup> and matrix-  
259 assisted laser desorption ionization-time of flight mass spectrometry detecting  $\beta$ -lactamases <sup>35</sup>.  
260 Optimization of the treatment strategy of infections caused by ESBL-producers is urgently  
261 needed, since the over-reliance on carbapenem will promote the emergence of carbapenem-  
262 resistant organisms <sup>36</sup>.

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265

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270 extraction.

271

272 **Conflict of interest**

273 No competing interest declared.

274

275 **Ethical Approval**

276 This study has been approved by the Institutional Review Board of the University of Hong  
277 Kong/ Hospital Authority Hong Kong West Cluster. (UW 10-078)

278

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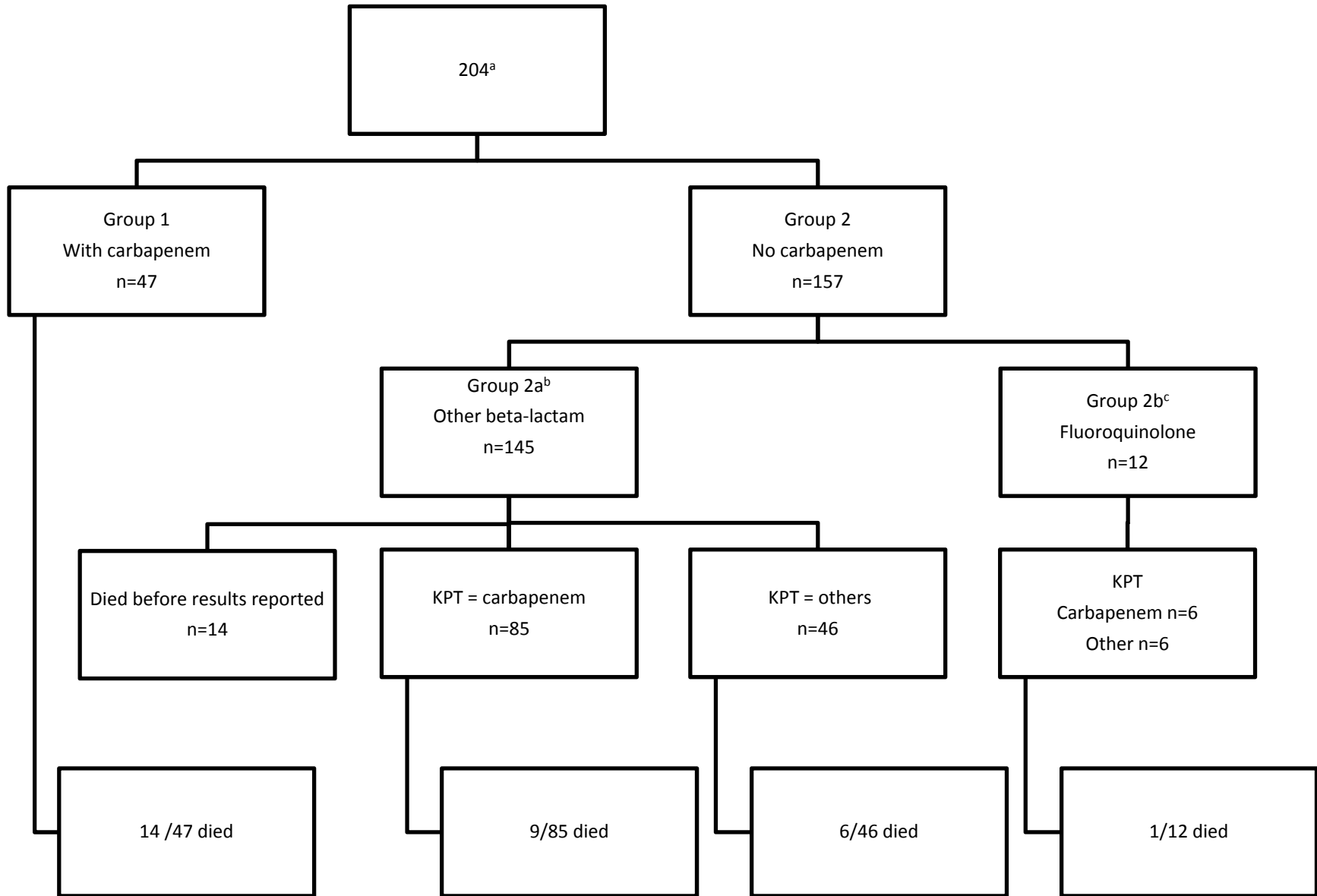
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421 **Figure legend**

422 Figure 1. Antimicrobial therapy and outcome in the 204 patients with ESBL-producing

423 *Escherichia coli* bacteremia.



<sup>a</sup> Twenty-three patients had polymicrobial bacteremia, in which *Klebsiella pneumoniae* was the most common co-isolate (43.5%, 10/23). Other organisms include *Bacillus* species (4 patients), *Proteus mirabilis* (3 patients), *Pseudomonas aeruginosa* (2 patients), *Enterococcus faecalis* (2 patients), *Bacteroides/* non-pigmented *Prevotella* group (1 patient), *Clostridium* species (1 patient), *Fusobacterium* species (1 patient), *Peptostreptococcus* species (1 patient), and Coagulase negative *Staphylococcus* (1 patient).

<sup>b</sup> BLBLI: 74 patients; first or second generation cephalosporin: 63 patients; third generation cephalosporin (cefotaxime, ceftriaxone, cefoperazone-sulbactam): 8 patients. For patients with BLBLI, 47 (63.5%) were concordant and 27 (36.5%) were discordant

<sup>c</sup> 4 were concordant; 8 were discordant