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

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Keyword: ESBL, *Escherichia coli*, resistance, community, cephalosporin

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Abstract

Objectives

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

Methods

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

Results

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

Conclusions

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

Introduction

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

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

70 producers [14]. 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

Methods

Setting and patient description

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

Bacterial identification and antimicrobial susceptibility testing

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

Definitions

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

Statistical analysis

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

Results

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

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

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

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

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

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

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

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

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

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

The result of this study highlights the therapeutic challenges faced by clinicians in areas where ESBL is highly prevalent. We submit that prudent choice of antimicrobial agents according to patient characteristics and disease severity should continue to be practiced [15]. Rapid determination of the identity and antibiotics susceptibility of the organisms is crucial 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 [33], molecular techniques detecting resistance genes [34] and matrix-
259 assisted laser desorption ionization-time of flight mass spectrometry detecting β-lactamases [35].
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 [36].
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Conflict of interest

No competing interest declared.

Ethical Approval

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

279 **Reference**

280 1. Abhilash KP, Veeraraghavan B, Abraham OC. Epidemiology and outcome of
281 bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing
282 Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India.
283 J Assoc Physicians India 2010;58 Suppl:13-7.
284 2. Cheng VC, Tai JW, Chan WM, Lau EH, Chan JF, To KK, Li IW, Ho PL, Yuen KY.
285 Sequential introduction of single room isolation and hand hygiene campaign in the
286 control of methicillin-resistant Staphylococcus aureus in intensive care unit. BMC
287 Infect Dis 2010;10:263.
288 3. Ho PL, Yeung MK, Lo WU, Tse H, Li Z, Lai EL, Chow KH, To KK, Yam WC.
289 Predominance of pHK01-like incompatibility group FII plasmids encoding CTX-M-
290 14 among extended-spectrum beta-lactamase-producing Escherichia coli in Hong
291 Kong, 1996-2008. Diagn Microbiol Infect Dis 2012; 73:182-6
292 4. Kang CI, Wi YM, Lee MY, Ko KS, Chung DR, Peck KR, Lee NY, Song JH.
293 Epidemiology and risk factors of community onset infections caused by extended-
294 spectrum beta-lactamase-producing Escherichia coli strains. J Clin Microbiol
295 2012;50:312-7.
296 5. Ho PL, Chow KH, Lai EL, Lo WU, Yeung MK, Chan J, Chan PY, Yuen KY.
297 Extensive dissemination of CTX-M-producing Escherichia coli with multidrug
298 resistance to 'critically important' antibiotics among food animals in Hong Kong,
299 2008-10. J Antimicrob Chemother 2011;66:765-8.
300 6. Ho PL, Wong RC, Yip KS, Loke SL, Leung MS, Mak GC, Chow FK, Tsang KW,
301 Que TL, group Cs. Antimicrobial resistance in Escherichia coli outpatient urinary
302 isolates from women: emerging multidrug resistance phenotypes. Diagn Microbiol
303 Infect Dis 2007;59:439-45.

7. Ho PL, Poon WWN, Loke SL, Leung MST, Chow KH, Wong RCW, Yip KS, Lai EL, Tsang KWT. Community emergence of CTX-M type extended-spectrum beta-lactamases among urinary Escherichia coli from women. J Antimicrob Chemoth 2007;60:140-4.

8. Ho PL, Chow KH, Lai EL, Lau EHY, Cheng VCC. Extended-spectrum-beta-lactamase-positive Escherichia coli mainly adds to, rather than replaces, extended-spectrum-beta-lactamase-negative E-coli in causing bacteraemia in Hong Kong, 2000-10. J Antimicrob Chemoth 2012;67:778-80.

9. Rodriguez-Bano J, Navarro MD, Retamar P, Picon E, Pascual A, Extended-Spectrum Beta-Lactamases-Red Espanola de Investigacion en Patologia Infecciosa/Grupo de Estudio de Infeccion Hospitalaria G. beta-Lactam/beta-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: a post hoc analysis of prospective cohorts. Clin Infect Dis 2012;54:167-74.

10. Falagas, M. E. and D. E. Karageorgopoulos. Extended-spectrum beta-lactamase-producing organisms. J Hosp Infect 2009;73: 345-54.

11. Livermore DM, Andrews JM, Hawkey PM, Ho PL, Keness Y, Doi Y, Paterson D, Woodford N. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? J Antimicrob Chemother 2012; 67:1569-77

12. Ortega M, Marco F, Soriano A, Almela M, Martinez JA, Munoz A, Mensa J. Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. J Antimicrob Chemother 2009;63:568-74.

13. Tumbarello M, Sanguinetti M, Montuori E, Trecarichi EM, Posteraro B, Fiori B, Citton R, D'Inzeo T, Fadda G, Cauda R, Spanu T. Predictors of mortality in patients

with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae: Importance of inadequate initial antimicrobial treatment. Antimicrob Agents Chemother 2007;51:1987-94.

14. Rodriguez-Bano J, Picon E, Gijon P, Hernandez JR, Cisneros JM, Pena C, Almela M, Almirante B, Grill F, Colomina J, Molinos S, Oliver A, Fernandez-Mazarrasa C, Navarro G, Coloma A, Lopez-Cerero L, Pascual A. Risk factors and prognosis of nosocomial bloodstream infections caused by extended-spectrum-beta-lactamase-producing Escherichia coli. J Clin Microbiol 2010;48:1726-31.

15. Cheng VCC, To KKW, Li IWS, Tang BSF, Chan JFW, Kwan S, Mak R, Tai J, Ching P, Ho PL, Seto WH. Antimicrobial stewardship program directed at broad-spectrum intravenous antibiotics prescription in a tertiary hospital. Eur J Clin Microbiol 2009;28:1447-56.

16. Clinical and Laboratory Standard Institute. Performance standards for antimicrobial susceptibility testing; Twentieth Informational Supplement. Document M100-S20. Wayne, PA. CLSI; 2010.

17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.

18. Kahlmeter G. Breakpoints for intravenously used cephalosporins in Enterobacteriaceae - EUCAST and CLSI breakpoints. Clin Microbiol Infect 2008;14:169-74.

19. Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, Reller LB. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 1997;24:584-602.

20. Khashab MA, Tariq A, Tariq U, Kim K, Ponor L, Lennon AM, Canto MI, Gurakar A, Yu Q, Dunbar K, Hutfless S, Kalloo AN, Singh VK. Delayed and Unsuccessful Endoscopic Retrograde Cholangiopancreatography are Associated with Worse Outcomes in Patients with Acute Cholangitis. Clin Gastroenterol Hepatol. 2012. doi:10.1016/j.cgh.2012.03.029

21. Melzer M, Toner R, Lacey S, Bettany E, Rait G. Biliary tract infection and bacteraemia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgrad Med J 2007;83:773-6.

22. Webster DP, Young BC, Morton R, Collyer D, Batchelor B, Turton JF, Maharjan S, Livermore DM, Bejon P, Cookson BD, Bowler IC. Impact of a clonal outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in the development and evolution of bloodstream infections by K. pneumoniae and Escherichia coli: an 11 year experience in Oxfordshire, UK. J Antimicrob Chemother 2011;66: 2126-2135.

23. Peirano G, van der Bij AK, Gregson DB, Pitout JD. Molecular epidemiology over an 11-year period (2000 to 2010) of extended-spectrum beta-lactamase-producing Escherichia coli causing bacteremia in a centralized Canadian region. J Clin Microbiol 2012;50:294-9.

24. Doernberg SB, Winston LG. Risk factors for acquisition of extended-spectrum beta-lactamase-producing Escherichia coli in an urban county hospital. Am J Infect Control 2012;40:123-7.

25. Ho PL, Chan WM, Tsang KW, Wong SS, Young K. Bacteremia caused by Escherichia coli producing extended-spectrum beta-lactamase: a case-control study of risk factors and outcomes. Scand J Infect Dis 2002;34:567-73.

377 26. Wu UI, Yang CS, Chen WC, Chen YC, Chang SC. Risk factors for bloodstream
378 infections due to extended-spectrum beta-lactamase-producing Escherichia coli. J
379 Microbiol Immunol Infect 2010;43:310-6.
380 27. Sankar S, Narayanan H, Kuppanan S, Nandagopal B. Frequency of extended-
381 spectrum beta-lactamase (ESBL)-producing Gram-negative bacilli in a 200-bed multi-
382 specialty hospital in Vellore district, Tamil Nadu, India. Infection 2012. doi:
383 10.1007/s15010-012-0261-6
384 28. Lo WU, Ho PL, Chow KH, Lai EL, Yeung F, Chiu SS. Fecal carriage of CTXM type
385 extended-spectrum beta-lactamase-producing organisms by children and their
386 household contacts. J Infect 2010;60:286-92.
387 29. Ho PL, Yip KS, Chow KH, Lo JY, Que TL, Yuen KY. Antimicrobial resistance
388 among uropathogens that cause acute uncomplicated cystitis in women in Hong
389 Kong: a prospective multicenter study in 2006 to 2008. Diagn Microbiol Infect Dis
390 2010;66:87-93.
391 30. Carattoli A. Animal reservoirs for extended spectrum beta-lactamase producers. Clin
392 Microbiol Infect 2008;14 Suppl 1:117-23.
393 31. Lowe CF, McGeer A, Muller MP, Katz K, for the Toronto EWG. Decreased
394 susceptibility to non-carbapenem antimicrobials in extended-spectrum beta-lactamase
395 producing Escherichia coli and Klebsiella pneumoniae in Toronto, Canada.
396 Antimicrob Agents Chemother 2012. doi:10.1128/AAC.00260-12
397 32. Hounsom L, Grayson K, Melzer M. Mortality and associated risk factors in
398 consecutive patients admitted to a UK NHS trust with community acquired
399 bacteraemia. Postgrad Med J 2011;87:757-62.
400 33. Cuellar-Rodriguez JM, Ponce-De-Leon A, Quiroz-Mejia R, Galindo-Fraga A, Rolon-
401 Montes-de-Oca AL, Hernandez-Duran M, Ruiz-Palacios GM, Sifuentes-Osornio J.

Rapid detection of ESBL-producing gram-negative bacteria isolated from blood: a reasonable and reliable tool for middle and low resource countries. Rev Invest Clin 2009;61:306-12.

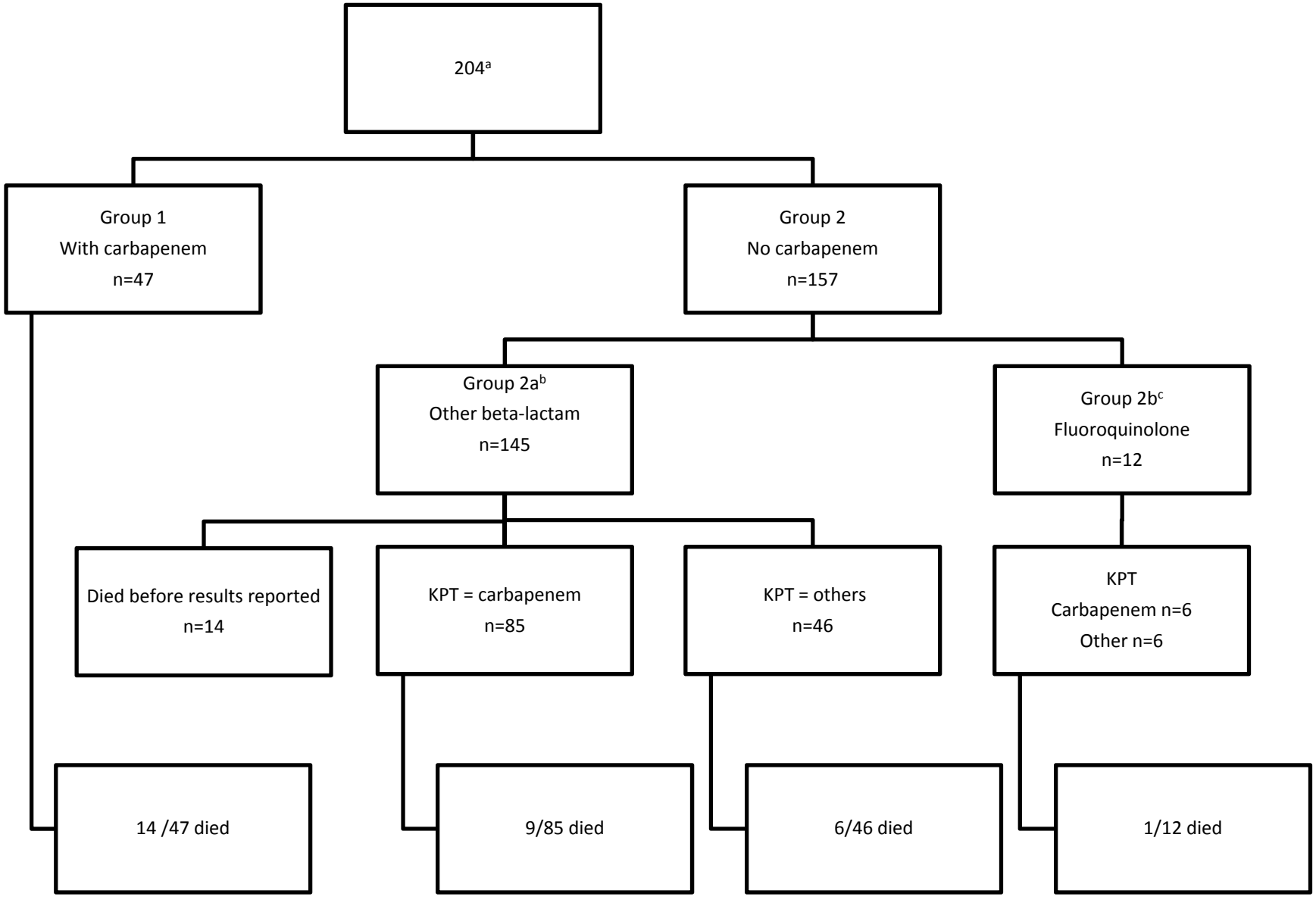
34. Fujita S, Yosizaki K, Ogushi T, Uechi K, Takemori Y, Senda Y. Rapid Identification of Gram-Negative Bacteria with and without CTX-M Extended-Spectrum beta-Lactamase from Positive Blood Culture Bottles by PCR Followed by Microchip Gel Electrophoresis. J Clin Microbiol 2011;49:1483-8.

35. Sparbier K, Schubert S, Weller U, Boogen C, Kostrzewa M. Matrix-assisted laser desorption ionization-time of flight mass spectrometry-based functional assay for rapid detection of resistance against beta-lactam antibiotics. J Clin Microbiol 2012;50:927-37.

36. Ho PL, Lo WU, Yeung MK, Lin CH, Chow KH, Ang I, Tong AH, Bao JY, Lok S, Lo JY. Complete sequencing of pNDM-HK encoding NDM-1 carbapenemase from a multidrug-resistant Escherichia coli strain isolated in Hong Kong. PLoS One 2011;6:e17989.

Figure legend

Figure 1. Antimicrobial therapy and outcome in the 204 patients with ESBL-producing *Escherichia coli* bacteremia.


204[a]
Group 1
With carbapenem
n=47
Group 2
No carbapenem
n=157
Group 2a[b]
Other beta-lactam
n=145
Group 2b[c]
Fluoroquinolone
n=12
Died before results reported
n=14
KPT = carbapenem
n=85
KPT = others
n=46
KPT
Carbapenem n=6
Other n=6
14 /47 died
9/85 died
6/46 died
1/12 died

[a] 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).

[b] 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

[c] 4 were concordant; 8 were discordant