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Microbiologic and Clinical Comparison of Patients Harboring *Escherichia coli* Blood Isolates with and without Extended-Spectrum *β*-Lactamases

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ABSTRACT

The clinical and microbiologic characteristics of 34 patients with extended-spectrum *β*-lactamase (ESBL) positive *E. coli* isolated from blood were compared to 66 bacteremic patients with ESBL negative *E. coli*, from January 2007 through December 2009. Of the 21 ESBL positive isolates available for PCR analysis, 13 were positive for CTX-M, 8 for TEM, 4 for SHV *β*-lactamases, with 6 possessing multiple enzymes. Twenty of 34 (59%) ESBL-positive and 41 of 66 (62%) ESBL-negative blood isolates were considered community-associated. All but one isolate in both groups had MICs of ≤1.0 μg/ml to meropenem. However, when compared to ESBL-negative isolates, ESBL-positive isolates were more frequently resistant to levofloxacin, trimethoprim/sulfamethoxazole and had higher MICs to gentamicin, tobramycin and piperacillin/tazobactam. The use of intravenous and urinary catheters was strongly associated with the isolation of *E. coli* bloodstream isolates in both groups of patients. Although hospital stay was similar in both groups, appropriate therapy was given in 87% of patients with ESBL positive vs. 98% of patients with ESBL negative isolates and mortality was greater for patients with ESBL positive isolates (26% vs. 17%). Since a large proportion of *E. coli* blood isolates were ESBL-positive and community-associated, carbapenems should be considered as initial empiric therapy for such infections in our locale.

Keywords: *Escherichia coli* Bacteremia; Extended-Spectrum *β*-Lactamases

1. Introduction

Escherichia coli harboring extended spectrum *β*-lactamases (ESBLs) has emerged as a global threat [1,2]. Organisms with these enzymes have been isolated from a multitude of sources including patients associated with healthcare settings, the community, foods, companion and non-companion animals [1]. While *E. coli* bloodstream infections were traditionally treated with late generation cephalosporins, increased identification of ESBL positive isolates has led to therapeutic dilemmas since such isolates often contain plasmid carrying genes which confer resistance to additional classes of antimicrobials [1,3]. *E. coli* possessing CTX-M *β*-lactamases are a relatively new type of ESBL which we and others have recently identified among hospitalized patients, residents of long-term care facilities, pediatric patients, and patients from the community, predominantly from urinary tract isolates [1,4-6]. This retrospective investigation was conducted to determine if such isolates are present in patients with bacteremia in our setting. By comparing ESBL-positive and -negative *E. coli* bloodstream isolates, we sought to classify ESBLs and identify characteristics such as community association, antibiotic susceptibility, factors for acquisition, antibacterial therapy and outcomes of patients in both groups.

2. Materials and Methods

2.1. Study Population

From January 1, 2007 through December 31, 2009, *E. coli* blood isolates were identified and obtained from the clinical microbiology laboratory at New York Hospital Queens (NYHQ). ESBL-positive *E. coli* were identified using BD Phoenix™ NMIC/ID-123 panels (Becton, Dickinson and Company, Sparks, MD). Comparison cohort of patients with ESBL-negative bloodstream isolates was matched by age and gender.

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2.2. Clinical Data Collection

This investigation was conducted as a quality improvement project and did not require IRB approval. Patients' charts were reviewed for demographic information including age, gender, previous exposure to healthcare settings, prior hospital admission by history, antimicrobial treatment within the past year and pre-existing comorbidities. Bloodstream infections were defined as community-associated when isolated from non-hospitalized patients receiving no antibiotics and not having any healthcare contact within the previous 30 days. Risk factors for acquisition included presence of urinary catheters, intravenous catheters, feeding tubes, endotracheal tubes, previous antimicrobial use, presence of *E. coli* in urine, nursing home residency and previous hospital admission within the last year. P-values were calculated using Excel Microsoft 2010 software. Antimicrobial treatment including antimicrobial therapy, dosage, length of therapy and in-hospital mortality was also collected from medical records. Appropriate therapy was defined as treatment with an antibacterial to which the organism was susceptible.

2.3. Microbiology Procedures

Minimim inhibitory concentrations (MICs) for ceftriaxone, ceftazidime, cefepime, piperacillin/tazobactam, trimethoprim/sulfamethoxazole, levofloxacin, gentamicin, amikacin, tobramycin, and meropenem were obtained and recorded for 31 ESBL positive and 54 ESBL negative *E. coli* isolates from antibiograms generated in the clinical microbiology laboratory using the using BD Phoenix™ NMIC/ID-123 panels (Becton, Dickinson and Company, Sparks, MD). Polymerase chain reaction (PCR) analysis was performed using primers for the CTX-M-1 group and CTX-M-15, as previously described [4]. Primers for TEM and SHV enzymes were used as described in [7].

3. Results

34 ESBL-positive and 66 ESBL-negative *E. coli* blood, single patient isolates, were identified from hospitalized patients during the study period. Of 34 ESBL-positive isolates, 20 (59%) and 41 (62%) of ESBL-negative isolates were considered as community-associated. The remaining patients in both groups were from long-term care facilities or coming from home with additional risk factors for acquisition. Of the 21 ESBL positive isolates available for PCR analysis, 13 were positive for CTX-M, 8 for TEM and 4 for SHV *β*-lactamases. 10 of the CTX-M positive isolates were identified as CTX-M-15. Six isolates possessed two or more classes of *β*-lactamases and 4 isolates were PCR negative for TEM, SHV and CTX-M enzymes. The majority of ESBL-positive isolates was also resistant to levofloxacin, trimethoprim/sulfamethoxazole and possessed higher MICs to gentamicin, tobramycin and piperacillin/tazobactam when compared to ESBL-negative isolates. All but one ESBL-positive isolate had MICs ≤1.0 μg/ml to meropenem (**Table 1**). A similar percentage of ESBL-positive and ESBL-negative *E. coli* isolates in patients were over the age of 65 (mean ages = 70.9 and 71.5 years, respectively), were female, and resided in nursing homes (**Table 2**). These findings were in accord with those of other studies [8-11]. Patients with venous and urinary catheters were risk factors associated with isolation of *E. coli* from the

Table 1. Antimicrobial susceptibility of *E. coli* isolates from blood.

	ESBL Positive (n = 31)			ESBL Negative (n = 54)		
Antimicrobial Agent	**MIC_{50}**	**MIC_{90}**	**MIC RANGE**	**MIC_{50}**	**MIC_{90}**	**MIC RANGE**
Amikacin	≤8	≤8	≤8 -16	≤8	≤8	≤8
Cefepime	8	>16	≤1 - >16	≤1	≤1	≤1
Ceftazidime	16	>16	1 - >16	≤0.5	≤0.5	≤0.5
Ceftriaxone	>32	>32	≤2 - >32	≤2	≤2	≤2 - 32
Gentamicin	≤2	>8	≤2 - >8	≤2	>8	≤2 - >8
Levofloxacin	>4	>4	≤1 - >4	≤1	>4	≤1 - >4
Meropenem	≤1	≤1	≤1 - 2	≤1	≤1	≤1
Piperacillin/tazobactam	8/4	>64/4	≤2/4 - >64/4	≤2/4	≤4/4	≤2/4 - 64/4
Tobramycin	8	>8	≤2 - >8	≤2	>8	≤2 - >8
Trimethoprim/sulfamethoxazole	>2/38	>2/38	≤0.5/9.5 - 2/38	≤0.5/9.5	>2/38	≤0.5/9.5 - >2/38

Table 2. Comparison of risk factors for patients with ESBL-positive and ESBL-negative *E. coli*.

Risk Factor	ESBL positive (n = 34)	ESBL negative (n = 66)	p-value
Age >65	21 (62)	45 (68)	0.41
Female	15 (44)	28 (42)	0.87
Nursing home residency	9 (26)	20 (30)	0.69
Previous hospital admission (<1 year)	15 (44)	23 (35)	0.37
Previous antimicrobial use (<1 year)	10 (29)	18 (31)*	0.91
Urinary catheter use	29 (85)	42 (69)**	0.08
Venous catheter use	24 (71)	26 (40)	0.001
Feeding tube use	11 (32)	17 (26)	0.32
Endotracheal tube use	12 (35)	16 (24)	0.24
E. coli presence in urine	16 (47)	39 (59)	0.16
Neutropenia	5 (15)	7 (11)	0.55
Diabetes mellitus	12 (35)	22 (39)***	0.76

*n = 59, **n = 61, ***n = 57.

Table 3. Mortality, length of stay, treatment and outcomes of bacteremic patients with ESBL-positive and ESBL-negative *E. coli* isolates.

Outcome/Treatment	ESBL positive (n = 31 for treatment data)	ESBL negative (n = 55 for treatment data)
In-hospital mortality	9 (26%)	11 (17%)
Mean length of stay (in days)	13.2 (1 to 39)	13.7 (1 to 71)
Median length of stay (in days)	12.5 (1 to 39)	11 (1 to 71)
Treatment with amikacin	5 (16)	2 (4)
Treatment with cefepime	6 (19)	11 (20)
Treatment with ceftazidime	0 (0)	0 (0)
Treatment with ceftriaxone	0 (0)	4 (7)
Treatment with gentamicin	16 (52)	23 (42)
Treatment with levofloxacin	17 (55)	39 (71)
Treatment with meropenem	19 (61)	17 (31)
Treatment with piperacillin/tazobactam	14 (45)	35 (64)
Treatment with tobramycin	0 (0)	0 (0)
Treatment with trimethoprim/sulfamethoxazole	3 (10)	2 (4)
Appropriate therapy	27 (87)	54 (98)

blood for both groups of patients. *E. coli* was also isolated from the urine in 47% and 59% of patients with ESBL-positive and ESBL-negative blood isolates, respectively (**Table 3**). In addition, one ESBL CTX-M-15 positive blood isolate was obtained from an 18 month-old female patient.

Finally, the majority of bacteremic patients with ESBL-positive isolates (61%) in our study, received meropenem alone or in combination with an aminoglycoside as initial therapy. 13% of these patients did not receive appropriate empiric or definitive antibiotics (**Table 3**). In addition, 19% of patients with ESBL positive isolates received cefepime and 45% piperacillin/tazobactam to which the organisms were not susceptible (**Table 3**). Treatment data was not available for three patients with ESBL-positive isolates and eleven patients with ESBL-negative isolates. Despite similar mean and median length of stays in both groups of patients, patients presenting with ESBL-positive *E. coli* had a greater in-hospital mortality rate.

4. Discussion

We and others have previously documented CTX-M enzymes in patients from hospitals, associated long-term care facilities, community-associated, and the pediatric population which were predominantly from urinary tract isolates [4-6,9]. This study records the preponderance of such enzymes, most notably CTX-M-15, in blood isolates from hospitalized and community-onset patients which was similar to the findings of others [9,12]. Our study also revealed that many risk factors associated with patients in whom ESBL-positive and ESBL-negative *E. coli* were isolated from blood were similar, with the exception of venous catheter use which was more common in bacteremic patients with ESBL-positive isolates (**Table 3**). Other investigations have also reported such results [9,10].

An additional and significant finding was the isolation of a CTX-M-15 harboring *E. coli* from the blood in an 18 month-old patient and may be a growing trend in this previously under recognized population [6,13]. We have recently reported an increase in community-associated ESBL-positive urine cultures from pediatric patients in our area and mentioned the possibility of progression to more serious disease [6,14]. The presence of ESBL-positive *E. coli* blood isolates in the pediatric population is of great concern and continued surveillance is warranted [13].

An understanding of the risk factors associated with ESBL-producing *E. coli* bloodstream infections and local antibiotic susceptibility patterns might lead to administration of appropriate initial antibacterial therapy since poorer outcomes might be expected [15]. Although one investigation documented the use of carbapenem and *β*-lactam/*β*-lactamase inhibitor combination therapy to decrease mortality in bloodstream infections with ESBL

producing isolates, other studies have not supported this [9,15,16]. Additional studies have shown that increased mortality was not statistically associated with ESBL production or inappropriate therapy [10,12,16]. Differences in outcome studies can be explained by associated variables including severity of illness of patients, comorbid conditions, time to initiation of antibiotics, and virulence factors associated with the organisms and may be independent of ESBL production [10,12,16,17]. While physicians should avoid broad-spectrum empiric therapy, continued surveillance and administration of carbapenems should be considered as empiric therapy for patients with bloodstream infections due to suspected ESBL positive *E. coli* in our community [18].

REFERENCES

[1] B. A. Rogers, H. E. Sidjabat and D. L. Paterson, "*Escherichia coli* O25b-ST131: A Pandemic, Multiresistant, Community-Associated Strain," *Journal of Antimicrobial Chemotherapy*, Vol. 66, No. 1, 2011, pp. 1-14. doi:10.1093/jac/dkq415

[2] J. D. D. Pitout and K. P. Laupland, "Extended-Spectrum *β*-Lactamase-Producing *Enterobacteriaceae*: An Emerging Public-Health Concern," *Lancet Infectious Diseases*, Vol. 8, No. 1, 2008, pp. 159-166. doi:10.1016/S1473-3099(08)70041-0

[3] J. D. D. Pitout, "Entraintestinal Pathogenic *Escherichia coli*: A Combination of Virulence with Antibiotic Resistance," *Frontiers in Microbiology*, Vol. 3, No. 1, 2012, pp. 1-7. doi:10.3389/fmicb.2012.00009

[4] C. Urban, N. Mariano, P. A. Bradford, M. Tuckman, S. Segal-Maurer, W. Wehbeh, L. Grenner, R. Colon-Urban, B. Johnston, J. R. Johnson and J. J. Rahal, "Identification of CTX-M *β*-Lactamases in *Escherichia coli* From Hospitalized Patients and Residents of Long-Term Care Facilities," *Diagnostic Microbiology and Infectious Disease*, Vol. 66, No. 4, 2010, pp. 402-406. doi:10.1016/j.diagmicrobio.2009.11.012

[5] H. Tiruvury, N. Mariano, L. Grenner, R. Colon-Urban, M. Erritouni, W. Wehbeh, S. Segal-Maurer, J. J. Rahal, B. Johnston, J. R. Johnson and C. Urban, "Identification of CTX-M *β*-Lactamases in *Escherichia coli* From the Community," *Diagnostic Microbiology and Infectious Disease*, Vol. 72, No. 3, 2012, pp. 248-252. doi:10.1016/j.diagmicrobio.2011.11.008

[6] K. L. Woods, J. R. Johnson, S. Padkowsky, N. Mariano, R. Colon-Urban, M. Hassanein, W. Wehbeh, B. D. Johnston, C. Clabots, S. Zahid and C. Urban, "Community Associated Escherichia coli Harboring CTX-M-15 *β*-Lactamases Isolated From Urine Cultures in Pediatric Patients," *Antimicrobial Agents and Chemotherapy*, Vol. 56, No. 4, 2012, pp. 2209-2210. doi:10.1128/AAC.00003-12

[7] H. E. Sidjabat, D. L. Paterson, J. M. Adams-Haduch, L. Ewan, A. W. Pasculle, C. A. Muto, G. B. Tian and Y. Doi, "Molecular Epidemiology of CTX-M-producing *Escherichia coli* at a Tertiary Medical Center in Western Pennsylvania," *Antimicrobial Agents and Chemotherapy*, Vol. 53, No. 11, 2009, pp. 4733-4739. doi:10.1128/AAC.00533-09

[8] K. B. Laupland, D. B. Gregson, D. L. Church, T. Ross and J. D. D. Pitout, "Incidence, Risk Factors and Outcomes of *Escherichia coli* Bloodsteam Infections in a Large Canadian Region," *Clinical Microbiology and Infection* Vol. 14, No. 11, 2008, pp. 1041-1047. doi:10.1111/j.1469-0691.2008.02089.x

[9] J. Rodriguez-Bano, E. Picon, J. R. Hernandez, M. Ruiz, C. Pena, M. Almela, B. Almirante, F. Grill, J. Golomina, A. Oliver, J. P. Horcajada, G. Navarro, A. Coloma and A. Pascaul, "Community-Onset Bacteremia Due to Extended-Spectrum *β*-Lactamase-Producing *Escherichia coli*: Risk Factors and Prognosis," *Clinical Infectious Diseases*, Vol. 50, No. 1, 2010, pp. 40-48. doi:10.1086/649537

[10] S. H. Park, S-M Choi, D-G. Lee, J. Kim, J-H. Choi, S-H Kim, J.-C. Kwon and J.-H. Yoo, "Emergence of Extended-Spectrum *β*-Lactamase-Producing *Escherichia coli* as a Cause of Community-Onset Bacteremia in South Korea: Risk Factors and Clinical Outcomes," *Microbial Drug Resistance*, Vol. 17, No. 4, 2011, pp. 537-544. doi:10.1089/mdr.2011.0072

[11] D. Marchaim, T. Gottesman, O. Schwartz, M. Korem, Y. Maor, G. Rahav, R. Karplus, T. Lazarovitch, E. Braun, H. Sprecher, T. Lachish, Y. Wiener-Well, D. Alon, M. Chowers, P. Ciobotaro, R. Bardenstein, A. Paz, I. Potas-man, M. Giladi, V. Schechner, M. J. Schwaber, S. Klarfeld-Lidji and Y. Carmeli, "National Multicenter Study of Predictors and Outcomes of Bacteremia upon Hospital Admission Caused by *Enterobacteriaceae* Producing Extended-Spectrum *β*-Lactamases," *Antimicrobial Agents and Chemotherapy*, Vol. 54, No. 12, 2010, pp. 5099-5104. doi:10.1128/AAC.00565-10

[12] V. P. Chaubey, J. D. D. Pitout, B. Dalton, T. Ross, D. L. Church, D. B. Gregson and K. B. Laupland, "Clinical Outcome of Empiric Antimicrobial Therapy of Bacteremia Due to Extended-Spectrum Beta-Lactamase Producing *Escherichia coli* and *Klebsiella pneumoniae*," *BMC Research Notes*, Vol. 3, 2010, pp. 116-122. doi:10.1186/1756-0500-3-116

[13] L. Chandramohan and P. A. Revell, "Prevalence and Molecular Characterization of Extended-Spectrum-*β*-Lactamase-Producing Enterobacteriaceae in a Pediatric Patient Population," *Antimicrobial Agents and Chemotherapy*, Vol. 56, No. 9, 2012, pp. 4765-4770. doi:10.1128/AAC.00666-12

[14] S. Boyer-Mariotte, P. Duboc, S. Bonacorsi, J. F. Lemeland, E. Bingen and D. Pinquier, "CTX-M-15-Producing *Escherichia coli* in Fatal Neonatal Meningitis: Failure of Empirical Chemotherapy," *Journal of Antimicrobial Chemotherapy*, Vol. 62, No. 6, 2008, pp. 1472-1474. doi:10.1093/jac/dkn362

[15] C. Lee, N. Lee, J. Yan, H. Lee, N. Ko, C. Chang, C. Wu, P. Chen, L. Wang and W. Ko, "Extended-Spectrum *β*-Lactamase-Producing Phenotype Signifies a Poor Prognosis for Patients with Cefpodoxime-Resistant *Escherichia coli* or *Klebsiella pneumoniae* Bacteremia," *Journal of Microbiology Immunology and Infection*, Vol. 42,

No. 4, 2009, pp. 3030-3039.

[16] K. A. Thom, M. L. Schweizer, R. B. Osih, J. C. McGregor, J. P. Furuno, E. N. Perencevich and A. D. Harris, "Impact of Empiric Antimicrobial Therapy on Outcomes in Patients with *Escherichia coli* and *Klebsiella pneumoniae* Bacteremia: A Cohort Study," *BMC Infectious Diseases*, Vol. 8, 2008, pp.116-125. doi:10.1186/1471-2334-8-116

[17] J. D. D. Pitout, "Extraintestinal Pathogenic *Escherichia coli*: A Combination of Virulence with Antibiotic Resistance," *Frontiers in Microbiology*, Vol. 3, 2012, pp. 1-7. doi:10.3389/fmicb.2012.00009

[18] Y. Doi, Y.S. Park, J. I. Rivera, J. M. Adams-Haduch, A. Hingwe, E. M. Sordillo, J. S. Lewis, W. J. Howard, L. E. Johnson, B. Polsky, J. H. Jorgensen, S. R. Richter, K. A. Shutt and D. L. Paterson, "Community-Associated Extended-Spectrum-*β*-Lactamase(ESBL)-Producing *Escherichia coli* Infection in the United States," *Clinical Infectious Diseases*, Vol. 56, No. 5, 2013, pp. 641-648. doi:10.1093/cid/cis942

