Published in final edited form as:

Am J Infect Control. 2009 August ; 37(6): 435–441. doi:10.1016/j.ajic.2008.09.019.

Extended-Spectrum β -Lactamase-Producing Pathogens in a Children's Hospital: A Five-Year Experience

Anne J. Blaschke, MD, PhD¹, Kent Korgenski, MT², Judy A. Daly, PhD^{2,3}, Bonnie LaFleur, PhD¹, Andrew T. Pavia, MD¹, and Carrie L. Byington, MD¹

¹ University of Utah, Department of Pediatrics, Salt Lake City, UT, USA

² Primary Children's Medical Center Microbiology Laboratory, Salt Lake City, UT, USA

³ University of Utah, Department of Pathology, Salt Lake City, UT, USA

Abstract

Background—Pediatric infection with bacteria producing extended-spectrum β -lactamases (ESBLs) has not been well described. We sought to determine the proportion of isolates producing ESBLs and the incidence of infection or colonization with these organisms in our tertiary care pediatric facility over 5 years. In addition, we sought to evaluate the characteristics of children affected.

Methods—We identified all *E. coli* or *Klebsiella* spp. cultured from children younger than 18 years of age at our facility between January 2003 and December 2007. Medical records were reviewed for affected children.

Results—Of 2697 *E. coli*, *K. pneumoniae*, and *K. oxytoca* cultured, 26 ESBL producers were isolated from 16 children. Rates of ESBL production among cultured isolates significantly increased, from 0.53% in the first half of the study period to 1.4% in the second. Incidence of a primary ESBL infection also increased significantly, from 0.14/10,000 patient encounters to 0.31/10,000. The majority of children infected or colonized with ESBL-producing organisms were those with chronic medical conditions, frequent hospitalizations, or a history of recurrent infection. However, four affected children were less than 5 months old, and evaluated in an outpatient setting.

Conclusions—Rates and incidence of ESBL infection increased over the study period. While most patients belonged to traditional risk groups for antibiotic-resistant infection, infants in the ambulatory setting were also affected, an at-risk population not previously described.

Keywords

Extended-spectrum β -lactamase; Gram-Negative Bacterial Infections; Hospital-associated infection; Drug Resistance; Pediatrics

Corresponding Author: Anne Blaschke, MD, PhD, Department of Pediatrics, Division of Pediatric Infectious Diseases, University of Utah, 2A100 SOM, 30 North 1900 East, Salt Lake City, UT 84132, (801) 581-6791 (ph), (801) 585-3789 (fax), anne.blaschke@hsc.utah.edu.

Conflict of Interest: All authors, no conflicts

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Gram-negative organisms are a frequent cause of infection in both adult and pediatric patients in the United States (US). In patients of all ages, Gram-negative pathogens are the most frequent cause of urinary tract infection (UTI) and as a group are second only to *Staphylococci* as a cause of bloodstream infection.^{1–3} In young infants, Gram-negative organisms are now the most common cause of serious bacterial infection.^{4–6}

Over the past 15 years surveillance in the US has demonstrated a significant increase in the prevalence of Gram-negative organisms producing extended-spectrum β -lactamases (ESBLs).⁷ These organisms produce variants of the TEM, SHV and CTX-M β -lactamases, and are resistant to all β -lactam antibiotics except carbapenems.^{8,9} Most data on prevalence, risk factors and outcomes for infection with an ESBL-producing organism are from studies in adult patients, or from studies confined to infants in the neonatal ICU (NICU). While two recent studies have reported on risk factors for bloodstream infection in children,^{10,11} the risks for other types of infection or for colonization in children are largely unknown. The purpose of our study was to determine the rates, incidence and outcomes of infection or colonization at any site with an ESBL-producing organism in our pediatric center, and to examine the characteristics of children affected.

Materials and Methods

The institutional review boards of Intermountain Healthcare (IH) and the University of Utah approved this study.

Setting

Primary Children's Medical Center (PCMC; Salt Lake City, UT) is a 252 bed tertiary-care children's hospital. PCMC is part of the IH network of hospitals, and is the only tertiary-care pediatric center in the intermountain region. The hospital serves as a local care facility for children in Salt Lake County and as a referral site for specialized pediatric care in the intermountain west including: Utah, Wyoming, Idaho, Montana, and portions of Nevada, Colorado, and Arizona.

Identification of ESBL-producing isolates and affected patients

IH maintains a computerized Electronic Data Warehouse (EDW) that contains clinical, laboratory, and microbiologic data for all patients in the IH system. The EDW was queried for all *E. coli* or *Klebsiella* spp. cultured from any site for children younger than 18 years of age cared for at PCMC between January 2003 and December 2007. Isolates were considered unique if they were cultured from a distinct patient, or from the same patient on a different admission or outpatient encounter. Multiple isolates from the same patient on the same encounter were counted as one isolate. The yearly species-proportion of isolates producing ESBLs was calculated using total cultured isolates of each species (1 per patient per encounter) as the denominator.

Definitions

Annual incidence of a primary ESBL infection was defined and calculated as the number of patients each year having their first-documented (in our system) positive culture for an ESBL-producing organism as the numerator, and the total number of PCMC patient encounters per year (including inpatient, outpatient and emergency room visits) as the denominator. Evidence that this infection was a new (or incident) event was determined by reviewing all earlier system-wide culture data available for each patient. A recurrent infection was defined as isolation of an ESBL-producing organism from a patient with a prior history of ESBL infection, but on a

different admission. Spread of infection was defined as isolation of an ESBL-producing organism from more than one site on either the same or a different admission. The definition of community-onset ESBL infection was adapted from Apisarnthanarak et al.¹² and included infections that occurred in patients who had never been hospitalized, or occurred < 48 hours after hospitalization in a patient without a history of hospital admission in the last 30 days. In addition the patient could not have been transferred from an outside hospital or long-term care facility.

Laboratory methods

All microbiologic studies were performed in the PCMC microbiology laboratory; ESBL testing has been performed here using the same methods since 1999. Enterobacteriaceae were identified to the species level using the Vitek2 GN identification card. Urine isolates were identified as *E. coli* if they had typical colony morphology (flat, lactose-fermenting) and were spot indole positive. If colonies did not have these characteristics, they were identified using the Vitek2. All isolates of *E. coli* and *Klebsiella* spp. were automatically screened for ESBL production as part of the susceptibility panel. Screening and confirmation followed Clinical and Laboratory Standards Institute (CLSI) guidelines and standards.¹³ Briefly, all *E. coli* and *Klebsiella* spp. identified and with susceptibility testing performed were screened for ESBL production using disk diffusion methodology on Mueller-Hinton agar. The ESBL screening drugs included cefpodoxime, cefotaxime, ceftazidime, ceftriaxone, and aztreonam for non-urine isolates and cefpodoxime alone for urine isolates. The ESBL screen was considered positive if one or more of the screening drugs had a zone diameter less than the recommended limit set by CLSI ESBL screening guidelines. An ESBL confirmatory test was performed on all isolates that were positive by ESBL screen. Cefotaxime, ceftazidime, cefotaxime/clavulanate, and ceftazidime/clavulanate susceptibility disks (BBL™) were tested following CLSI disk diffusion guidelines. If a ≥ 5 -mm increase in zone diameter for an antimicrobial agent tested in combination with clavulanate was found when compared to its zone size when tested alone, it was identified as an ESBL producer. *E. coli* and *Klebsiella* spp. were the only species evaluated for ESBL expression in the PCMC microbiology laboratory in 2003–2006. *Proteus mirabilis* was added in 2007, but was not included in the study due to lack of data prior to 2007.

Patient data collection

For children with ESBL-positive isolates, medical records were abstracted by a single investigator (AJB) for demographic and clinical data including: medical history, site of initial culture, recurrence or spread, and outcome. ESBL isolates were considered “colonizing” using the Centers for Disease Control/National Healthcare Safety Network definition.¹⁴ As this was a retrospective study, “not causing adverse clinical signs or symptoms” was defined by the absence of specific treatment for the isolate, or discontinuation of antibiotic therapy <48 hours following detection of the organism. In all other cases, the ESBL-producing isolate was considered a causative agent of infection. The IH inpatient pharmacy database was queried to determine prior and initial antibiotic therapy for all patients.

Statistical Analysis

Fishers exact test was used to calculate both the difference in the proportion of ESBL-producing organisms and the difference in incidence rates during the two halves of the study period. The Cochran-Armitage test was used to examine the trend in rates over time. A p-value of 0.05 was considered the cut-off for significance.

Results

Rates of ESBL production

2697 total isolates of *E. coli*, *K. pneumoniae*, and *K. oxytoca* were identified over the study period. Twenty-six ESBL-producing organisms were isolated, for an overall rate of 0.96%. Of the 26 ESBL-producing isolates, 18 (69%) were *E. coli*, 6 (23%) were *K. pneumoniae* and 2 (8%) were *K. oxytoca*. See Table 1. Over the 5 years examined rates of ESBL production increased; although this trend was apparent, it was not statistically significant. As can be seen in the table, there was a noticeable increase in the proportion of isolates (primarily *E. coli*) producing ESBLs in 2006 and 2007. Analyzing the data for all species over the first and second halves of the study period, the proportional increase in ESBL-producing isolates was statistically significant, with 0.53% isolates producing ESBLs in the first 30 months as compared to 1.4% in the second, ($p = 0.03$). A more significant increase was seen when only *E. coli* isolates were analyzed, with rates of ESBL production at 0.29% and 1.4% in the first and second halves of the study period respectively ($p = 0.007$).

Incidence of ESBL infection

Outbreaks were not a concern during the study period, and patients were not related by time period of infection or by unit. We did observe that patients infected with an ESBL-producing organism tended to have recurrence of infection with the same species of ESBL-producer (Table 2). We thus defined the first-documented culture positive for an ESBL as a “primary infection” (See Methods) and analyzed the incidence of primary infection over time. The small number of patients infected with ESBL-producing organisms in our study did not allow for analysis of trend, however analyzed in two equal time periods, the incidence of primary ESBL infection increased significantly in the second half of the study. In the first 30 months 0.14/10,000 patient encounters were associated with the first-isolation of an ESBL-producing organism while between July 2005-Dec 2007 0.31/10,000 were associated ($p = 0.01$). The relative risk of having a primary ESBL infection in the second half of the study period was 2.2 (95% confidence interval 1.2 – 4.1).

Sources and Characteristics of Isolates

The 26 ESBL-producing isolates were cultured from urine (18), respiratory secretions (3), blood (3), and abscess fluid (2). Six (23%) were defined as colonizers (see Methods), including all of the respiratory tract isolates and 3 urine isolates. No patient with a colonizing isolate developed invasive disease with the same species. One patient had 2 different species of ESBL-producing urinary isolate (*K. pneumoniae*, colonizing; *E. coli*; infecting) on 2 different admissions.

Twenty isolates (77%) were considered to have been causative agents of infection, including 15 urinary isolates, 3 bloodstream isolates and 2 isolates from abscess fluid. Three of the fifteen isolates causing urinary infection (20%) were associated with an ESBL-producing organism of the same species isolated from an additional sterile site [bloodstream (2), liver abscess (1)]. In two of these cases, the additional organism was isolated on a separate admission or outpatient encounter, and thus considered a recurrence of infection.

Antibiotic susceptibility data indicated that carbapenems were the only class of antibiotics to which all isolates were susceptible. Levels of resistance to other antimicrobial agents were high. Data are shown in Table 3. For patients with recurrent infection, a single isolate from each recurrence was included in the susceptibility analysis ($n=26$).

Characteristics of Children with ESBL Infection

Patient characteristics are shown in Table 2. Patients with recurrent infection (n = 6) all had a history of chronic medical condition, anatomic abnormality or prolonged hospitalization. Five of these had recurrent UTI. Sixty-three percent of patients (10/16) met the definition of community-onset infection (See Methods), although most had been hospitalized within the last year. Fifty percent of children with ESBL-producing isolates in this study were under 2 years old, and five were infants aged 1 to 4.5 months. Three of these 5 had been born prematurely, but only one was an inpatient when the ESBL-producing organism was isolated. The other two had prior NICU stays of about two weeks. One infant was a previously healthy US-born full-term baby, and one was a full-term infant adopted from Africa. Five patients, including the US-born full-term infant, had life-threatening infections [bloodstream (3), retropharyngeal abscess (1), liver abscess (1)]. Information on prior inpatient antibiotic therapy was available for all patients.

Treatment and Outcomes of ESBL Infection

Data on initial antibiotic therapy was available for 14 of the 16 patients; 12/14 (86%) were initially treated with an agent that was not active against the infecting organism, including four of the five children with life-threatening infection. Morbidities included 2 patients with UTI that required a central catheter and intravenous antibiotics, 2 patients that required surgical intervention to clear their infection (drainage of liver abscess, resection of ureteral remnant), and 2 patients that required prolonged antibiotic therapy. No child died.

Discussion

ESBL-producing organisms are increasingly common worldwide, and represent an emerging infectious threat.^{2,3,8} Our study documents a marked increase in both the proportion of ESBL producers and the incidence of primary ESBL infection over the 5 year study period, indicating ESBL-producing organisms may be an emerging problem in US pediatric institutions. Similar to adult studies and other pediatric studies,^{10,11,15} most children from whom ESBL-producing organisms were isolated had chronic medical issues and recurrent infection. Unique to this study was the identification of ESBL-producing isolates from young infants evaluated in outpatient settings. We found a comparatively low prevalence of ESBL-producing *E. coli* and *Klebsiella* spp. when compared to adult studies in the US and to pediatric studies outside the US.^{7,11,16,17}

Rates of ESBL production among isolates from children at our institution between 2003 and 2007 were low, but similar to those reported by SENTRY investigators for US pediatric institutions in 2004.² Among Gram-negative organisms isolated from children in the SENTRY study, 1.9% of *E. coli* and 1.1–3.2% of *Klebsiella* spp. were ESBL producers, compared to 0.87% and 1.3% respectively in our study. A recent French study also reported relatively low rates of ESBL-production among Enterobacteriaceae (not including *K. pneumoniae*) at 1.4%.¹⁷ High rates of ESBL production have been reported for organisms isolated from high-risk settings in the US and internationally. ICU surveillance in the US reported the prevalence of resistant *K. pneumoniae* isolates at 20.6% in 2003,⁷ and two recent studies reported the prevalence of ESBL-producing organisms in pediatric bloodstream infections in the US and Korea^{10,11} to be between 7–17.9% for *E. coli* and 18–52.9% for *Klebsiella* spp.

The overall proportion of isolates producing ESBLs at our institution more than doubled in the final 30 months. Additionally, the incidence of a primary ESBL infection was 2.2 times greater when compared to the first 2 ½ years. As primary infection often led to recurrence in our chronically ill children, it seems likely that the burden of ESBL-producing pathogens in

pediatrics will continue to increase. Prospective studies in a variety of settings are needed in order to implement adequate control strategies.

As has been seen in adults,¹⁸ urine was the most common site of isolation of ESBL-producing organisms in our study. In 3 cases of UTI, the urinary infection preceded or was concurrent with a more invasive infection with the same organism. Notably, two of these secondary invasive infections occurred 2 months (liver abscess) and 11 months (bloodstream infection) later, indicating probable ongoing colonization. Although the isolation of a colonizing organism in our cohort did not predict subsequent infection, these data suggest that a history of infection with a resistant Gram-negative organism, including a urine isolate, should be considered in the choice of initial therapy for subsequent infections. Unfortunately, as shown in this and other studies,^{7,9,19} high levels of resistance to multiple classes of antibiotics are common in ESBL producers, and thus initial empiric therapy with a carbapenem may be necessary.

Most children in our study had chronic medical conditions, anatomic abnormalities or frequent hospital admissions. While all but one child had been hospitalized during the year before their primary ESBL infection, most (13/16) had been hospitalized for less than 48 hours when the culture was obtained. Only three of these children had been hospitalized in the last 30 days, defining 10/16 (63%) of our primary infections as community-onset.¹² Chronic medical conditions, frequent hospital admissions and antibiotic exposure are described as risk factors for long-term ESBL colonization and community-onset infection in adults,^{15,20–22} and our affected pediatric patients had similar characteristics. An understanding of which children are likely to be colonized with ESBL-producing organisms is crucial to the choice of effective initial therapy for infection.

A disturbing finding in our study was the isolation of ESBL-producing organisms from four young infants presenting to the emergency department or outpatient clinic. Two of the infants had a history of prematurity, and had spent time in a NICU following birth, although both had uncomplicated stays of approximately 2 weeks. A number of studies have examined ESBL-producing organisms in the NICU, including risk factors for colonization and infection.^{19, 23–26} Reported risk factors include very low birth weight, antibiotic exposure, as well as length of NICU stay. Mean length of stay prior to colonization can be as short as 9 days^{24,26} and may explain the colonization of the two NICU graduates in our study. A third infant, however, born at term and with no significant prior hospitalization, had a life-threatening infection with ESBL-producing *E. coli* at 4.5 months of age. While studies have been published documenting methicillin-resistant *S. aureus* (MRSA) infection in the normal newborn nursery,^{27–29} as well as mother-to-child transmission of MRSA,^{30–32} no data exists on infection with ESBL-producing organisms in healthy newborns. Other studies have not reported the isolation of ESBL-producing organisms from infants in the outpatient setting, and their presence in this population is a substantial concern. In particular, due to the high morbidity and mortality associated with Gram-negative sepsis in young infants and the reliance on ampicillin and 3rd generation cephalosporins for initial therapy in outpatient settings, the emergence of ESBLs poses a significant threat.

A fourth infant in our study was a recent adoptee from Africa found to have a UTI caused by an ESBL-producing *E. coli*. Recent studies from Africa have reported on the presence of ESBL-producing Enterobacteriaceae,^{33–36} and have shown particularly high rates of resistance in *Klebsiella* spp. The child in our study had been adopted from an orphanage in Ethiopia; a single study from that region reported ESBL rates among *Klebsiella* spp. in Ethiopia at 33.3%.³⁷ Rates of ESBL-production among *E. coli* in Ethiopia are unknown. As drug resistance among Gram-negative pathogens rises throughout the world, further studies will be needed to assess the risk of colonization among internationally adopted children.

No child with ESBL infection in our study died. While factors associated with mortality were not specifically examined here, we can hypothesize that our low mortality rate may be related to the overall low number of ESBL-producing pathogens at our institution, and the preponderance of urinary tract as opposed to invasive isolates. It is possible that there are other differences in the virulence of our isolates or in our patient population that could explain this low mortality, but this is outside the scope of the current study

Our study has several limitations. Overall rates and incidence of ESBL-producing organisms at our institution were low, and our results may not be applicable to medical centers and regions with higher rates. The classification of isolates as infecting or colonizing was made retrospectively; we did not distinguish between infection and colonization in our overall data analysis in order to capture all ESBL isolates in our pediatric patient population. Our pharmacy database query was limited to inpatient antibiotics prescribed within the IH system and outpatient prescriptions could not be documented, potentially falsely decreasing the proportion of patients with a history of prior antibiotic exposure. Finally, this is a descriptive, retrospective study without a control group, therefore we cannot define risk factors or associations here. Children in our study, however, did have many characteristics associated with resistant infection in reports from adults.^{3,15,18}

Gram-negative infection is a significant problem in pediatrics, and as resistance increases among these pathogens, treatment will become more difficult. The limited pipeline of new antibiotics is particularly an issue for children as safety, pharmacokinetic data and FDA approval typically lag years behind that for adults. Future studies will need to better address the role that colonization plays in pediatric infection, the role of prior antibiotic therapy, and the role of increasing infection rates in adult hospitals, particularly as it relates to maternal transfer of ESBL-producing organisms to newborn infants. Continued surveillance and an understanding of those factors associated with infection and colonization is essential to develop containment strategies that prevent these organisms becoming a common problem in pediatric hospitals and the community.

Acknowledgments

Sources of Support: AJB is supported by an NIH/NICHD Child Health Research Career Development Award (5K12HD001410-04) and the Primary Children's Medical Center Foundation

References

1. Streit JM, Jones RN, Sader HS, Fritsche TR. Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). *Int J Antimicrob Agents* 2004;24(2):111–8. [PubMed: 15288308]
2. Fedler KA, Biedenbach DJ, Jones RN. Assessment of pathogen frequency and resistance patterns among pediatric patient isolates: Report from the 2004 SENTRY Antimicrobial Surveillance Program on 3 continents. *Diagn Microbiol Infect Dis* 2006;56(4):427–36. [PubMed: 16938419]
3. Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997–2002). *Diagn Microbiol Infect Dis* 2004;50(1):59–69. [PubMed: 15380279]
4. Byington CL, Rittichier KK, Bassett KE, Castillo H, Glasgow TS, Daly J, et al. Serious bacterial infections in febrile infants younger than 90 days of age: the importance of ampicillin-resistant pathogens. *Pediatrics* 2003;111(5 Pt 1):964–8. [PubMed: 12728072]
5. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. *N Engl J Med* 2002;347(4):240–7. [PubMed: 12140299]

6. Levine EM, Ghai V, Barton JJ, Strom CM. Intrapartum antibiotic prophylaxis increases the incidence of gram-negative neonatal sepsis. *Infect Dis Obstet Gynecol* 1999;7(4):210–3. [PubMed: 10449272]
7. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32(8):470–85. [PubMed: 15573054]
8. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev* 2005;18(4):657–86. [PubMed: 16223952]
9. Babic M, Hujer AM, Bonomo RA. What's new in antibiotic resistance? Focus on beta-lactamases. *Drug Resist Updat* 2006;9(3):142–56. [PubMed: 16899402]
10. Zaoutis TE, Goyal M, Chu JH, Coffin SE, Bell LM, Nachamkin I, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species in children. *Pediatrics* 2005;115(4):942–9. [PubMed: 15805368]
11. Kim YK, Pai H, Lee HJ, Park SE, Choi EH, Kim J, et al. Bloodstream infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in children: epidemiology and clinical outcome. *Antimicrob Agents Chemother* 2002;46(5):1481–91. [PubMed: 11959586]
12. Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing *Escherichia coli* infections in Thailand: a case-case-control study. *Am J Infect Control* 2007;35(9):606–12. [PubMed: 17980240]
13. Performance Standards for Antimicrobial Susceptibility Testing; Sixteenth Informational Supplement M100-S16. Volume 26 no 3: Clinical and Laboratory Standards Institute 2006.
14. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36(5):309–32. [PubMed: 18538699]
15. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. *J Antimicrob Chemother* 2005;56(1):52–9. [PubMed: 15917288]
16. Bonomo RA. Multiple antibiotic-resistant bacteria in long-term-care facilities: An emerging problem in the practice of infectious diseases. *Clin Infect Dis* 2000;31(6):1414–22. [PubMed: 11096012]
17. Raymond J, Nordmann P, Doit C, Vu Thien H, Guibert M, Ferroni A, et al. Multidrug-resistant bacteria in hospitalized children: a 5-year multicenter study. *Pediatrics* 2007;119(4):e798–803. [PubMed: 17403822]
18. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for infection and impact of resistance on outcomes. *Clin Infect Dis* 2001;32(8):1162–71. [PubMed: 11283805]
19. Gupta A, Ampofo K, Rubenstein D, Saiman L. Extended spectrum beta lactamase-producing *Klebsiella pneumoniae* infections: a review of the literature. *J Perinatol* 2003;23(6):439–43. [PubMed: 13679928]
20. Harris AD, McGregor JC, Johnson JA, Strauss SM, Moore AC, Standiford HC, et al. Risk factors for colonization with extended-spectrum beta-lactamase-producing bacteria and intensive care unit admission. *Emerg Infect Dis* 2007;13(8):1144–9. [PubMed: 17953083]
21. Colodner R, Rock W, Chazan B, Keller N, Guy N, Sakran W, et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. *Eur J Clin Microbiol Infect Dis* 2004;23(3):163–7. [PubMed: 14986159]
22. Rodriguez-Bano J, Navarro MD, Romero L, Martinez-Martinez L, Muniain MA, Perea EJ, et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in nonhospitalized patients. *J Clin Microbiol* 2004;42(3):1089–94. [PubMed: 15004058]
23. Singh N, Patel KM, Leger MM, Short B, Sprague BM, Kalu N, et al. Risk of resistant infections with Enterobacteriaceae in hospitalized neonates. *Pediatr Infect Dis J* 2002;21(11):1029–33. [PubMed: 12442024]
24. Pessoa-Silva CL, Meurer Moreira B, Camara Almeida V, Flannery B, Almeida Lins MC, Mello Sampaio JL, et al. Extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in a neonatal

- intensive care unit: risk factors for infection and colonization. *J Hosp Infect* 2003;53(3):198–206. [PubMed: 12623321]
25. Linkin DR, Fishman NO, Patel JB, Merrill JD, Lautenbach E. Risk factors for extended-spectrum beta-lactamase-producing Enterobacteriaceae in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2004;25(9):781–3. [PubMed: 15484805]
 26. Boo NY, Ng SF, Lim VK. A case-control study of risk factors associated with rectal colonization of extended-spectrum beta-lactamase producing *Klebsiella* sp. in newborn infants. *J Hosp Infect* 2005;61(1):68–74. [PubMed: 15953660]
 27. Nguyen DM, Bancroft E, Mascola L, Guevara R, Yasuda L. Risk factors for neonatal methicillin-resistant *Staphylococcus aureus* infection in a well-infant nursery. *Infect Control Hosp Epidemiol* 2007;28(4):406–11. [PubMed: 17385145]
 28. Community-associated methicillin-resistant *Staphylococcus aureus* infection among healthy newborns--Chicago and Los Angeles County, 2004. *MMWR Morb Mortal Wkly Rep* 2006;55(12):329–32. [PubMed: 16572100]
 29. James L, Gorwitz RJ, Jones RC, Watson JT, Hageman JC, Jernigan DB, et al. Methicillin-resistant *Staphylococcus aureus* infections among healthy full-term newborns. *Arch Dis Child Fetal Neonatal Ed* 2008;93(1):F40–4. [PubMed: 17412749]
 30. Behari P, Englund J, Alcasid G, Garcia-Houchins S, Weber SG. Transmission of methicillin-resistant *Staphylococcus aureus* to preterm infants through breast milk. *Infect Control Hosp Epidemiol* 2004;25(9):778–80. [PubMed: 15484804]
 31. Gastelum DT, Dassey D, Mascola L, Yasuda LM. Transmission of community-associated methicillin-resistant *Staphylococcus aureus* from breast milk in the neonatal intensive care unit. *Pediatr Infect Dis J* 2005;24(12):1122–4. [PubMed: 16371885]
 32. Morel AS, Wu F, Della-Latta P, Cronquist A, Rubenstein D, Saiman L. Nosocomial transmission of methicillin-resistant *Staphylococcus aureus* from a mother to her preterm quadruplet infants. *Am J Infect Control* 2002;30(3):170–3. [PubMed: 11988712]
 33. Frank T, Arlet G, Gautier V, Talarmin A, Bercion R. Extended-spectrum beta-lactamase-producing Enterobacteriaceae, Central African Republic. *Emerg Infect Dis* 2006;12(5):863–5. [PubMed: 16710958]
 34. Brink A, Moolman J, da Silva MC, Botha M. Antimicrobial susceptibility profile of selected bacteraemic pathogens from private institutions in South Africa. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 2007;97(4):273–9. [PubMed: 17446952]
 35. Bouchillon SK, Johnson BM, Hoban DJ, Johnson JL, Dowzicky MJ, Wu DH, et al. Determining incidence of extended spectrum beta-lactamase producing Enterobacteriaceae, vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* in 38 centres from 17 countries: the PEARLS study 2001–2002. *Int J Antimicrob Agents* 2004;24(2):119–24. [PubMed: 15288309]
 36. Hirakata Y, Matsuda J, Miyazaki Y, Kamihira S, Kawakami S, Miyazawa Y, et al. Regional variation in the prevalence of extended-spectrum beta-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998–2002). *Diagn Microbiol Infect Dis* 2005;52(4):323–9. [PubMed: 16165001]
 37. Seid J, Asrat D. Occurrence of extended spectrum beta-lactamase enzymes in clinical isolates of *Klebsiella* species from Harar region, eastern Ethiopia. *Acta tropica* 2005;95(2):143–8. [PubMed: 15993831]

Table 1
Isolates ESBL/total species isolates (%ESBL; 95% CI)

Year	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>K. oxytoca</i>	Total
2003	1/422 (0.24; 0.01, 1.3)	2/62 (3.2; 0.39, 11.2)	0/45 (0)	3/529 (0.57; 0.12, 1.7)
2004	1/380 (0.26; 0.01, 1.5)	0/83 (0)	2/56 (3.6; 0.44, 12.3)	3/519 (0.58; 0.12, 1.7)
2005	3/397 (0.76; 0.16, 2.2)	0/64 (0)	0/48 (0)	3/509 (0.59; 0.12, 1.7)
2006	6/393 (1.5; 0.56, 3.3)	2/84 (2.4; 0.29, 8.3)	0/46 (0)	8/523 (1.5; 0.66, 3.0)
2007	7/475 (1.5; 0.59, 3.0)	2/80 (2.5; 0.30, 8.7)	0/62 (0)	9/617 (1.5; 0.67, 2.8)
Total	18/2067 (0.87; 0.52, 1.4)	6/373 (1.6; 0.59, 3.5)	2/257 (0.78; 0.09, 2.8)	26/2697 (0.96; 0.63, 1.4)

Table 2**Patient Characteristics (n = 16)**

Mean Age	6.3 years
Age Range	1 month – 17 years
Age < 2 Years at First Infection	8 (50%)
Male	8 (50%)
Chronic Illness, Anatomic Abnormality or Prolonged Hospitalization	12 (75%)
Premature Infant	3 (19%)
Urinary Isolate (Primary Infection)	12 (75%)
ESBL Organism Isolated from >1 Site	3 (19%)
Recurrent Infection or Colonization	6 (38%)
Mean Number of Recurrences (Children with > 1 Infection)	1.7 (range 1 – 4)
Recurrence with the Same Species of ESBL Hospitalization Prior to First Infection:	5 (of 6 with recurrence; 83%)
In Past 12 Months	15* (94%)
In Past 30 Days	6 (38%)
In Past 48 hours	3 (19%)
Antibiotic Therapy in 30 Days Prior to First Infection (Inpatient Only)	5 (31%)
β-Lactam Agent	4 (of 5; 80%)
Appropriate Initial Antibiotic Therapy	2 (of 14 with available data; 14%)
Primary Infection in Final 30 months of the Study Period	11 (69%)

* Includes 1 patient hospitalized only in the normal newborn nursery after birth

Table 3

Antibiotic Susceptibility Data

Antibiotic	Susceptible isolates ^a /# tested (% susceptible; 95% CI)
Imipenem	18/18 (100; 81, 100)
Nitrofurantoin	15/18 (83; 59, 96)
Gentamicin	12/25 (48; 28, 69)
Ciprofloxacin	10/22 (45; 24, 68)
TMP-SMZ	6/24 (25; 9.8, 47)

Note: TMP-SMZ, trimethoprim sulfamethoxazole

^a Isolates were considered resistant to all β -lactam antibiotics, including β -lactam/ β -lactamase inhibitor combinations