Potential Perinatally Acquired Extended Spectrum β -Lactamase *Escherichia coli* Urinary Tract Infection in an Infant

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Extended-spectrum β -lactamases (ESBL) are produced mainly by members of the Enterobacteriaceae family and confer resistance to most β -lactam antibiotics. Because of limited treatment options, ESBL infections are typically more challenging to treat resulting in poor outcomes, increased complications, and mortality. Because ESBL-producing organisms are primarily seen in critically ill patients, along with those patients having prolonged hospital stays, extensive courses of antimicrobials, and/or use of invasive medical devices (i.e., urinary catheters, central venous lines, or endotracheal tubes), guidelines regarding the management of ESBL-producing organisms in the pediatric population are scant. A review of current recommended treatment options for infections caused by ESBL-producing organisms centers on the use of carbapenems, with some supportive literature regarding the utility/effectiveness of other non- β -lactam therapy. We present a case report of an 8-month-old female diagnosed with a urinary tract infection due to ESBL-producing *Escherichia coli* successfully treated with sulfamethoxazole/trimethoprim. Multidrug resistant infections in pediatric patients without risk factors remains an important field of study because these unique infections may pose a problem when choosing an effective empiric antimicrobial therapy.

ABBREVIATIONS AAP, American Academy of Pediatrics; CBC, complete blood count; CFU, colony-forming unit; *E coli*, *Escherichia coli*; ESBL, extended-spectrum β -lactamase; IM, intramuscular; MDR, multidrug resistant; UTI, urinary tract infection; WBC, white blood cell

KEYWORDS antibiotics; β -lactam antibiotics; drug resistance; *Escherichia coli*; pediatrics; urinary tract infections

J Pediatr Pharmacol Ther 2020;25(3):266–269

DOI: 10.5863/1551-6776-25.3.266

Background

Extended-spectrum β -lactamases (ESBL) are produced mainly by members of the Enterobacteriaceae family, conferring resistance to most commonly prescribed β -lactam antibiotics, including penicillins, cephalosporins, and aztreonam.¹ β -lactamases hydrolyze the β -lactam ring, resulting in inactivation of the antibiotic. Because of this, ESBL infections tend to be more challenging to treat, resulting in poor outcomes, increased complications, and mortality.²

Several risk factors exist for colonization and infection with ESBL-producing organisms. ESBL-producing organisms most commonly occur in critically ill patients, those with prolonged hospital stays, and patients who require invasive medical devices such as urinary catheters, central venous lines, or endotracheal tubes.¹ According to several studies, the median length of hospital stay in patients infected with ESBLs ranges from 11 to 67 days.^{1,2} Other risk factors for the acquisition of ESBL-producing organisms include patients receiving hemodialysis, total parenteral nutrition, and prior antibiotic use.

Children diagnosed with urinary tract infections (UTIs) may present with fever ($>38^{\circ}\text{C}$), foul-smelling urine, urinary incontinence, abdominal or flank pain, and hematuria.^{3,4} Females younger than 1 year are typically at an increased risk of UTI compared with females greater than 1 year, along with their male counterparts. Regardless of symptoms, experts recommend all febrile infants aged 2 to 24 months, with no distinct cause of infection, receive an evaluation for UTI.³ Urinalyses that indicate infection may be remarkable for leukocyte esterase, nitrite, blood, and protein. The American Academy of Pediatrics (AAP) recommends obtaining urine samples using straight catheterization or suprapubic aspiration in pediatric patients to minimize contamination.

A review article of literature published from January 2000 to July 2014 described the incidence of ESBL-producing *Escherichia coli* ranged from 0 to 1.67 per 10,000 in infants diagnosed with UTI.² Currently, there are limited data on the incidence of ESBL-producing organisms in pediatric patients without known risk factors. Available literature suggests there may be an increased incidence of ESBL-producing organisms in pediatric patients with certain risk factors, such as low

birth weight, extended hospitalizations, and recent antibiotic use.⁵⁻⁷ Clinical practice guidelines published by the AAP recommend empiric therapy for febrile infants aged 2 to 24 months, including amoxicillin-clavulanate, sulfamethoxazole/trimethoprim, or cephalosporin.³ Consistent with the AAP empiric therapy recommendations, an infant presenting with symptoms of a UTI would likely be started on one of these regimens without considering activity against ESBL-producing organisms because of low prevalence. Given that the prevalence of ESBL-producing organisms may be increasing in community-acquired UTIs, it is essential to provide clinical guidance on the topic.⁵ We present a rare case of an 8-month-old female patient with no known risk factors, diagnosed with ESBL-producing *E coli*.

Case

An 8-month-old female presented to the emergency department with a chief complaint of fever. Other symptoms included decreased appetite and foul-smelling urine. Initial vitals in the emergency department were remarkable for rectal temperature 39.6°C, pulse 155 beats per minute, and respiratory rate 36 breaths per minute. Physical examination findings revealed a 9.27-kg infant in no respiratory distress, without vomiting, and tolerating oral fluids without difficulty. History revealed the patient's perinatal course was remarkable for term birth via uncomplicated, spontaneous vaginal delivery at 40 weeks and 1 day gestation to a group B streptococcus negative mother. There was thin meconium present at birth without signs of aspiration. Patient had persistent tachypnea her first day of life and was given ampicillin and gentamicin as a sepsis precaution. Subsequent blood cultures were negative and antibiotic therapy was discontinued after 48 hours. Following that event, the patient had no significant medical history and was otherwise healthy. Further evaluation included a CBC, which was remarkable for leukocytosis (WBC count 24.8 k/ μ L), but otherwise unremarkable for anemia, thrombocytopenia, or left shift bandemia. A straight catheterization urinalysis was remarkable for leukocyte esterase 500 leukocytes/ μ L and >1.0 mg/dL blood, but negative for nitrites and other abnormalities. Serology for influenza type A and B antigen, as well as Rapid RSV testing were also negative. Blood culture was obtained, and the patient received an empiric dose of ceftriaxone 50 mg/kg IM 1 time. Documented rectal temperatures decreased to 37.8°C 30 minutes after administration of ibuprofen 10 mg/kg suspension, with patient becoming afebrile after 2 hours. Patient was diagnosed with a UTI and concomitant otitis media. After clinical improvement, patient was discharged with a prescription for amoxicillin 100 mg/kg/day oral suspension for 10 days without hospital admission.

Three days after emergency department discharge, the patient presented to the family medicine clinic for a well-child examination. Review of her blood culture

taken 3 days prior reported no growth to date. However, review of the urine culture identification and susceptibility report revealed >100,000 colony-forming units (CFUs)/mL Gram-negative bacilli, identified as ESBL-producing *E coli*, resistant to penicillins and cephalosporins (Table).

Upon questioning, the patient's mother denied any issues with hygiene, physical abuse, or sexual abuse. The mother also denied history of previous UTIs or central lines and records indicated no antibiotic use in the 8 months prior to presentation. The patient had no previous illnesses to suggest immunodeficiency and no other significant past medical history.

After further discussion with infectious disease and pediatric urology specialists, a repeat straight catheterization urine culture was obtained at the family medicine clinic 5 days after her well-child examination to confirm initial urine culture findings. Repeat urine culture was again positive for 1000 CFU/mL Gram-negative bacilli, identified as ESBL-producing *E coli*. The urine culture and sensitivity report disclosed susceptibility to ciprofloxacin, levofloxacin, meropenem, nitrofurantoin, tetracycline, tobramycin, and sulfamethoxazole/trimethoprim (Table). The patient was initiated on 22.5 mg/kg sulfamethoxazole and 4.5 mg/kg trimethoprim oral suspension every 12 hours for 7 days to ensure appropriate antimicrobial therapy based on susceptibilities. A repeat, straight catheterization urine culture was obtained 1 month later, which revealed no growth confirming bacterial eradication. While the infant improved with antimicrobial therapy, the medical team may have considered obtaining renal and bladder ultrasonography as recommended by AAP guidelines.³

Following the patient's rare diagnosis, further review of maternal history revealed that the mother was seen at the family medicine clinic for acute pyelonephritis 1 week after delivery of the patient. Although the urinalysis performed at that time revealed leukocytosis, hematuria, and proteinuria, a culture was not obtained. The mother was given 1 g ceftriaxone IM at the clinic and cephalexin 500 mg 4 times a day for 10 days as outpatient therapy. At the patient's 6-week postpartum visit, despite resolution of urinary symptoms, a urinalysis with culture was repeated and revealed 1000 CFU/mL Gram-negative bacilli, identified as ESBL-producing *E coli* with a similar susceptibility pattern to that of her child (Table). Because of the mother's improvement on a β -lactam regimen 1 month prior and her lack of symptoms at this visit, this multidrug resistant (MDR) bacteria most likely represents a colonization. This infers that proper history, including maternal and close-contacts history, is obligatory in an otherwise unexplainable case such as this.

Discussion

Current literature describes risk factors for ESBL-producing organisms in pediatric patients as low birth

Table. Urine Culture Results for Mother and Child

Antibiotic	Urine Culture Results*					
	Child's ED		Child's Repeat Straight Catheterization		Mother's 6-Week Postpartum	
	mg/L	Interpretation	mg/L	Interpretation	mg/L	Interpretation
Ampicillin	>16	R	>16	R	>16	R
Ampicillin/sulbactam	>16/8	R	>16/8	R	>16/8	R
Aztreonam	>16	R	>16	R	>16	R
Cefazolin	>16	R	>16	R	>32	R
Cefoxitin	≤ 4	R	—	R	—	R
Ceftazidime	—	R	—	R	—	R
Ceftriaxone	>32	R	>32	R	>32	R
Ciprofloxacin	≤ 0.5	S	≤ 0.5	S	≤ 0.5	S
Gentamicin	≤ 2	S	≤ 2	S	≤ 2	S
Levofloxacin	≤ 1	S	≤ 1	S	≤ 1	S
Meropenem	≤ 0.5	S	≤ 0.5	S	≤ 0.5	S
Nitrofurantoin	≤ 16	S	≤ 16	S	≤ 16	S
Piperacillin/tazobactam	—	R	—	R	—	R
Tetracycline	≤ 2	S	≤ 2	S	<1	S
Tobramycin	≤ 2	S	≤ 2	S	1	S
Trimethoprim/sulfamethoxazole	$\leq 0.5/9.5$	S	$\leq 0.5/9.5$	S	<0.5/9.5	S

ED, emergency department; R, resistant; S, sensitive

* Gram-negative bacilli identified as extended-spectrum β -lactamase positive *E coli*.

weight, prolonged hospital stay, and recent antibiotic use.⁵⁻⁷ However, we must inquire about and document a thorough maternal infectious disease history, including recent or historic infections, MDR colonization, or history of any close contacts who may be colonized with such organisms. All of which may be considered significant risk factors and help guide initial empiric antibiotic selection in infants with UTI. The above case describes an ESBL-producing *E coli* infection in an 8-month-old female who did not have any obvious risk factors. The only documented antibiotics given to the patient were ampicillin and gentamicin during her first 48 hours of life. It is unlikely that this early-life antibiotic use contributed to her ESBL-producing organism infection, given that it was followed by 8 antibiotic-free months. However, it cannot be entirely discounted because there is currently no study that explores infections caused by MDR organisms in pediatric patients who were treated empirically for neonatal sepsis.

An ESBL-producing organism causing infection in an 8-month-old without documented or obvious risk factors is both concerning and intriguing. Children with ESBL infections have comparable outcomes to adults with similar infections including, prolonged hospitalization, frequent complications, and increased risk of mortality.⁵ Without the presence of risk factors in pediatric patients, it is likely that empiric therapy will not

cover the ESBL infection and the patient will go days without proper treatment while awaiting culture results. As seen with this patient's successful treatment with sulfamethoxazole/trimethoprim, community resistance patterns and susceptibility reports are imperative for determining appropriate therapy following pathogen identification. We describe a case of potential familial transmission of an ESBL *E coli* from a mother to infant. The causal relationship suggests the infant may have acquired the ESBL *E coli* as a result of the birthing process, shared familial fecal microbiome, or close contact with a potentially colonized mother. Although we cannot conclusively state these were the modes of infection without molecular typing of the urinary isolates in both infant and contacts, it does present a potential avenue for infection given our patient was without risk factors for MDR infection and because of the similarities of the susceptibility reports between mother and child. One important aspect of this case that cannot be overlooked is the contribution of proper infection control practices on the acquisition of MDR organism infections, in this case ESBL. Although we cannot definitively state how this organism was acquired, this is also an option. As noted in the literature, proper infection control practices are necessary to prevent in those potentially at risk for infection, even without identifiable risk factors. Unless current identification and isolation procedures are

observed, the increased incidence of reported ESBL isolates will only cause subsequent increases for those without risk factors, such as the patient we describe in this case report.

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Ethical Approval and Informed Consent Given the nature of this study, institution review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under Exempted criterion.

Accepted November 14, 2019

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