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ORIGINAL RESEARCH

Risk Factors For and Outcomes of Multidrug-Resistant *Escherichia coli* Infections in Children

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ABSTRACT

Introduction: The recent increase in multidrug-resistant (MDR) *Escherichia coli* infections is not well described in children. We determined the risk factors and outcomes of extraintestinal *E. coli* infections in children in our region.

Methods: We conducted a retrospective cohort study of children ≤18 years in Olmsted County, MN, USA, between January 1, 2012 and December 31, 2012. MDR isolates were defined as resistant to ≥3 antibiotic classes.

Results: A total of 368 children each contributed 1 isolate. Isolates were predominantly community-associated (82%) and from urine (90%), and outpatients (86%); 46 (13%) isolates were MDR. In multivariable analysis, genitourinary (GU) tract anomaly (OR 2.42, 95% CI 1.03–5.68), invasive devices (OR 3.48, 95% CI 1.37–8.83) and antibiotic use at presentation (OR 2.62, 95% CI 1.06–6.47) were associated with MDR *E. coli*. Children with MDR infections were more likely to have a complex infection (35% vs. 17%, $P = 0.026$), less likely to receive effective empiric antibiotics (47% vs. 74%, $P < 0.001$), had longer time to receipt of effective antibiotics (median 19.2 vs. 0.6 h, $P < 0.001$), and longer hospitalization (median 10 vs. 4 days, $P = 0.029$) than children with non-MDR infections.

Conclusion: Pediatric MDR *E. coli* infection was associated with GU tract anomaly, invasive devices, antibiotic use, delays in effective therapy and longer hospitalization.

Keywords: Antimicrobial resistance; *E. coli*; Multidrug-resistant *E. coli*

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INTRODUCTION

Escherichia coli is the most common Gram-negative pathogen in humans, and the leading cause of urinary tract infections (UTI) in children and bacteremia and meningitis in infants [1–4]. The incidence of antimicrobial-resistant *E. coli* infections is increasing globally [5–7] and contributing to poor outcomes [8–10] and increased healthcare costs [11]. The emergence of antimicrobial resistance in *E. coli* has

increased faster than the development of new antibiotics, leading to a paucity of therapeutic agents for highly antimicrobial-resistant strains.

Despite the increasing prevalence of antimicrobial-resistant *E. coli*, risk factors for infection or colonization with antimicrobial-resistant *E. coli* and outcomes associated with such infections have not been well studied in children. While a few pediatric studies have evaluated infections with extended spectrum β-lactamase (ESBL)-producing strains [12], none have investigated associations with other resistance phenotypes, including resistance to multiple drug classes. Furthermore, these studies are limited by small sample sizes, restricted populations (e.g., neonates or oncology patients) [13] or infectious syndromes (bacteremia), and were published several years ago, prior to the emergence of the pandemic, multidrug-resistant (MDR) *E. coli* clone, ST131 [14]. Additionally, no recent study has addressed risk factors for community-associated, multidrug-resistant (CA MDR) *E. coli* infections in children.

Awareness of risk factors for MDR *E. coli* infections in children would help clinicians more quickly identify and effectively treat children with resistant infections, potentially improving outcomes. Therefore, we determined risk factors and outcomes of MDR *E. coli* infection among children seen at the Mayo Clinic.

METHODS

We conducted a retrospective cohort study of children with *E. coli* infections who were evaluated at the Mayo Clinic Children's Hospital in Rochester, MN, USA, in 2012. The Mayo Clinic Institutional Review Board approved this study. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Study Population

Patients were identified by querying the Mayo clinical microbiology laboratory database for all cultures (including polymicrobial cultures) with growth of *E. coli* from extraintestinal sources (blood, sterile body fluids, urine, respiratory, wound) from children 0–18 years of age, obtained from January 1, 2012 through December 31, 2012. We included only children who had documented MN state research authorization (Minnesota Statute, section 144.295). We excluded children without state research authorization or whose *E. coli* isolates lacked antimicrobial susceptibility results. If a patient had multiple positive cultures during the study period, the first isolate was included, or sterile sources were prioritized over non-sterile sources (i.e. blood was included rather than urine).

Definitions

An isolate was classified as multidrug-resistant (MDR) if it was resistant to any antibiotic in 3 or more of the following 8 drugs/drug classes: (1) ampicillin/sulbactam, (2) piperacillin/tazobactam, (3) trimethoprim/sulfamethoxazole (TMP/SMX), (4) fluoroquinolones (ciprofloxacin or levofloxacin), (5) aminoglycosides (gentamicin, tobramycin, or amikacin), (6) 1st- or 2nd-generation cephalosporins (cefazolin, cephalothin, or cefuroxime), (7) extended-spectrum cephalosporins (ceftriaxone, cefotaxime, ceftazidime or cefepime), and (8) carbapenems (meropenem or ertapenem) [15]. A pan-susceptible isolate (PS) was susceptible to all of the drugs listed above.

We distinguished infection from colonization among isolates from respiratory, urine, or wound specimens. A urinary *E. coli* isolate represented a UTI when the patient exhibited all of the following: UTI symptoms such as fever, abdominal pain or dysuria, pyuria (defined as >5 white blood cells/hpf or a positive leukocyte esterase test), and monomicrobial growth of *E. coli* at $>10^5$ CFU per mL. Lower respiratory tract specimens represented infection (pneumonia, bronchitis or tracheitis) when patients had the following: fever, dyspnea or cough, and supportive objective findings (infiltrates on chest imaging or signs of airway inflammation on bronchoscopy). *E. coli* from wound cultures represented wound infections when patients had accompanying signs of ongoing inflammation from the culture site such as pain, discharge or fever. Patients who had urine, respiratory and wound *E. coli* isolates, but did not fulfill the above criteria for infection, were considered to be colonized.

Empiric antibiotics were defined as those administered prior to availability of *E. coli* antimicrobial susceptibility results. An empiric antibiotic was considered effective if it was active against the isolate in vitro and was clinically appropriate for the site of infection (e.g., an oral antibiotic was considered inappropriate for a bloodstream infection). Nosocomial, healthcare-associated (HA) and community-associated (CA) infection were defined as previously described [16, 17]. A complex infection was defined as *E. coli* infection in any non-urine site or in a child who had any of the following: immune compromise, GU abnormality, upper urinary tract infection or hospitalization. A non-complex infection was defined as *E. coli* UTI in an immunocompetent child without GU abnormalities (except neurogenic bladder) or upper urinary tract infection, and who was managed as an outpatient [18].

Variables that were abstracted from the electronic medical record as potential risk factors and outcomes (e.g., age, location of care at time of specimen collection, etc.) are shown in Tables 1 and 5.

Statistical Analysis

Continuous variables were summarized with medians and interquartile ranges (IQRs), while categorical features were summarized with counts and percentages. The ability of each feature to distinguish between MDR isolates and non-MDR isolates was evaluated using a univariable logistic regression model. A multivariable model to predict MDR isolates was developed using stepwise selection, with the *P* value for a feature to enter or leave the model set to 0.05.

RESULTS

Demographic Characteristics

During the study period, 368 children each contributed 1 *E. coli* isolate. The median patient age was 7 years. Most isolates were community-associated (82%) and collected from outpatients (86%) and females (86%). The predominant specimen type was urine (90%). Infection versus colonization could be evaluated for 346 children; of these, 318 (92%) had infection and 28 (8%) had colonization. Thirty-seven (10%) had 1 or more invasive devices at the time of culture collection (Table 1).

Antimicrobial Susceptibilities

Among all isolates, 194 (53%) were PS, 128 (35%) were resistant to 1–2 drug classes and 46 (13%) were MDR (Table 2). The majority of the MDR isolates were from urine (83%), with the remainder from respiratory (9%), blood (7%) and intraabdominal (1%) sources. Among the 46 MDR isolates, 23 (50%) were resistant to 3 drug classes, most commonly ampicillin/sulbactam, TMP/SMX, and a 1st-generation cephalosporin. Six isolates were resistant to 6 drug classes and 1 isolate was resistant to all 8 drug classes (Table 2). Ten isolates (22%) displayed resistance to extended spectrum cephalosporins.

Risk Factors for MDR *E. coli* Infection or Colonization

Univariable analysis of children with MDR versus non-MDR isolates identified 10 variables that were significantly associated with colonization or infection with MDR *E. coli*: healthcare acquisition (OR 3.13, 95% CI 1.50–6.55), nosocomial acquisition (OR 3.86, 95% CI 1.14–13.11), cerebrospinal anomaly (OR 3.56, 95% CI 1.45–8.73), genitourinary (GU) tract anomaly (OR 4.68, 95% CI 2.27–9.63), receipt of biologics in the previous 30 days (OR 10.13, 95% CI 2.19–46.82), surgery in the previous 90 days (OR 3.79, 95% CI 1.66–8.6)), presence of an invasive device at the time of culture collection (OR 7.14, 95% CI 3.34–15.30), any hospitalization in the preceding 1 year (OR 3.69, 95% CI 1.94–7.00), and antibiotic use at the time of specimen collection (OR 5.22, 95% CI 2.47–11.06) or within the preceding 3 months (OR 2.25, 95% CI 1.20–4.21) (Table 3). In multivariable analysis, the following variables were independently associated with MDR *E. coli*

Table 1 Demographic and clinical characteristics of children with *E. coli* infection or colonization at Mayo Clinic Children's Hospital, 2012

Characteristic	No. (%) $n = 368$ unless indicated
Age in years, median (IQR)	7 (3–15)
Female	317 (86)
Specimen type	
Urine	331 (90)
Blood	10 (3)
Other[a]	27 (7)
Patient location at time of specimen collection	
Outpatient[b]	315 (86)
Inpatient	53 (14)
Site of acquisition ($n = 365$)	
Community-associated	298 (82)
Health care-associated	53 (15)
Nosocomial	14 (3)
Sexual activity ($n = 349$)	52 (15)
Circumcision ($n = 33$)	15 (45)
Chronic constipation in the previous 1 year ($n = 367$)	54 (15)
Voiding dysfunction in the previous 1 year ($n = 367$)[c]	66 (18)
Intermittent urinary catheterization at time of specimen collection ($n = 366$)	22 (6)
Any hospitalization in the past 1 year ($n = 362$)	99 (27)
Urinary tract infection in the past 1 year ($n = 364$)	103 (28)
E. coli isolates in the past 1 year from any specimen source ($n = 355$)	45 (13)
E. coli infections in the past 1 year from any specimen source ($n = 351$)	40 (11)
Structural/functional anomalies within the past 1 year	
Cerebrospinal	26 (7)
Craniofacial	5 (1)
Genitourinary tract	46 (13)
Transplant in the past 30 days	
Hematopoietic stem cell	0
Solid organ	1 (<1)
Immunosuppressive therapy within the previous 30 days	
Chemotherapy	1 (<1)

Table 1 continued

Characteristic	No. (%)$n = 368$ unless indicated
Biologics[d]	7 (2)
High dose steroids[e]	0
Malignancy in the previous 2 years	
Solid organ	2 (<1)
Hematologic	0
Neutropenia within the previous 14 days[f]	2 (<1)
Mechanical ventilation within the previous 30 days	12 (3)
Extracorporeal membrane oxygenation within the previous 30 days	2 (1)
Dialysis within the previous 3 months	2 (1)
Any invasive device present at time of specimen collection ($n = 366$)[g]	36 (10)
Invasive procedure within the past 90 days	
Surgical	32 (9)
Non-surgical[h]	13 (4)
Any antibiotic use	
At time of specimen collection ($n = 361$)	40 (11)
Within the past 3 months ($n = 360$)	113 (31)
Within the past 12 months ($n = 363$)	196 (54)
Any international travel ($n = 77$)	21 (27)
Prematurity (ages ≤1 month only; $n = 14$)	4 (29)
Diabetes	1 (<1)
Cultures representing true infection ($n = 346$)[i]	318 (92)

IQR interquartile range

[a] Includes non-sterile sources (e.g., wound swabs, surgically collected sterile tissue, peritoneal fluid, bile and respiratory tract specimens)

[b] Includes clinic and emergency room

[c] Abnormal elimination patterns such as frequent or infrequent voids, urgency, infrequent stools/constipation, withholding maneuvers, etc.

[d] Includes TNF-alpha, IL-1 and IL-6 inhibitors

[e] Given daily or on alternate days for 14 days or more at ≥2 mg/kg per day of prednisone or its equivalent, or ≥20 mg/day if patient weighs more than 10 kg

[f] Absolute neutrophil count less than 500 cells/ml

[g] Includes urinary catheter, central venous catheter, arterial line, chest tube, endotracheal tube, tracheostomy tube, dialysis catheter, nephrostomy tube, ventriculo-peritoneal shunt, external ventricular drain, stents and prostheses

[h] Examples include endoscopy, tooth extraction, etc.

[i] Clinical symptoms and objective criteria of inflammation/infection present at site of culture, e.g., UTI symptoms (fever or abdominal pain or dysuria, etc.) and pyuria required for classification as UTI

Table 2 Antimicrobial susceptibility of *E. coli* isolates from 368 pediatric patients at Mayo Clinic Children's Hospital, 2012

Antimicrobial	No. (%) resistant $n = 368$ except where specified
Ampicillin	159 (43)
Beta-lactam/beta-lactamase inhibitor combination	
Ampicillin/sulbactam ($n = 158$)	119 (75)
Piperacillin/tazobactam	3 (1)
Trimethoprim/sulfamethoxazole	73 (20)
Fluoroquinolone	
Ciprofloxacin	24 (7)
Levofloxacin	22 (6)
Aminoglycoside	
Amikacin	1 (<1)
Gentamicin	20 (5)
Tobramycin	14 (4)
1st-generation cephalosporin	
Cephalothin ($n = 331$)	92 (28)
Cefazolin	78 (21)
Extended spectrum cephalosporin	
Ceftriaxone	10 (3)
Cefepime	4 (1)
Carbapenem	
Ertapenem	1 (<1)
Meropenem	1 (<1)
Nitrofurantoin ($n = 332$)	3 (1)
Fosfomycin ($n = 13$)	0 (0)
MDR[a]	46 (13)
3 drug classes	23 (6)
4–7 drug classes	22 (6)
8 drug classes	1 (<1)

[a] MDR defined as resistance to any antibiotic in 3 or more of 8 drug classes, including ampicillin/sulbactam, piperacillin/tazobactam, trimethoprim/sulfamethoxazole (TMP/SMX), fluoroquinolones (ciprofloxacin or levofloxacin), aminoglycosides (gentamicin, tobramycin, or amikacin), 1st- or 2nd-generation cephalosporins (cefazolin, cephalothin, or cefuroxime), extended-spectrum cephalosporins (ceftriaxone, cefotaxime, ceftazidime or cefepime), and carbapenems (meropenem or ertapenem)

Table 3 Univariable analysis of risk factors for multidrug-resistant *E. coli* colonization or infection

Feature	MDR ($n = 46$) No. (%)	Non-MDR ($n = 322$) No. (%)	Odds ratio (95% CI)	*P*
Age in years, median (IQR)	6 (2–14)	7 (3–15)	0.99 (0.94–1.04)	0.64
Gender				
Female	37 (80)	280 (98)	1.0 (reference)	0.23
Male	9 (20)	42 (13)	1.62 (0.73–3.60)	
Race ($n = 360$)				
Caucasian	40 (87)	272 (87)	1.0 (reference)	0.95
All others	6 (13)	42 (13)	0.97 (0.39–2.43)	
Specimen type				
Urine	38 (83)	293 (91)	1.0 (reference)	0.083
Non-urine	8 (17)	29 (9)	2.13 (0.91–4.99)	
Site of acquisition ($n = 365$)				
Community-associated	28 (62)	270 (84)	1.0 (reference)	0.002
Healthcare-associated	13 (29)	40 (13)	3.13 (1.50–6.55)	0.031
Nosocomial	4 (9)	10 (3)	3.86 (1.14–13.11)	
Patient location at time of specimen collection				
Outpatient	35 (76)	280 (87)	1.0 (reference)	0.054
Inpatient	11 (24)	42 (13)	2.10 (0.99–4.44)	
Cerebrospinal anomaly diagnosed within past 1 year	8 (17)	18 (6)	3.56 (1.45–8.73)	0.006
Craniofacial anomaly diagnosed within past 1 year	1 (2)	4 (1)	1.77 (0.19–16.16)	0.61
GU tract anomaly diagnosed within past 1 year ($n = 366$)	15 (33)	31 (10)	4.68 (2.27–9.63)	<0.001
Intermittent urinary catheterization at time of specimen collection ($n = 366$)	4 (9)	18 (6)	1.64 (0.53–5.09)	0.39
Mechanical ventilation within the previous 30 days	1 (2)	11 (3)	0.63 (0.08–4.98)	0.66
Receipt of biologic agent within the previous 30 days	4 (9)	3 (1)	10.13 (2.19–46.82)	0.003
Surgery within the past 90 days	10 (22)	22 (7)	3.79 (1.66–8.63)	0.002
Non-surgical invasive procedure within the past 90 days	4 (9)	9 (3)	3.31 (0.98–11.23)	0.055
UTI in the past 1 year ($n = 364$)	16 (36)	87 (27)	1.53 (0.79–2.97)	0.21

Table 3 continued

Feature	MDR ($n = 46$) No. (%)	Non-MDR ($n = 322$) No. (%)	Odds ratio (95% CI)	*P*
Sexual activity ($n = 349$)	8 (19)	44 (14)	1.36 (0.59–3.13)	0.47
Chronic constipation in the previous 1 year ($n = 367$)	6 (13)	48 (15)	0.85 (0.34–2.12)	0.73
Voiding dysfunction in the previous 1 year ($n = 367$)	9 (20)	57 (18)	1.13 (0.52–2.46)	0.77
Any invasive device present at the time of specimen collection ($n = 366$)	15 (33)	21 (7)	7.14 (3.34–15.30)	<0.001
E. coli isolates in the past 1 year from any specimen source ($n = 355$)	7 (16)	38 (12)	1.36 (0.57–3.27)	0.49
E. coli infections in the past 1 year from any specimen source ($n = 351$)	7 (16)	33 (11)	1.57 (0.65–3.81)	0.32
Hospitalization in the past 1 year ($n = 362$)	24 (53)	75 (24)	3.69 (1.94–7.00)	<0.001
Any antibiotic use at the time of specimen collection ($n = 361$)	14 (32)	26 (8)	5.22 (2.47–11.06)	<0.001
Any antibiotic use within the past 3 months ($n = 360$)	22 (48)	91 (29)	2.25 (1.20–4.21)	0.012
Any antibiotic use within the past 12 months ($n = 363$)	30 (65)	166 (52)	1.71 (0.89–3.25)	0.11

CI confidence interval

infection or colonization: presence of a GU tract anomaly (OR 2.42, 95% CI 1.03–5.68), presence of an invasive device (OR 3.48, 95% CI 1.37–8.83) and antibiotic use at the time of specimen collection (OR 2.62, 95% CI 1.06–6.47) (Table 4).

Similar results were obtained on univariable analysis when children with colonization were excluded, when ampicillin was included as a drug class in the definition of MDR, and when children with MDR *E. coli* were compared with those with PS *E. coli* (data not shown). When the subset of patients with CA infections ($n = 268$) was analyzed, there were 23 (8.6%) MDR specimens and 245 (91.4%) non-MDR specimens. When children with CA MDR infections were compared to those with CA non-MDR infections, hospitalization in the preceding 1 year (OR 3.15, 95% CI 1.25–7.99) was the only risk factor significantly associated with MDR on univariable analysis. When children with CA MDR *E. coli* infections were compared with those with CA PS *E. coli* infections, multivariable analysis revealed that GU tract anomaly (OR 5.23, 1.49–18.32) and hospitalization in the preceding 1 year (OR 2.66, 1.06–6.69) were significantly associated with CA MDR *E. coli* infection.

Outcomes of Infection with MDR *E. coli*

Compared with children with non-MDR infections, children with MDR infections were more likely to have a complex infection (35% vs. 17%, $P = 0.026$), less likely to receive effective empiric antibiotics (47% vs. 74%, $P < 0.001$) and had significantly longer time from culture collection to receipt of effective antibiotics (median 19.2 vs. 0.6 h, $P < 0.001$). The duration of antibiotic treatment was slightly longer for children with MDR infections compared with those with non-MDR infections (11 vs. 10 days, $P = 0.027$). The hospital length of stay was longer for children with MDR infections compared with those with non-MDR infections (10 vs. 4 days, $P = 0.029$). Cure rates did not differ significantly between the groups although

Table 4 Multivariable analysis of risk factors for colonization or infection with MDR *E. coli*

Risk factor	OR (95% CI)	*P*
Genitourinary tract anomaly within the past 1 year	2.42 (1.03–5.68)	0.043
Invasive device at the time of specimen collection[a]	3.48 (1.37–8.83)	0.009
Antibiotic use at the time of specimen collection	2.62 (1.06–6.47)	0.037

OR odds ratio, *CI* confidence interval

[a] Includes urinary catheter, central venous catheter, arterial line, chest tube, endotracheal tube, tracheostomy tube, dialysis catheter, nephrostomy tube, ventriculo-peritoneal shunt, external ventricular drain, stents and prostheses

children with MDR strains tended to have more recurrences than those with non-MDR strains (35% vs. 19%, $P = 0.28$) (Table 5).

DISCUSSION

We determined risk factors associated with MDR *E. coli* causing a variety of infectious syndromes by evaluating a contemporary cohort of children, and demonstrated that children with MDR *E. coli* infections have worse outcomes than those with more drug-susceptible *E. coli* infections.

We found three independent risk factors associated with MDR *E. coli* colonization or infection: presence of a GU tract anomaly, presence of an invasive device, and antibiotic use at the time of specimen collection. Our finding that a child with a pre-existing GU tract anomaly is approximately 2.5 times more likely to be colonized or infected with an MDR *E. coli* strain than a non-MDR strain is consistent with the findings of Topaloglu et al. in their study of risk factors for community-acquired ESBL UTIs (caused by *E. coli* or *Klebsiella* species) in Turkish children [19]. Children with GU tract anomalies often require surgical interventions, intermittent urinary catheterization, and antibiotics for prophylaxis or treatment of frequent UTIs. These factors may explain why these children are at high risk for colonization or infection with MDR *E. coli*. We also found that children with any type of invasive device present at the time of specimen collection were 3.5 times more likely to be colonized or infected with MDR than non-MDR *E. coli*. These children may have healthcare-acquisition of MDR strains, as invasive devices reflect severe illness and extensive healthcare contact. Additionally, they may be heavily colonized with MDR *E. coli* strains due to biofilm formation and disruption of the host microbiome [20, 21], severe illness, and antibiotic exposure. Although the association of drug-resistant *E. coli* and vascular or urinary catheter use has been documented in adult studies [22, 23], this has not been consistently observed in pediatric studies. Zaoutis et al. [12], in a study of children with ESBL-producing Gram-negative bloodstream infections, found that the presence of a central venous or urinary catheter was not a risk factor for ESBL infection. Our inclusion of all types of invasive devices (central venous catheters, ventriculo-peritoneal shunts, etc.) may explain why we found an association between invasive devices and MDR *E. coli* infection. Lastly, previous broad-spectrum antibiotic use is a well-described risk factor for infection with drug-resistant Gram-negative infections in adults and children [9, 12, 13, 24], and our study provides further evidence for this association.

In the subset of children with community-acquired infections, the above risk factors were not significantly associated with MDR *E. coli*, likely because our study was underpowered to detect small differences between groups. However, when we excluded children with isolates that were resistant to 1 or 2 agents (and potentially pre-MDR) from this analysis and compared children with CA MDR *E. coli* to those with CA, pan-susceptible *E. coli*, GU tract anomalies and prior hospitalization were identified as significant risk factors for MDR

Table 5 Comparison of outcomes among children with MDR and non-MDR *E. coli* infections

Outcome	MDR ($n = 34$)[a] *n* (%)	Non-MDR, ($n = 284$) *n* (%)	*P*
Hospitalization for treatment of infection	8 (24)	35 (12)	0.11
Duration of hospitalization in days ($n = 43$)[b]	10 (4.5–20.5)	4 (2–6)	0.029
Complexity of infection[c]			
Complex	12 (35)	49 (17)	0.026
Non-complex	21 (62)	231 (81)	
Unclear[d]	1 (3)	4 (1)	
Number of empiric antibiotics[e]			
1	24 (71)	233 (82)	0.11
>1	10 (29)	51 (18)	
Effective empiric antibiotics[f]	16 (47)	210 (74)	0.001
Time from specimen collection to initiation of effective antibiotic in hours[b, f]	19.2 (1–55)	0.6 (0–6)	<0.001
Duration of total antibiotic therapy in days[b]	11 (9–13)	10 (7–10)	0.027
Outcome of infection			
Cure with no recurrence	22 (65)	218 (77)	0.28
Cure with recurrence	12 (35)	55 (19)	
Death	0	1 (<1)	
Unknown[d]	0	10 (3)	

[a] Excludes children with colonization

[b] Summarized with median (IQR)

[c] A complex infection was defined as *E. coli* infection in any non-urine site or in a child who had any of the following; immune compromise, GU abnormality, upper urinary tract infection or hospitalization. A non-complex infection was defined as *E. coli* UTI in an immunocompetent child without GU abnormalities (except neurogenic bladder) and no evidence of upper urinary tract infection, and who was managed as an outpatient

[d] Due to incomplete information, loss to follow-up or mortality unrelated to *E. coli* infection

[e] Empiric antibiotic was defined as antibiotic administered at the time of culture collection, culture positivity or onset of illness, prior to availability of antimicrobial susceptibility results

[f] Empiric antibiotic was active against isolate in vitro and appropriate for site of infection

infection, likely because there were greater differences in these variables between high-risk and low-risk groups. This suggests that in children, even in community settings, MDR *E. coli* infections tend to occur in those with comorbidities and healthcare exposure, but are not common among relatively healthy subjects.

Our analyses of outcomes of infection with MDR versus non-MDR isolates revealed that children with MDR infections were more likely to have a complex infection, but that the final outcome of infection did not differ between groups. This is similar to findings by Zaoutis et al. who found no mortality differences

between children with ESBL and non-ESBL *E. coli* and *Klebsiella* bloodstream infections [12]. In contrast, a study in Taiwan by Tsai et al. [13] of neonates with MDR Gram-negative bacteremia showed higher mortality among those with MDR than those with non-MDR strains. Similarly, a study in Korea by Kim et al. [9] found higher mortality for children with ESBL *E. coli* and *Klebsiella* bloodstream infections compared to those with non-ESBL-producing strains. The higher mortality observed in these studies compared with our study may be due to more severe infection in the Asian cohorts (which focused on bloodstream infections and included a large proportion of immunocompromised patients), or geographic differences in antimicrobial resistance. It is also likely that our study was underpowered to detect a difference in mortality between the two groups, given that death is an uncommon outcome of *E. coli* infections in children in the United States. This is in contrast to studies of adults with *E. coli* infections which report higher mortalities. We hypothesize that this difference is due to higher prevalence of drug-resistant *E. coli* in the adult population. This higher prevalence is likely a consequence of more frequent antibiotic exposure and healthcare contact in adults compared to children, a higher number of comorbidities; and inclusion of elderly adults resident in chronic care facilities.

In our study, children with MDR isolates were less likely than children with non-MDR isolates to receive effective empiric antibiotics and had a significantly longer time to receipt of effective antibiotics. While this has been reported among neonates in Taiwan with MDR Gram-negative bloodstream infections, this is the first US study to demonstrate a longer time to appropriate antibiotic therapy among children with MDR *E. coli* infections. Clinicians may not anticipate MDR *E. coli* when selecting empiric antibiotics, especially among outpatients, which made up the bulk of our cohort. The longer duration of antibiotic therapy and length of hospital stay noted in children with MDR *E. coli* infections have also not been demonstrated in other pediatric studies, and may be explained by more severe or complicated infections, or delayed effective therapy among patients with MDR strains.

Our study has the following limitations. We collected data retrospectively which may have led to selection and misclassification biases. Our study was conducted in 2012 and, although our hospital antibiogram has not indicated a change in resistance patterns to suggest that MDR *E. coli* has expanded more broadly in the community, more recent studies to confirm or refute this are necessary. Urine was the predominant source of *E. coli* isolates in this study, so our findings may not be applicable to infections or colonization at other body sites. We had few MDR and ESBL isolates and may have had insufficient power to detect differences between some risk factors and outcomes, especially in the subgroup analysis of CA infections. We did not collect data about diet, pets, and household contacts with infection, all of which have been previously implicated in CA *E. coli* infections [25–28], as medical records regarding these exposures were incomplete. Although we captured the bulk of antibiotic exposures in our cohort, we may have missed antimicrobials that were prescribed outside of Mayo Clinic. Lastly, our study was conducted in a single geographic region and limited to individuals who provided MN research authorization. Therefore, findings may not be generalizable to other communities or institutions with different patient populations and antibiotic resistance phenotypes.

CONCLUSION

In conclusion, in our region of the US Upper Midwest, MDR *E. coli* infections were associated with genitourinary tract anomaly, history of recent invasive devices, and recent antibiotic use, and poor outcomes, including delay in initiation of effective antibiotic therapy and longer hospital stay. Our findings demonstrate the need for strategies to predict, prevent and treat drug-resistant *E. coli* infections, particularly those caused by MDR strains. Such strategies might include implementation of inpatient and outpatient antibiotic stewardship programs, improved infection control practices, provider education about the epidemiology,

outcomes, and risk factors for MDR *E. coli* infections, and the development of novel diagnostics that enable rapid detection of MDR *E. coli*.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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