Multiresistant *E. coli* urine infections in children: a case–control study

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**ABSTRACT**

**Objective** Urinary tract infections (UTIs) caused by resistant organisms are increasing which poses challenges when selecting empirical antimicrobial therapy. The aim of this study is to determine risk factors for multiresistant *Escherichia coli* UTIs in children.

**Design** We included all reported urinary isolates from a children’s hospital collected between January 2010 and June 2013. Patients who had multiresistant *E. coli* UTIs were identified and a retrospective review of medical records performed. Patient-specific clinical and demographic factors were compared with age-matched and gender-matched controls with non-multiresistant *E. coli* UTIs. Univariable and multivariable statistical analysis were performed to determine significant risk factors for multiresistant organism *E. coli* UTIs.

**Results** In total, there were 2692 positive urine cultures, 1676 (62.3%) from 1169 patients were *E. coli*. Multiresistant *E. coli* was isolated from 139 (8.3% of all *E. coli*) cultures in 99 patients. Thirteen incomplete medical records were excluded, leaving 86 patients, matched with 86 controls. In multivariable regression, the only significant risk factor was antibiotic use in the previous month (adjusted OR 3.0, 95% CI 1.4 to 6.2), but not previous hospital admission (adjusted OR 1.4, 95% CI 0.6 to 2.9), being an inpatient at the time of diagnosis (adjusted OR 2.4, 95% CI 0.8 to 7.4) and previous instrumentation (adjusted OR 1.0, 95% CI 0.4 to 2.4).

**Conclusions** This is the first case–control study to examine multiresistant UTI in Australian children. Clinicians should be judicious in the use of antibiotics in treatment and prophylaxis of UTIs. In children presenting with UTI and recent antibiotic exposure, amoxicillin-clavulanic acid appears to be an appropriate empiric antibiotic choice in our population.

**INTRODUCTION**

Urinary tract infections (UTIs) are among the most common bacterial infections of childhood. Correct choice of empiric antibiotic therapy is important because delay in initiating appropriate treatment of UTI in children may lead to morbidity associated with pyelonephritis or bacteraemia and may increase the risk of long-term renal damage in predisposed children.1 However, the rise in prevalence of UTIs caused by resistant organisms creates challenges when deciding on empiric antibiotic therapy.2–7

Choice of empiric therapy should be guided by local patterns of antibiotic resistance as well as patient-specific characteristics. Some of the patient-specific factors which have been shown to be associated with a risk of UTIs caused by resistant organisms include antimicrobial exposure9–14 from 30 to 84 days prior to UTI diagnosis,2 9 15 use of prophylactic antibiotics in children who had recurrent UTI,2 4 8 14–16 multiple hospital admissions and international travel.2 17 Additionally, several studies have identified urological anomalies as a risk factor.2 10 13 18 However, children with urological abnormalities will often have been exposed to other risk factors such as hospitalisation and prior antibiotic exposure, and in general, these previous studies have not specified whether children with isolated genitourinary abnormalities without antibiotic exposure are at an increased risk of resistant UTI.

In order to guide empiric antibiotic choice, we sought to report the pattern of organisms associated with UTIs in a contemporary cohort of hospitalised children. To identify risk factors for development of multiresistant organism (MRO) UTIs, we performed a case–control study specifically of children with multiresistant *E. coli* UTI.

**MATERIALS AND METHODS**

In this study, we describe bacterial species isolated from positive urine cultures in children aged 18 years and younger at Sydney Children’s Hospital between 2010 and 2013 and conducted a case–control study.
within this population to identify risk factors for multiresistant E. coli UTI.

Urine cultures included were those with reported significant microbial growth (positive) collected from children aged 18 years and younger who were patients of Sydney Children’s Hospital between January 2010 and June 2013. All urine samples were processed in a single laboratory according to standardised protocols, and antibiotic susceptibility testing was performed using the calibrated dichotomous sensitivity (CDS) method. A significant growth in urine samples collected by either clean catch or freshly inserted catheter was defined as ≥10⁷ organisms/L. Any growth was considered significant if samples were collected from suprapubic aspirates or at cystoscopy. Urine cultures obtained from ileal conduits, nephrostomies, bag and pouch urines were excluded. Urine samples that did not specify a method of collection were also excluded.

MRO were defined according to the 2011 international consensus statement as organisms with acquired resistance to one or more antibiotics in three or more different antibiotic classes. We described the presence of multiresistant Gram-negative organisms as these are the most common causative organisms for UTIs. The antibiotic classes considered for E. coli were nitrofurantoin, penicillins, cephalosporins, carbapenems, sulfonamides, quinolones, aminoglycosides, monobactams and polypeptides.

Patient-level information obtained from the pathology database was name, date of birth, medical record number, sex, date sample was received, location of patient, method of collection, isolate and antimicrobial susceptibilities. The antibiotic susceptibilities routinely analysed for E. coli were nitrofurantoin, ampicillin, amoxicillin, amoxicillin-clavulanic acid, cephalozin, cephalaxin, ceftriaxone, cepafelime, imipem (as a surrogate for meropenem), sulfadiazine, trimethoprim, norfloxacin, gentamicin and amikacin.

In our case–control study, cases were children who had a positive urine culture with a multiresistant E. coli. These were matched 1:1 with a control group, drawn from children who had a positive urine culture with a non-multiresistant E. coli. Controls were matched to cases for age and gender. If there was more than one age-matched and gender-matched control, the control patient with a positive urine culture closest in time frame to the case patient was chosen. Case patients who had multiple episodes of UTIs during the study time period had the earliest episode analysed. Patient-specific clinical and demographic factors were compared between groups.

When planning the study, we calculated the sample size required for a case-control study with one control per case. We estimated the probability of exposure among controls as 0.25. If the true OR for disease in exposed subjects relative to unexposed subjects was 2.5, we would need 84 patients per group to be able to reject the null hypothesis that this OR equals 1 with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis was 0.05.

Demographic risk factors analysed were country of birth and Aboriginal (Australian Indigenous) ethnicity. Aboriginality was self-reported by parents or carers. Subjects were also assigned to a decile representing socioeconomic status, using residential postcode and the Index of Relative Socioeconomic Advantage and Disadvantage from the Australian Bureau of Statistics. A postcode that was on the fourth decile or lower was classified as in the lower socioeconomic group and a postcode that was on the fifth decile and over was classified as the higher socioeconomic group. We also included whether the child was covered by private health insurance as another marker of socioeconomic status.

Further data about potential risk factors obtained from patient records included antibiotic exposure in the previous month, including prophylactic antibiotics—either for UTIs or for other infections, for example, co-trimoxazole as Pneumocystis jirovecii pneumonia prophylaxis in patients undergoing chemotherapy; current treatment with antibiotic therapy (within the last 24 hours); history of previous UTI; previous hospital admission and any documented overseas travel. Previous instrumentation of the genitourinary tract encompassed catheterisation (including intermittent catheterisation, suprapubic catheterisation and catheterisation for radiological procedures) surgical procedures (including cystoscopy and complex genitourinary surgery) and a combination of both. Immunosuppression was defined as a patient being on current immunosuppressive medication for solid organ transplantation and patients currently being treated with chemotherapy for malignancy. Genitourinary abnormalities included vesicoureteric reflux, urinary tract obstruction and other congenital anomalies of the kidney and urinary tract. Neurogenic bladder was classified separately and included children with a spinal cord abnormality and diagnosed neurogenic bladder, including children who performed intermittent catheterisation and those who did not.

Univariable and multivariable statistical analyses were performed using SPSS V23. A X² analysis was performed on all the documented risk factors. For risk factors that had a p-value of <0.05 on univariable analysis, a conditional logistic regression analysis was then performed.

RESULTS

A total of 2692 positive urine cultures were obtained during this study period from 1832 individual patients (figure 1). Of these 2202 (82%) were due to Gram-negative organisms (online supplementary file 1) and 308 (11.4%) were caused by multiresistant Gram-negative organisms. E. coli was the causative organism of 1676 (62%) UTIs in 1169 patients and was the most
commonly isolated MRO (139, 5% of all UTI, 8.3% of all *E. coli* infections). Sixty-two *E. coli* (3.7% of all *E. coli*) were classified as extended spectrum beta-lactamase (ESBL) producers. See figure 2 for antibiotic resistance in MRO *E. coli* isolates.

The 139 MRO *E. coli* infections occurred in 99 children, 86 of who were included in the case–control study. The median age of both cases and controls was 2.8 (range 0–16.2) years and 65% were females. The patient characteristics and covariates analysed are in table 1. The antibiotic resistance of *E. coli* in this study population is shown in the appendix 2 in the online supplementary file 1.

On univariable analysis, being an inpatient at the time of diagnosis, antibiotic use in the previous month, previous hospital admission and previous instrumentation were associated with an increased risk of MRO *E. coli* UTIs (table 1). Having a known urological anomaly failed to reach statistical significance at *p*=0.05. Overseas travel and number of people in the household were not reported due to a large amount of missing data and poor documentation in the medical record. Aboriginality was recorded but was not analysed as there were only two patients who identified themselves as aboriginal.

When a multivariable logistic regression analysis was performed on the risk factors with a *p* value of <0.05 on univariable analysis, only antibiotic use in the previous month (including antibiotic prophylaxis) was associated with an increased risk of multiresistant *E. coli* UTIs (adjusted OR 3.0, 95% CI 1.4 to 6.2; *p*<0.01). These results are shown in table 2.

**DISCUSSION**

In this study, we found that 6% of UTIs diagnosed in an Australian tertiary children’s hospital were caused by multiresistant Gram-negative organisms. As expected, the majority of all UTI as well as more than half of multiresistant infections were caused by *E. coli*. In our case–control analysis, we found that prior antibiotic use, including antibiotic prophylaxis was the sole significant risk factor for MRO *E. coli* UTI in children. Being an inpatient at the time of diagnosis, previous hospital admission and previous instrumentation were significant risk factors on univariable analysis but not on multivariable analysis.

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**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All patients, n=172 (%)</th>
<th>Cases, n=86 (%)</th>
<th>Controls, n=86 (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>71 (41.3)</td>
<td>35 (40.1)</td>
<td>36 (41.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1–6</td>
<td>40 (23.3)</td>
<td>20 (23.3)</td>
<td>20 (23.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;6</td>
<td>60 (34.9)</td>
<td>30 (34.9)</td>
<td>30 (34.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Female Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>112 (65.1)</td>
<td>56 (65.1)</td>
<td>56 (65.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VUR</td>
<td>23 (13.4)</td>
<td>14 (16.3)</td>
<td>9 (10.5)</td>
<td>1.7 (0.7 to 4.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>3 (1.2)</td>
<td>3 (3.5)</td>
<td>0 (0)</td>
<td>7.3 (0.4 to 143)</td>
<td>0.08</td>
</tr>
<tr>
<td>Complicated/other</td>
<td>28 (16.3)</td>
<td>16 (18.6)</td>
<td>12 (15.0)</td>
<td>1.4 (0.6 to 3.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>14 (8.1)</td>
<td>9 (10.5)</td>
<td>5 (5.8)</td>
<td>1.8 (0.6 to 5.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Antibiotic use in the previous month</td>
<td>69 (40.1)</td>
<td>48 (55.8)</td>
<td>21 (24.4)</td>
<td>3.9 (2.0 to 7.5) &lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis†</td>
<td>33 (18.8)</td>
<td>25 (29.1)</td>
<td>8 (9.3)</td>
<td>3.8 (1.6 to 9.0) &lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Current antibiotic treatment</td>
<td>12 (7.0)</td>
<td>9 (10.5)</td>
<td>3 (3.5)</td>
<td>3.1 (0.8 to 11.8) 0.10</td>
<td></td>
</tr>
<tr>
<td>Inpatient at time of diagnosis</td>
<td>24 (14.0)</td>
<td>18 (16.3)</td>
<td>6 (2.3)</td>
<td>3.5 (1.3 to 9.3) 0.01</td>
<td></td>
</tr>
<tr>
<td>Previous hospital admission</td>
<td>89 (51.7)</td>
<td>55 (64.0)</td>
<td>34 (39.4)</td>
<td>2.4 (1.3 to 4.5) &lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Previous instrumentation</td>
<td>42 (24.4)</td>
<td>28 (32.6)</td>
<td>14 (16.3)</td>
<td>2.2 (1.1 to 4.6) 0.03</td>
<td></td>
</tr>
<tr>
<td>Previous UTI</td>
<td>67 (40.0)</td>
<td>40 (46.5)</td>
<td>27 (31.4)</td>
<td>1.8 (0.95 to 3.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>10 (5.8)</td>
<td>8 (9.3)</td>
<td>2 (2.3)</td>
<td>4.5 (0.93 to 21.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Born in Australia</td>
<td>163 (94.8)</td>
<td>83 (96.5)</td>
<td>80 (93.0)</td>
<td>0.6 (0.14 to 2.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Private health insurance</td>
<td>72 (41.9)</td>
<td>37 (43.0)</td>
<td>35 (40.7)</td>
<td>0.8 (0.4 to 1.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>Postcode decile (five and above)</td>
<td>153 (89.0)</td>
<td>77 (89.5)</td>
<td>76 (88.4)</td>
<td>1.1 (0.4 to 3.1) 0.80</td>
<td></td>
</tr>
</tbody>
</table>

* Cases and controls were matched for age and gender.
† Antibiotic use in the previous month included antibiotic prophylaxis.
MR, multiresistant; NA, not applicable; UTI, urinary tract infection.

**Table 2** Risk factors analysed by multivariable logistic regression

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR (95% CI)</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use in the previous month</td>
<td>3.0 (1.4 to 6.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inpatient at time of diagnosis</td>
<td>2.4 (0.8 to 7.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous instrumentation</td>
<td>1.0 (0.4 to 2.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>Previous hospital admission</td>
<td>1.4 (0.6 to 2.9)</td>
<td>0.43</td>
</tr>
</tbody>
</table>
This is the first case–control study to examine risk factors for multiresistant *E. coli* in Australian children. The setting of a tertiary children’s hospital allowed inclusion of a broad range of children, including some more likely to have complicated medical conditions, previous hospital admissions and urological abnormalities. Our reported prevalence of 8.3% of multiresistant *E. coli* is almost identical to a recent American study set in the emergency department and primary care clinics of a university affiliated hospital at 8.9%.17

To our knowledge, this is the first case–control study conducted in children using the current international consensus definition of multiresistant *E. coli* UTI as resistance to three or more antibiotic classes.20 The study is thus more inclusive than previous studies which identified risk factors in different settings or analysed resistance in ESBL producers or organisms or with resistance to specific antimicrobials only.2 12 13 14

The main finding of this study adds to the growing body of evidence regarding the risks of extensive antibiotic use for individuals. A recent meta-analysis of five studies found that urinary bacterial isolates from children who had received previous prescriptions for antibiotics in primary care were more than 10 times likely to be resistant to antibiotics (not necessarily multiresistant).21 Furthermore, the findings of one study suggested that this increased risk could persist for up to 6 months after antibiotic use.9

Local antibiotic susceptibilities are important in informing guidelines for empiric antibiotic selection. In this study, there were no organisms resistant to imipenem. All MRO *E. coli* isolates were resistant to ampicillin, likely due to the presence of more than one beta-lactamase-producing gene as almost 50% of *E. coli* possess a TEM beta lactamase. Empiric oral antibiotic selection is more limited if MRO is suspected or confirmed. In our study, nitrofurantoin was the oral agent with the lowest resistance rate but, while it reaches high concentration in urine, nitrofurantoin has poor tissue penetration and may therefore be ineffective in treating pyelonephritis. Oral nitrofurantoin is also not readily available in liquid form. Therefore, empiric use of nitrofurantoin should be restricted to episodes of cystitis in older children. Amoxicillin-clavulanic acid was the only other oral agent to which most of the multiresistant *E. coli* were susceptible. Therefore, in a child with known prior antibiotic exposure including children on prophylactic antibiotics, oral amoxicillin-clavulanic acid appears to be a suitable first-line oral agent while awaiting confirmed antibiotic sensitivities. In our patient group, if an intravenous agent is required in a child who is septic and in need of urgent treatment, with MRO suspected, then intravenous meropenem could be considered. During this study period, intravenous amoxicillin-clavulanic acid was not available in Australia.

This study has several limitations. As a retrospective study, some potential risk factors, particularly international travel and numbers of people in the household, were poorly documented in the medical record. As we relied on documentation, it is possible that a full history of prior antibiotic use was not obtained and some other data may have been missing. We did not analyse clinical presentations of the patients, which could be included in future studies to determine if this factor assists in the prediction of antibiotic resistance. Our study population was generally of a high socioeconomic background and it is possible we were underpowered to show an influence of sociodemographic factors on MRO prevalence.

**CONCLUSIONS**

This case–control study in Australian children confirms that prior antibiotic exposure is a risk factor for UTI with MRO, and therefore clinicians should be judicious in the use of antibiotics for both prophylaxis and empiric treatment of UTIs. This includes the need for accurate clinical, bedside and laboratory diagnosis to reduce unnecessary courses of antibiotic therapy. In children presenting with UTI with recent antibiotic exposure (including prophylaxis), amoxicillin-clavulanic acid appears to be an appropriate empiric oral antibiotic choice in our population. Further prospective studies should be conducted to further elucidate risk factors for developing MRO UTIs.

**Contributors** SK initially proposed the idea for the project, the study design and was the main supervisor of GR. GR performed the literature review, collected and analysed data and wrote the draft manuscript. Data analysis was supported by KAM, biostatistician. PT supplied data and contributed to data analysis. BM, SK and PT were involved in writing the final manuscript. The guarantor of this paper is SK.

**Competing interests** None declared.

**Ethics approval** Human Research Ethics Committee at the Sydney Children’s Hospital Network and the SESIAHS Northern Hospital Network.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*Arch Dis Child* 2018 103: 336-340 originally published online September 12, 2017
doi: 10.1136/archdischild-2017-312831

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