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Multidrug resistance in urinary *E. coli* higher in males compared to females

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Abstract

Background Urinary tract infections (UTIs) are common however the widespread use of antibiotics has led to a rise in antimicrobial resistance (AMR) amongst uropathogens, rendering a significant proportion of infections resistant to first line treatment. AMR in UTIs may differentially affect men and women, younger and older patients. The purpose of this study was to investigate MDR (multi-drug resistance) and AMR in males and females in an Australian health district.

Methods There were 85,844 *E. coli* urinary isolates (2007–2020) analysed from adult patients. An *E. coli* isolate with MDR was defined as resistant to at least 1 agent in ≥ 3 antimicrobial classes. Chi-square tests and relative risk were calculated by comparing resistance in males and females and by age for antibiotics commonly used to treat UTIs in hospital and community collected samples.

Results There was a higher proportion of MDR *E. coli* in males compared to females in both the community (6.4% vs. 5.2%, $P < 0.001$) and hospital datasets (16.5% vs. 12.8%, $P < 0.001$). The proportions of MDR for both males and females were significantly higher in the hospital setting. Resistance rates were higher in males compared to females for amoxicillin, amoxicillin/clavulanate, cephalexin and norfloxacin ($p < 0.005$), though not for trimethoprim. Antibiotic resistance was seen to increase over time.

Conclusions A higher proportion of MDR *E. coli* were noted in urine samples from males compared with females, possibly due to the increased likelihood of prior treatment for UTIs in men. Antimicrobial stewardship interventions could be targeted towards this cohort to address increasing rates of AMR.

Keywords *E. coli*, Antibiotic resistance, Urinary tract infections, Multidrug resistance

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Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections and reason for urological referral [1]. Women are at a greater risk of UTIs than men and the risk increases with age [1]. In men, UTIs are associated with increasing age and underlying urinary tract disorders such as benign prostatic hypertrophy [2, 3]. In both men and women, the most common uropathogen causing UTIs is *Escherichia coli*, responsible for over half of urinary tract infections [4]. Antibiotic treatment failure can result in urinary sepsis, renal abscesses and impairment of renal function [5].

Antimicrobial resistance (AMR) and multi-drug resistance (MDR) *E. coli* are a major threat to public health outcomes due to limited treatment options [6]. Whilst AMR is a naturally occurring phenomenon in bacteria, resistance accelerates when antimicrobials are misused or overused [7, 8]. Almost 50% of prescribed antimicrobials to patients may be unwarranted [8]. It is recognised that the *E. coli* antimicrobial resistance levels are on the rise [9]. *E. coli* gain resistance through horizontal gene transfer. The common mechanisms involve genes that code for extended-spectrum beta-lactamases (ESBLs), as well as mobile genetic elements such as integrons, transposons and conjugative plasmids [10]. Amoxicillin resistance is common in *E. coli* and frequently conferred by the TEM-1/TEM-2 β-lactamase [11]; because of the high level of resistance, amoxicillin is not recommended as empiric therapy for UTI [12]. For trimethoprim and fluoroquinolones, resistance through mutations in dfrA and qnr genes respectively are often co-located with ESBLs [13, 14].

Limited literature exists on the comparisons of AMR between males and females [15–17]. To the best of our knowledge, no literature exists in Australia. The rising rates of MDR *E. coli* pose significant risks for treatment failures and complications, necessitating an urgent examination of resistance patterns in different populations. We previously demonstrated increasing rates of resistance in community and hospital settings [11]. Using these databases, we compared urinary *E. coli* MDR rates between men and women in the region of the Illawarra Shoalhaven Local Health District (ISLHD) of New South Wales, Australia. Secondary aims included examining differences in AMR based on age, and on community and hospital laboratory settings.

Materials and methods

Setting

The Illawarra Shoalhaven region is serviced by one public hospital-based laboratory at the Wollongong Hospital, part of the NSW Health Pathology network, and primarily by one private laboratory Southern.IML Pathology (S.IML). S.IML largely receives outpatient referrals from general practitioners and specialists, via 85 community-based collection centres [11]. The pathology has an outreach collection service which is responsible for sample collection in residential-aged care facilities. It also services five private hospitals that do not have an emergency department [11]. Approximately 2% of urine specimens processed by S.IML come from private hospitals in the area and the rest are from community isolates [11]. Similarly, Wollongong Hospital NSW Health Pathology has its laboratory based at Wollongong Hospital, with samples mainly from inpatient and ED referrals. It services eight public hospitals with two intensive care units and five emergency departments. Approximately two thirds of urine samples processed by NSW Health Pathology at Wollongong Hospital facility originate from emergency departments [11]. This study uses data from both laboratories. For the purpose of this study, urine samples processed by the S.IML laboratory is defined as community and samples processed by NSW Health pathology as hospital.

Data collection

Ethics approval was obtained through the ISLHD UOW Joint Human Research Ethics Committee (2019/ETH03729). *E. coli* urinary isolate data including susceptibility results obtained from S.IML pathology over the period 1/1/2007–31/12/2018 was combined with NSW Health Pathology-Wollongong Hospital data over the period 1/1/2007–31/12/2020. Upon receipt in the laboratory, urine samples were processed using standard microbiological procedures. The majority of samples in the laboratory are mid-stream according to the clinical request form. Test collection instructions include transportation to the laboratory within one hour or refrigeration at 4 °C during transit to preserve the integrity of the sample in the instance of any delay. Upon receipt in the laboratory, urine samples were inoculated onto blood agar, MacConkey agar, and CHROMagar media for bacterial isolation according to local laboratory protocols. Plates were incubated at 37 °C for 24–48 h. A culture was considered positive for UTI if the bacterial count was $\geq 10^7$ colony-forming units (cfu) per litre, based on standard laboratory recommendations. This cut off is widely used for UTI diagnosis in clinical practice [18], and previous studies examining antimicrobial resistance have similarly employed this criterion [15, 17, 19]. Samples yielding three or more bacterial species were classified as contaminated and excluded from further analysis. Data included date of isolation, site of collection, organism identification, and susceptibility results. Antibiotics tested included amoxicillin, amoxicillin/clavulanate, cephalexin, ciprofloxacin, nitrofurantoin, trimethoprim. Because nitrofurantoin was not consistently reported by both laboratories, this agent was excluded. There was a short period where quinolone

therapy was unavailable in Australia, and so norfloxacin disc testing was interrupted. Susceptibility testing was performed as described previously [11]. Briefly, AMR to the five antimicrobials assessed was determined using the Calibrated Dichotomous Susceptibility (CDS) method in the hospital laboratory and in the community laboratory until 2014, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method in the community laboratory thereafter [11]. Interpretation of results was conducted in accordance with established clinical breakpoints for *E. coli* susceptibility. For each patient, only the first isolate was included per year.

Statistical analysis

Data analysis was conducted using R Studio (R Foundation for Statistical Computing, Vienna, Austria). Data from patients under 18 years old were excluded. The population was divided into two age groups: younger (under 65) and older (65 and above). MDR was defined according to an international expert proposal from the European Centre for Disease Prevention and Control (ECDC) and Centers for Disease Control and Prevention (CDC), whereby MDR was defined as resistance to at least 1 agent in ≥3 antimicrobial classes [20]. Chi-square and relative risk analyses were conducted to evaluate the difference in antibiotic resistance between males and females for the two age groups for the two databases to allow for comparison between hospital collected samples and community collected samples. A Bonferroni correction was applied to account for multiple comparisons for both MDR (significant at $P<0.01$) and AMR (significant at $P<0.005$) analyses.

Results

There were 58,632 urine samples that isolated *E. coli* from the community and 27,212 from the hospital laboratory (Table 1). The hospital cohort were older than the community cohort (Community: median 64, interquartile range (IQR) 77−45; Hospital: median 74, IQR 83−56). The majority of the samples were from females in both community and hospital settings (88.5% and 81.4%, respectively). There was a higher proportion of males in the older age group compared to younger in both community and hospital settings (Table 1).

MDR *E. coli* isolates were significantly more common in males compared to females in both community (432/6719, 6.4% vs. 2681/51913, 5.2%, $P<0.001$) and hospital (833/5057, 16.5% vs. 2846/22155, 12.8%, $P<0.001$). MDR *E. coli* as a proportion were more than double in the hospital (3,679/27,212, 13.5%) compared to the community (3,113/58,632, 5.3%).

Figure 1 shows MDR trends over the study period in males and females, in both hospital and community settings. MDR in males rose from 8.1 to 21.2% in the hospital, and from 2.9 to 9.8% in the community. For females, similar rises were observed from 7.4 to 18.6% in the hospital, and from 1.8 to 7.4% in the community setting. MDR rate of increase was higher in males [$R^2=0.866$ (community); 0.815 (hospital)], compared to females [$R^2=0.869$ (community); 0.902 (hospital)].

There was a significantly higher relative risk for MDR in males compared to females for both age groups ($P<0.01$) in the hospital (Table 2). The rate of MDR in males were also higher than in females in the community, however, the difference did not reach statistical significance (Table 2).

In the community, resistance of amoxicillin was significantly higher in younger (<65) males compared to younger females ($P<0.005$). In contrast, resistance was higher in older males for amoxicillin/clavulanate and for cephalexin ($P<0.005$). However, resistance to trimethoprim was higher in older (≥65) females compared to older males ($P<0.005$).

In the hospital isolates, resistance rates were significantly higher in males compared to females in both age categories for four out of the five antibiotics tested, with the exception of trimethoprim. The relative risks ranged from 1.11 to 1.95 (Table 2). The highest resistance was observed for amoxicillin (over 40% in all subgroups, Table 2).

Discussion

The major finding of this study was the higher proportion of MDR *E. coli* isolated in males compared to females in both the community and hospital settings. To the best of our knowledge, this is the first study to report this association in Australia. Our study also confirmed that MDR *E. coli* is higher in the hospital setting for both males and females, with the highest rate among older males (16.6%).

Table 1 Overall demographics of urine samples from community and hospital settings

	Community		Hospital	
	Male (*n*=6,719)	Female (*n*=51,913)	Male (*n*=5,057)	Female (*n*=22,155)
Age n (%)				
Younger (<65)	2411 (35.9%)	27,158 (52.3%)	1326 (26.2%)	8092 (36.5%)
Older (≥65)	4308 (64.1%)	24,755 (47.7%)	3731 (73.8%)	14,063 (63.5%)
MDR	432 (6.4%)	2681 (5.2%)	833 (16.5%)	2846 (12.8%)

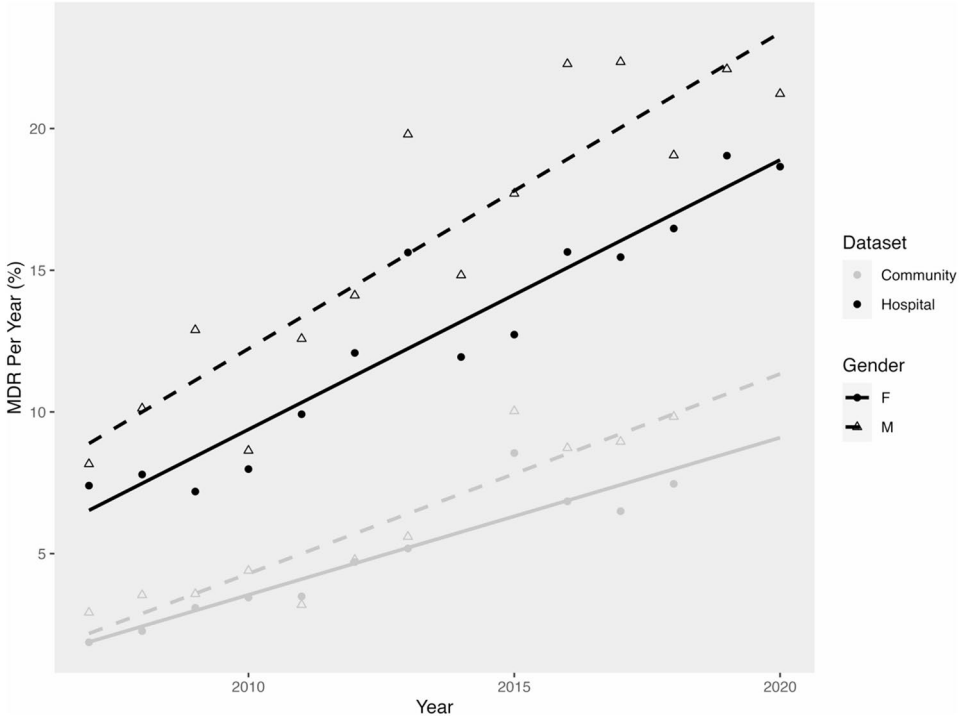


Fig. 1 Trend in MDR over the data-collection periods for both male (Δ, dashed line) and female (●, solid line) patients in community (grey) and hospital (black) datasets. The x-axis represents year, and the y-axis represents total MDR percentage per year

Importantly, we also demonstrated increasing MDR *E. coli* over time in both sexes, more markedly in males, in both hospital and community settings.

The finding of greater MDR rates in males is notable given that UTIs are far more common in females. A systemic review and meta-analysis found that females are 27% more likely than males to be prescribed antibiotics in primary care settings [21]. Limited data comparing MDR in urinary *E. coli* isolates by gender is available. Antibiotic resistance has been found more commonly in urinary *E. coli* isolates from males than from females [15, 22–24]. One smaller study examining community-acquired UTI demonstrated statistically higher MDR in *E. coli* isolates in males [16]. This could be due to the fact that when UTIs occur in males, they are more likely to be associated with structural abnormalities (i.e. renal stones, malignancies, long term stents, etc.) resulting in challenges in eradicating infection, increased antibiotic use and enabling development of resistance [25].

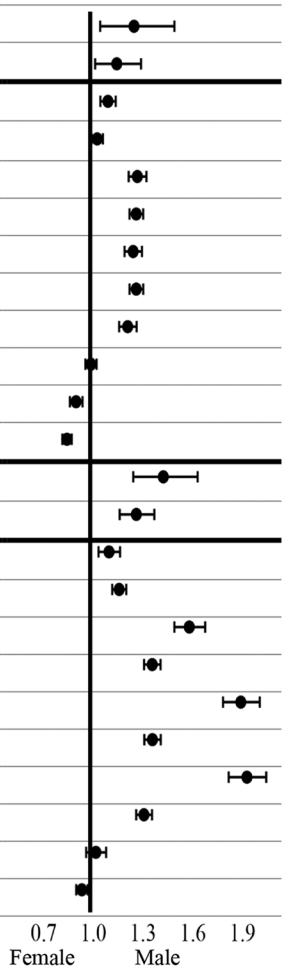
MDR rates are expectedly higher in the hospital setting compared to community, likely due to the higher complexity of patients presenting for tertiary care [26, 27], whereas uncomplicated UTIs are largely diagnosed and managed in the community [28]. Our findings of increasing MDR over time is alarming and reflects the increasing resistance globally. A study in the United States indicated that the prevalence of MDR urinary *E. coli* increased from 9.1 to 17.0% between 2001 and 2010 [29]. Similarly, in Australia, MDR rates increased from 4.5% in 2008 to 7.6% in 2012 [30],. In our study, MDR rates of 6.4% in the community, and as high as 16.5% in the hospital are worrying since Australia is considered a low prevalence country for AMR.

Identifying the mechanisms of MDR was beyond the scope of this study. Increasing rates of MDR *E. coli* are associated with extended-spectrum beta-lactamases (ESBLs) and co-located resistance mechanisms on transferable plasmids [31]. ESBL-producing *E. coli* have increased in Australia [32], and have been found more commonly in urinary samples from men [22]. Some of the risk factors associated with ESBL-producing *E. coli* infections include urinary stones, use of broad-spectrum antimicrobials, advanced age, prior surgeries, indwelling catheters, and recent prescription of antibiotics [33–35]. Infections caused by MDR bacteria, including ESBLs, result in poorer clinical outcomes [36].

In the hospital setting, significantly higher AMR was seen in males, compared to females, for four of the five tested antibiotics, except trimethoprim. According to the national antibiotic guidelines, trimethoprim is recommended as a first-line oral empirical antibiotic for uncomplicated UTIs due to low risk of adverse outcomes from treatment failure [12]. It could be postulated that trimethoprim resistance is higher in females as a result of trimethoprim exposure, since a greater proportion of uncomplicated infections occur in this group. Our

Table 2 MDR and antibiotic resistance in males and females for urinary *E. Coli* samples isolated in community and hospital settings, by age group

			Male			Female				
	Antibiotic	Age group	Total (n)	R (n)	R (%)	Total (n)	R (n)	R (%)	Corrected p-value*	Relative risk (95% CI)
Community	MDR	Younger	2411	130	5.4%	27158	1171	4.3%	0.015	
		Older	4308	302	7.0%	24756	1510	6.1%	0.025	
	Amoxicillin	Younger	2410	1826	42.4%	27170	10078	40.7%	P<0.001	
		Older	4306	1129	46.9%	24773	11495	42.3%	0.035	
	Amoxicillin/ Clavulanate	Younger	2410	260	6.0%	27157	1170	4.7%	0.011	
		Older	4304	113	4.7%	24754	991	3.7%	P<0.001	
	Cephalexin	Younger	2411	259	6.0%	27158	1165	4.7%	0.042	
		Older	4306	89	3.7%	24759	796	2.9%	P<0.001	
	Norfloxacin	Younger	2256	214	5.4%	25198	1221	5.4%	0.062	
		Older	3984	95	4.2%	22834	865	3.4%	0.980	
	Trimethoprim	Younger	2411	683	15.9%	27163	4568	18.5%	0.071	
		Older	4305	382	15.9%	24765	4703	17.3%	P<0.001	
Hospital	MDR	Younger	1326	214	16.1%	8092	953	11.8%	P<0.001	
		Older	3731	619	16.6%	14063	1893	13.5%	P<0.001	
	Amoxicillin	Younger	1327	646	48.7%	8109	3544	43.7%	P<0.001	
		Older	3735	1814	48.6%	14093	5825	41.3%	P<0.001	
	Amoxicillin/ Clavulanate	Younger	1323	135	10.2%	8098	517	6.4%	P<0.001	
		Older	3736	429	11.5%	14101	1178	8.4%	P<0.001	
	Cephalexin	Younger	1328	109	8.2%	8116	349	4.3%	P<0.001	
		Older	3739	314	8.4%	14122	862	6.1%	P<0.001	
	Norfloxacin	Younger	1325	109	8.2%	8112	343	4.2%	P<0.001	
		Older	3734	272	7.3%	14112	776	5.5%	P<0.001	
	Trimethoprim	Younger	1327	269	20.3%	8114	1590	19.6%	0.592	
		Older	3738	660	17.7%	14116	2624	18.6%	0.199	



R = resistant

P values calculated compare males and females within each age group

* = Bonferroni correction for multiple comparisons (For AMR, significant at P<0.005, for MDR, significant at P<0.01).

AMR – Antimicrobial Resistance

MDR – Resistant to at least 1 agent in ≥3 antimicrobial classes

findings are consistent with increased rates of resistance (20%) to trimethoprim among urinary *E. coli* isolates in Australia [12], which is worrying, since this is the first-line antibiotic recommended for treatment of uncomplicated UTIs in our country [12]. Our findings indicate that caution should be exercised in using trimethoprim as a first line agent in UTIs, due to a higher rate of resistance. In terms of changing the empirical therapy based on resistance percentage, a UK based study indicated alternatives such as Fosfomycin and Nitrofurantoin were only cost effective at 30–35% resistance rates to trimethoprim respectively [37]. Infectious Diseases Society of America also continues to recommend trimethoprim when resistance rates are below 20% [38].

Furthermore, the findings in this study show a relatively lower rates of resistance to fluoroquinolones compared to other continents, indicating resistance as high as 30.8% in Europe and over 40% in Asia [39]. The relative low rates of resistance to fluoroquinolones in Australia is likely as a result of lack of use of these antibiotics in

animal agriculture as well as strict prescribing regulations, where the use of ciprofloxacin as an empiric agent is not recommended in any Australian guidelines [40]. Overall, our data indicate that the inclusion of information on gender and settings in the local antibiograms may assist to optimise empirical therapy.

Limitations

Important limitations of our study include the lack of patient metadata. The incorporation of patient comorbidities, history of antibiotic prescriptions, symptoms, and other information (i.e. urinary catheters, method of urine collection), may have provided further insight into risk factors for multi-resistant infections. This study focussed on *E. coli* which is by far the most common cause of UTI and an organism in which there is no intrinsic resistance to the antibiotics tested. Finally, due to the large power of our study, statistically significant differences were observed that may not necessarily correspond to similar magnitude of clinical significance.

Conclusions

This study demonstrated increasing rates of MDR among urinary *E. coli* isolates in an Australian local health district, which was more prominent in males compared to females, in particular in the hospital setting. This body of work contributes to our understanding of changes in resistance patterns, providing valuable insight for clinicians to make informed antibiotic choices for UTIs in certain patient groups. The result highlights the need for caution when using trimethoprim as a first-line agent, emphasises clinician awareness of potential MDR and the risk of initial therapy failure and underscores the importance of obtaining cultures for susceptibility results before antibiotics, to guide effective treatment.

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Author contributions

All authors contributed to this research project. CK, SM, SJ, CS were responsible for the initial conceptualization of the project. CK, NK, CC contributed to data curation. Formal analysis was undertaken by NK, CC. The original draft of the manuscript was produced by NK, under the supervision of SM, CC, KJM, CK. Final review and editing of the manuscript was undertaken by all authors.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval

Ethics approval was obtained through the ISLHD UOW Joint Human Research Ethics Committee (2019/ETH03729). As individual patients were not identified, the need for individual informed consent was waived by the same ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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