Multi-drug resistance of *Escherichia coli* from the urinary tract

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ABSTRACT

Objectives: Resistance to antimicrobials of different structural classes has arisen in a multitude of bacterial species. This may complicate the therapeutic management of infections, including those of the urinary tract. The aim of this study is to show that antibiotic resistance surveillance is essential.

Methods: A total of 11,126 urine samples were received at Sultan Qaboos University Hospital (SQUH), Muscat, Sultanate of Oman, for one year period (2001), they were cultured for bacterial pathogen and sensitivity was performed for all significant isolates.

Results: Eight hundred and eighty-four samples were culture positive with *Escherichia coli* (*E.coli*) (N=445) as the most common *enterobacteriaceae*, followed by *Klebsiella pneumoniae* (N=161), unidentified Coliforms (N=56) and *Klebsiella species* (N=33). High rate of resistance to β-Lactams was seen for all *Enterobacteriaceae*, maximum resistance was against ampicillin (78.6%) followed by co-amoxiclav (44.6%), but cefuroxime demonstrated the least resistance. Resistance to quinolone ranged from 4.7%-21.2% for all *Enterobacteriaceae,* cotrimoxazole resistance for all *Enterobacteriaceae* was 32.1%. Multi-drug resistance of *E.coli* was analyzed, 11.2% (50 of 445) were resistant to 3 or more antimicrobials and considered multidrug resistant. Among the multidrug-resistant isolates, 88% were resistant co-amoxiclav or cotrimoxazole, gentamicin 62%, ciprofloxacin 66%, and nitrofurantoin 32%. The predominant phenotype among multidrug-resistant isolates (26%; 13 of 50) included resistance to co-amoxiclav, gentamicin, and cotrimoxazole. This was the most common phenotype followed by 20%, of co-amoxiclav, cotrimoxazole and ciprofloxacin.

Conclusion: In view of the current prevalence of multi-drug resistance among urinary tract isolates of *E.coli* at the SQUH (11.2%), continued surveillance will be beneficial.

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The majorities of urinary tract infections (UTIs) occur in female and are treated empirically at the out patient department if their symptoms suggest acute uncomplicated bacterial cystitis.[1-3] The pathogens causing UTIs are fairly well known and *Escherichia coli* (*E.coli*) is the main etiologic agent particularly in outpatients.[1,2,4-7] Guidelines recently published by the Infectious Diseases Society of America (IDSA), United States of America (USA), recommend cotrimoxazole as initial therapy for bacterial cystitis, when cotrimoxazole resistance prevalence is <20%.[8] Worldwide prevalence of *E.coli* resistant to cotrimoxazole varies considerably in published reports, with current estimates ranging between 18%-50%.[1,2,4-7] The recent published report on cotrimoxazole resistance for *E.coli* from UTIs in North America range between 18%-25%,[1,5-7] suggesting that cotrimoxazole could soon cease to be a first-line therapeutic option.[1] The rate of resistance to cotrimoxazole at Sultan Qaboos University Hospital (SQUH), Muscat, Oman is so high (45%) that we do not recommend the use of cotrimoxazole as the first line of treatment in UTI patients. In North America, co-amoxiclav resistance rate of *E. coli* isolated from UTIs is generally higher than those for cotrimoxazole and was

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reported to be approaching 40%.[1,5-7] There is a well-known correlation of cross-resistance between antimicrobials, such as cotrimoxazole and ampicillin. When the cross-resistance is extensive, we get multiple drug resistance (MDR). The rate of MDR has risen over the years and at present in North America the MDR is at 7.1%,[9] ampicillin and cotrimoxazole are the most predominant antimicrobials in MDR. The purpose of this study was to demonstrate the susceptibility profiles of common UTI isolates, particularly of *E.coli* with specific attention to the prevalence of MDR at the SQUH. This was achieved using SQUH Information System (HIS-Microbiology) for the period of 1 January 2001 to 31 December 2001.

Methods. Sultan Qaboos University Hospital, is a teaching tertiary care hospital in Oman. The microbiology laboratory carries out investigations for both in and out patients and the diagnostic data was stored on a modern computer system. From 1 January 2001 to 31 December 2001, 11,126 samples of urine were received and 884 were culture positive. There were 695 (79%) enterobacteriaceae identified out of which 445 (64%) were *E.coli*. Sensitivity testing was performed by accepted standard controlled laboratory procedure of Stokes and Waterworth.[10] All isolates were tested for the following antimicrobials: ampicillin, co-amoxiclav, cefuroxime, naladixic acid, norfloxacin (tested for 8 months isolates only), ciprofloxacin, cotrimoxazole, nitrofurantoin, and gentamicin. This information was subsequently retrieved from SQUH information system for analysis. Multi drug resistance was defined as resistance to 3 or more commonly used antimicrobials for the treatment of UTI.

Results. The main *enterobacteriaceae* organisms isolated from urine samples were *E.coli, Klebsiella pneumoniae* (*Klebs. pneumoniae*), *Klebsiella species (Klebs. spp),* and unidentified Coliforms, which accounted for more than 78% of all isolates. **Table 1** shows the resistance rate of 695 *Enterobacteriaceae*, resistance to ampicillin was the highest for all organisms, ranging from 68.3-100%. Resistance to co-amoxiclav ranged from 11-44.6%. Among the β-Lactams, resistance was significantly lower to cefuroxime ranging between 5.6-17.9%. In the group of quinolone, resistance to norfloxacin ranged from 4.7-20.7%, followed by naladixic acid 5.6-20.7% and ciprofloxacin 4.3-21.2%. However, there was no significant difference for the 3 quinolones for most of the organisms, except between naladixic acid (20.7%) and ciprofloxacin (10.3%) for the *E.coli*. Overall, *E.coli* isolates demonstrated low resistance to nitrofurantoin 5.4%, cefuroxime 7.4% and ciprofloxacin 10.3%. Resistance to cotrimoxazole was higher for *E. coli* but low for *Klebs. pneumoniae* and coliforms. Inversely *E.coli* resistance to nitrofurantoin was low but high for *Klebs. spp* and coliforms whereas resistance to gentamicin was low for all organisms. *E.coli* was generally more resistant than *Klebs. pneumoniae*, except for ampicillin and nitrofurantoin, whereas all *Klebs. spp* were more resistant than *Klebs. pneumoniae*. **Table 2** shows *E.coli* resistance to various combinations. Most of the isolates (65.8%) were either sensitive to all antimicrobials or resistant to a single agent, predominantly to cotrimoxazole. There were 50 *E.coli*, which were resistant to 3 or more of these antibiotics (MDR), accounting for 11.2% of *E.coli*. Most of MDR isolates 70% (N=35) were resistant to 3 antimicrobials, 24% (N=12) were resistant to 4 drugs and 6% (N=3) were resistant to all 5 antimicrobials. **Table 3** shows the detail of combinations of 50 MDR isolates. Multiple drug resistance phenotypes identified, with concurrent resistance to co-amoxiclav, gentamicin, and cotrimoxazole accounted for 26% of MDR isolate. Co-amoxiclav and cotrimoxazole were components of 88% each individually (44 of 50) of the MDR isolates and a combination of both involved in 78%. Similarly, 66% (N=33), 62% (N=31), and 32% (N=16) of MDR isolates were resistant to ciprofloxacin, gentamicin, and nitrofurantoin, When co-amoxiclav and cotrimoxazole are excluded then only 10% (N=5) of *E.coli* are MDR?

Discussion. Since the majority of UTIs are empirically treated, continuous update of data on antimicrobial susceptibility patterns would be of great help to guide empiric treatment especially when urinary tract pathogens are showing increasing antimicrobial resistance. It is recommended that in communities where the rate of resistance to cotrimoxazole is greater than 20% among UTI isolate, alternative antimicrobial agents should be considered as first-line treatment.[7] To achieve these recommendations there is the need to perform regular surveillance to make sure that the activities of cotrimoxazole and other antimicrobials are monitored and that emerging resistance trends, such as multidrug resistance, are identified. The 4 common *Enterobacteriaceae* isolates demonstrated an overall high rate of resistance to β-Lactams, with maximum resistance seen against ampicillin followed by co-amoxiclav, but cefuroxime demonstrated the least resistance. Ampicillin has been excluded from further analysis and consideration because of exceptionally high resistance. It has also not been used empirically in *enterobacteriaceae* treatment of UTI. It seems therefore that there is no oral β-Lactams available to use empirically except cefuroxime. Findings in this study were significantly higher than those reported in USA[6] and Canada.[9] Resistance rate of 9.5% to ciprofloxacin was the lowest among the quinolone for all *enterobacteriaceae*. Norfloxacin demonstrated resistance of 10.4% for all *Enterobacteriaceae*, followed by naladixic acid resistance of 15.8%, which was greater than the other quinolone. Cotrimoxazole resistance to *E.coli* was 45%, but overall resistance to other *enterobacteriaceae* was much lower at 8.4%, resistance

Table 1 - Antimicrobial resistant rates of urinary tract *Enterobacteriaceae*.

Antimicrobial agents	*E.coli* N=445 n (%)	*Klebs. pneumoniae* N=161 n (%)	*Klebs. spp* N=33 n (%)	*Coliforms* N=56 n (%)
Ampicillin,	304 (68.3)	161 (100)	33 (100)	44 (78.6)
Co-amoxiclav	165 (37.1)	18 (11.2)	9 (27.3)	25 (44.6)
Cefuroxime	33 (7.4)	9 (5.6)	4 (12.1)	10 (17.9)
Naladixic acid	92 (20.7)	9 (5.6)	5 (15.1)	4 (7.1)
Norfloxacin*	35 (12)	5 (4.7)	6 (20.7)	2 (5.7)
Ciprofloxacin	46 (10.3)	7 (4.3)	7 (21.2)	6 (10.7)
Cotrimoxazole	201 (45.2)	11 (6.8)	6 (18.2)	4 (7.1)
Gentamicin	49 (11)	3 (1.8)	2 (6.1)	4 (7.1)
Nitrofurantoin	24 (5.4)	43 (26.7)	28 (84.8)	21 (37.5)

*Norfloxacin sensitivity was performed against 291 *E.coli*, 106 *Klebs. pneumoniae*, 29 *Klebs. spp* and 35 *Coliforms* only.
E.coli - Escherichia coli, *Klebs. - Klebsiella, Klebs. spp - Klebsiella species*

Table 2 - Resistance to one or more antimicrobial of 445 urinary tract isolates of *Escherichia coli*.

n of agents isolates were resistant	Isolates n (%)	n of isolates and percentage of resistant: Cotrimoxazole n (%)	Co-amoxiclav n (%)	Nitrofurantoin n (%)	Ciprofloxacin n (%)	Gentamicin n (%)
0	167 (37.5)	- -	- -	- -	- -	- -
1	126 (28.3)	68 (53.9)	38 (30.1)	11 (8.7)	5 (4)	4 (3.2)
2	102 (22.9)	91 (89.2)	86 (84.3)	3 (2.9)	12 (11.8)	12 (11.8)
3	35 (7.9)	30 (85.7)	30 (85.7)	8 (22.9)	19 (54.3)	18 (51.4)
4	12 (2.7)	11 (91.7)	11 (91.7)	5 (41.7)	11 (91.7)	10 (83.3)
5	3 (0.7)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)

11.2% (50 of 445) of isolates were resistant to 3 or more antimicrobials and defined as multi-drug resistance

Table 3 - Antimicrobial resistance of 50 multi-drug resistance (MDR) *Escherichia coli* urinary tract isolates.

Antibiotics	Isolates n	MDR isolates %	Total isolates %
Co-amoxiclav, co-trimoxazole, gentamicin	13	(26)	**(2.9)**
Co-amoxiclav, co-trimoxazole,ciprofloxacin	10	(20)	**(2.2)**
Co-amoxiclav, co-trimoxazole, nitrofurantoin	2	(4)	**(0.4)**
Co-amoxiclav, gentamicicn, nitrofurantoin	1	(2)	**(0.2)**
Co-trimoxazole, gentamicin, ciprofloxacin	2	(4)	**(0.4)**
Nitrofurantoin, ciprofloxacin, co-trimoxazole	3	(6)	**(0.7)**
Nitrofurantoin, ciprofloxacin, co-amoxiclav	2	(4)	**(0.4)**
Ciprofloxacin, gentamicin, co-amoxiclav	2	(4)	**(0.4)**
Co-trimoxazole, co-amoxiclav, gentamicicn, nitrofurantoin	1	(2)	**(0.2)**
Co-trimoxazole, co-amoxiclav, gentamicicn, ciprofloxacin	7	(14)	**(1.6)**
Co-amoxiclav, gentamicin, nitrofurantoin, ciprofloxacin	1	(2)	**(0.2)**
Co-amoxiclav, ciprofloxacin, nitrofurantoin, co-trimoxazole	2	(4)	**(0.4)**
Gentamicin, nitrofurantoin, ciprofloxacin, co-trimoxazole	1	(2)	**(0.2)**
Co-trimoxazole, co-amoxiclav, nitrofurantoin, gentamicin, ciprofloxacin	3	(6)	**(0.7)**

to nitrofurantoin conversely resistance was low for *E.coli* 5.4% but high for other *Enterobacteriaceae* at 37%. The reason for this opposite effect of the 2 drugs is unknown. This excludes these drugs also from empiric considerations. Gentamicin over all resistance was 83.3% and seems to perform better than other antibiotics except naladixic acid, nitrofurantoin and cefuroxime for *E.coli*. The data of this study demonstrated that a gentamicin, ciprofloxacin and nitrofurantoin, resistant phenotype without concurrent resistance to other classes of antimicrobials is low (3.1, 4 and 8.7%), whereas prevalence of resistance to cotrimoxazole and augmentin was high. Cotrimoxazole and co-amoxiclav in combination were 76% of the component of MDR. It was also observed that when cotrimoxazole and co-amoxiclav are not included in the calculations the MDR drops from 11.2-1.1%. To better understand and respond to increasing antimicrobial resistance, it is recommended that hospitals and communities establish a mechanism to look at the local resistance pattern in UTI, so that a correct regimen for empiric treatment be assessed regularly in light of changing susceptibility patterns. Physicians should be aware of current antimicrobial susceptibility patterns for *E. coli* and other UTI pathogens in their local communities, as antimicrobial susceptibilities change over time and vary geographically. Clearly, the current prevalence of multidrug resistance among urinary tract isolates of *E. coli* at SQUH (11.2%) suggests that monitoring these phenotypes is important and should be a consideration as the guidelines for the empiric treatment of UTIs.

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