Antimicrobial resistance in community and nosocomial Escherichia coli urinary tract isolates from Chennai, South India in 2007

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ABSTRACT

Escherichia coli are the commonest cause of community and nosocomial urinary tract infection (UTI). Antibiotic treatment is usually empirical relying on susceptibility data from local surveillance studies. We therefore set out to determine levels of resistance to 9 commonly used antimicrobial agents amongst all urinary isolates obtained over a 12 month period. **Methods:** Antimicrobial susceptibility to ampicillin, amoxicillin/clavulanate, cephalexin, cefpodoxime, norfloxacin, amikacin, nitrofurantoin, trimethoprim and imipenem was determined for 14,678 *E. coli* urinary isolates obtained from community and hospitalised patients in Chennai, South India. **Results:** Imipenem was the most active agent (100% susceptible), followed by nitrofurantoin and amikacin (94% each). High rates of resistance to ampicillin (82%) and co-trimoxazole (76%), often in combination with norfloxacin were observed in both sets of isolates. Although 65% of the isolates exhibited resistance to multiple drug classes, resistance to cefpodoxime, indicative of extended spectrum β-lactamase production, was observed in 40% of community and 60% of nosocomial isolates. **Conclusion:** With the exception of nitrofurantoin, resistance to agents commonly used as empirical oral treatments for UTI was extremely high. Levels of resistance to trimethoprim and ampicillin render them unsuitable for empirical use. Continued surveillance and investigation of other oral agents for treatment of UTI in the community is required

INTRODUCTION

Escherichia coli is the predominant cause of both community and nosocomial urinary tract infection (UTI). In India, norfloxacin, trimethoprim, nitrofurantoin and first generation cephalosporins are usually recommended for empirical treatment of episodes of uncomplicated cystitis in the community,[1] while parenteral cephalosporins and aminoglycosides are reserved for complicated infections or pyelonephritis. In North America a cut off point of 20% has been suggested as the level of resistance at which an agent should no longer be used empirically.[2] A UK study of the antimicrobial susceptibility of bacterial pathogens causing UTI in 1999–2000 showed high levels of resistance to trimethoprim, amoxicillin and oral cephalosporins.[3] while a study of three collections of *E. coli* strains obtained from patients in London in 1991, 1999 and 2004 showed rates of trimethoprim resistance of over 30%.[4] The emergence of strains producing extended spectrum β-lactamases (ESBL's) and others exhibiting quinolone resistance now threatens the empirical use of both cephalosporins and ciprofloxacin[5] seriously limiting treatment regimens. In order to determine current levels of resistance to antibiotics commonly used locally for empirical treatment, we reviewed susceptibility to ampicillin, amoxicillin/clavulanate, cephalexin, cefpodoxime, norfloxacin, amikacin, nitrofurantoin, trimethoprim and imipenem amongst all *E. coli* urinary isolates obtained in our laboratory over a 1 year period.

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MATERIALS AND METHODS

All *E. coli* isolates recovered from urine samples submitted for microscopy, culture and sensitivity to our laboratory between 1st January and 31st December 2006 were included. Samples originating from General practice, Accident and Emergency or other primary care destinations were considered representative of community isolates while samples originating from patients hospitalised for 48 hrs

or more on general or specialised wards were considered nosocomial.

Primary isolation of strains from urine specimens was performed using cystine lactose electrolyte deficient (CLED) agar (Hi Media, India) and bacterial counts quantified by inoculation of 0.04 µl of urine onto CLED agar as per standard procedures.[6] Sensitivity testing was performed by the Kirby-Bauer's disc diffusion method (according to the procedure of CLSI guidelines M100-S13)[7] using ampicillin (10µg), cephalexin (30µg), amikacin (30µg), norfloxacin (10µg), nitrofurantoin (300µg), trimethoprim-sulphamethoxazole (1.25/23.75µg), amoxicillin/clavulanate (20/10µg) and cefpodoxime (10µg) discs and imipenem(10µg) using Mueller–Hinton agar.

Multi-drug resistance was defined in this analysis as resistance to three or more of the following antibiotics: amoxicillin/clavulanate, cefpodoxime, norfloxacin and amikacin.

Differences in the prevalence of antibiotic resistance between groups were analysed using the χ^2 test. Strength of association was assessed by calculation of odds ratios with 95% confidence intervals

RESULTS

A total of 14,678 *E. coli* isolates were cultured from urine samples over the study period. Of these 10,083 (68.7%) were considered community isolates while 4,595 (31.3%) were of nosocomial origin. 12,540 (85.7%) were from women and 2,093 (14.3%) from men (45 sex unknown). 1,227 (10.3%) were from children < 12 years of age.

The frequency of antimicrobial susceptibility of all isolates to the nine antibiotics is shown in tables 1, 2, 3. Imipenem was the most active agent (100% susceptible) followed by nitrofurantoin (94%) and amikacin (94%). Ampicillin and trimethoprim were the least active agents with 82% and 76% of isolates exhibiting resistance respectively.

Isolates from men were significantly more resistant to all nine agents than isolates from women (Table 1). In particular, resistance to cephalexin, cefpodoxime, amikacin and norfloxacin was observed more than twice as frequently in isolates from men (odds ratios = 2.5).

A significant difference between paediatric and adult isolates was seen for all agents except amoxicillin/clavulanate. Resistance to cephalexin, norfloxacin, amikacin, nitrofurantoin and cefpodoxime was more common in adults while ampicillin (OR 0.72) and trimethoprim (OR 0.76) resistance was associated with paediatric strains (Table 2).

Nosocomial isolates were more resistant than community isolates to all agents tested. The prevalence of amikacin (OR 5.00), norfloxacin (OR 4.79), and cefpodoxime (OR 4.57) resistance exhibited the most marked differences (Table 3).

Patterns of multi-drug resistance are shown in table 4. Ampicillin resistance in combination with trimethoprim resistance was more frequently observed than resistance to the single agent alone, the combination of ampicillin and trimethoprim resistance was also seen in combination with amoxicillin/clavulanate and norfloxacin. Resistance to all agents except imipenem was the most common multi-drug resistant phenotype and was observed in 65% of isolates.

DISCUSSION

In India, the most uncomplicated urinary tract infections are treated in the community with short courses of empirical

Table 1: Frequency of antibiotic susceptibility in relation to sex

	Female (n = 12,540)	Male (n = 2,093)		
Antibiotic	**Resistant (%)**	**Resistant (%)**	**p**	**OR (CI95%)**
Ampicillin	79.8	83.7	≤ 0.001	1.50 (1.35-1.67)
Amoxicillin/clavulanate	62.4	80.8	≤ 0.001	1.85 (1.61-2.13)
Cephalexin	60	60.8	≤ 0.001	2.52 (2.19-2.90)
Cefpodoxime	52.5	68.2	≤ 0.001	2.72 (2.30-3.22)
Amikacin	5.2	12.9	≤ 0.001	2.72 (2.30-3.22)
Norfloxacin	64.2	71.3	≤ 0.001	2.57 (2.25-2.93)
Trimethoprim	72.8	80.6	≤ 0.001	1.28 (1.15-1.42)
Nitrofurantoin	5.4	8.6	≤ 0.001	1.64 (1.35-1.99)
Imipenem	0	0	NA	

Table 2: Frequency of antibiotic susceptibility in relation to age

	< 16 years	≥ 16 years		
Antibiotic	**Resistant (%)**	**Resistant (%)**	**p**	**OR (CI95%)**
Ampicillin	82.3	74.3	≤ 0.001	0.72 (0.64-0.81)
Amoxicillin/clavulanate	62.9	78.7	≤ 0.001	1.07 (0.89-1.29)
Cephalexin	58.2	60.6	≤ 0.001	1.33 (1.07-1.64)
Cefpodoxime	54.0	57.9	≤ 0.001	2.03 (1.48-2.78)
Amikacin	3.6	6.6	≤ 0.001	1.90 (1.39-2.59)
Norfloxacin	65.9	72.7	≤ 0.001	2.34 (1.83-2.99)
Trimethoprim	76.3	69.4	≤ 0.001	0.76 (0.67-0.85)
Nitrofurantoin	5.4	6.1	≤ 0.001	1.68 (1.24-2.28)
Imipenem	0	0	NA	

Table 3: Frequency of antibiotic susceptibility among community & nosocomial isolates

	Community	Nosocomial		
Antibiotic	**Resistant (%)**	**Resistant (%)**	**p**	**OR (CI95%)**
Ampicillin	73.9	85.0	≤ 0.001	1.59 (1.41-1.79)
Amoxicillin/clavulanate	62.0	86.8	≤ 0.001	2.69 (2.33-3.11)
Cephalexin	58.3	65.6	≤ 0.001	3.78 (3.29-4.36)
Cefpodoxime	56.7	62.6	≤ 0.001	4.57 (3.85-5.41)
Amikacin	4.6	19.4	≤ 0.001	5.00 (4.24-5.88)
Norfloxacin	59.3	72.9	≤ 0.001	4.79 (4.20-5.46)
Trimethoprim	79.1	68.4	≤ 0.001	1.46 (1.30-1.64)
Nitrofurantoin	5.3	10.4	≤ 0.001	2.08 (1.71-2.53)
Imipenem	0	0	NA	

Table 4: Distribution of ten most frequently observed antibiotic resistance patterns.

Antibiotic	**Resistance %**
Susceptible	6
AMP, CO	8
AMP	5
CO	3
AMP,AMC,CO	2
AMP,AMC	2
AMP,NOR,CO	2
AMP,AMC,CP,AK,NOR,CO,CPD	3
AMP,AMC,CP,NOR,CO,CPD	65
AMP,NIT,CO	1
Others	3
	100

AMP = Ampicillin, AMC = amoxicillin/clavulanata, CP = cephalexin, AK = amikacin, NOR = norfloxacin, NIT = nitrofurantoin, CO = co-trimoxazole, CPD = cefpodoxime

antibiotics. This relies on susceptibility data from local surveillance schemes as in many cases urine samples are only sent for microbiological evaluation following treatment failure, recurrent or relapsing infection. Although the levels of resistance we observed among community isolates may therefore overestimate the true rate of resistance in the community, the high levels of resistance to ampicillin and co-trimoxazole raise concerns over the use of these agents. This was particularly evident amongst isolates from children, which were more likely to exhibit resistance to ampicillin and co-trimoxazole compared to those from adults. Increased resistance to the other agents in adults is likely to reflect their wider use both empirically and as second line therapies in relapsing, complicated or nosocomial infection. The higher rates of resistance to all agents observed in males are likely to reflect the complicated nature of UTI in men.[8] Infection in this group usually occurs in the setting of underlying anatomical or functional abnormalities or following instrumentation of the urinary tract and the use of prophylactic antimicrobials. Data on resistance rates in *E. coli* collected

at a teaching hospital from 1995–2000 reveal year on year increases in resistance to amoxicillin, cefuroxime, amikacin and norfloxacin.[9] Resistance to comparable agents in 2005 shows marked elevations in resistance to amikacin (6.3% v 3.2%) and in particular norfloxacin (12% v 1.9%). Resistance to cefpodoxime, which may signify ESBL production[10] was seen in 50% of isolates overall, often in combination with resistance to quinolones, aminoglycosides and trimethoprim. Although cefpodoxime resistance was more typical of nosocomial isolates, significant resistance was also observed in the community. These isolates most likely represent CTX-M producing strains of *E. coli* which have disseminated widely throughout Asia in post 2000[11] with those producing CTX-M-15 being most widespread in India.[12]

CONCLUSION

Nitrofurantoin remained the most active agent and as it can be administered orally and is highly concentrated in urine, it may therefore be the most appropriate agent for empirical use in uncomplicated (community acquired) UTI. Empirical treatment for nosocomial UTI or infection with multi-drug resistant isolates remains challenging with many authorities recommending parenteral carbapenems (imipenem, ertapenem or meropenem)[13] especially where ESBL producing isolates may be involved. The increasing rates of resistance to uropathogenic *E. coli* isolates reported worldwide[14-15] warrants evaluation of other treatments such as fosfomycin[16] or possibly novel cephalosporin/inhibitor combinations.[17]

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