Research paper

Antimicrobial susceptibility patterns and empirical prescribing practices in adult in-patients with urinary tract infection in a tertiary care hospital in Sri Lanka: is there a need for changing clinical practices?

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Abstract

Introduction: Knowledge of local antimicrobial susceptibility is essential for prudent empiric therapy of urinary tract infection (UTI).The aim of this study is to describe antimicrobial susceptibility patterns and empirical prescribing practices in adult in-patients with UTI.

Methods: The study was carried out at a tertiary care hospital in Sri Lanka. Data was collected from consecutive adult in-patients with positive urine culture and clinical features compatible with UTI. Antibiotic sensitivity testing was done using Joan Stokes method. The etiological uropathogens, antibiotic susceptibility rates (ASR), association between ASR and background variables and empirical prescribing practices were analyzed.

Results: Seven hundred and forty five subjects were studied. Mean (SD) age was 48.2 (19) years and 441(59.2%) were females. Coliforms were the commonest isolates (85.6%). Overall, 76.8% of the isolates were susceptible to nitrofurantoin (coliforms 74.9%, *Streptococcus* spp. 100%, *Staphylococcus* spp. 95.6%). Overall susceptibility was < 50%, to many antimicrobials. Among coliforms and pseudomonas isolates, susceptibility to ciprofloxacin was 37.7% and 29.4% respectively. The susceptibility rates of coliforms varied according to age, gender, origin of UTI and presence of co-morbidities. Three hundred and eighty one (51.1%) subjects received empirical antimicrobials. Ciprofloxacin was the most frequently prescribed empirical antimicrobial (208/381; 54.6%). Despite high susceptibility, nitrofurantoin was empirically prescribed in only 9.2% patients.

Conclusions: Susceptibility was low to many first and second line antimicrobials used to treat UTI in adults. There was obvious discrepancy between empirical prescribing practices and the susceptibility pattern of isolates. Incorporation of local surveillance data in clinical practice will be useful to optimize the use of empirical antimicrobial therapy.

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Introduction

Urinary tract infection (UTI) is a common medical problem. It causes considerable morbidity and if complicated, can cause severe renal damage. Furthermore, it is a common source of life-threatening Gram-negative septicaemia.

Empirical antimicrobial therapy is recommended for urinary tract infection based on limited and predictable spectrum of aetiological microorganisms.[1,2] However, increasing antimicrobial resistance among these urinary pathogens poses a challenge. Resistance rates to antimicrobials like amoxicillin and co-trimoxazole are high world-wide and resistance to fluoroquinolones too is rising in some parts of the world.[3-7] Furthermore susceptibility patterns of the microorganisms show significant geographical variations.[3-12] One of the important factors contributing to high resistance rates is the inappropriate use of antimicrobials.[13-14]

Knowledge of local antimicrobial susceptibility patterns among urinary isolates will guide clinicians to deliver effective treatment to their patients presenting with UTIs while avoiding unnecessary usage of broader spectrum and costly antibiotics as empiric therapy. Furthermore, knowledge of antimicrobial susceptibility patterns among urinary isolates is required to formulate evidence based regional/national guidelines on antimicrobial use in UTIs.

There is limited data on antimicrobial susceptibility patterns in urinary tract infections in Sri Lanka. There are two reports looking at specific groups, one in pregnant mothers and the other in children but small sample size (less than 60) is a limitation in both of these studies.[15,16] A larger study done in adults reports microbiological data without any relation to clinical data.[17] However, certain clinical details like normal urinary tract against abnormal urinary tract or community acquired against hospital acquired infection could be important with regard to the causative organism and its susceptibility pattern. A more recent study done by Dissanayake et al. (2012) has described the distribution and characteristics of Extended-Spectrum β-Lactamase producing *Escherichia coli* and *Klebsiella* species among urinary isolates in a tertiary care hospital.[18] There are no local studies on empirical prescribing practices in UTI.

Hence this study was planned to describe the etiologically implicated uropathogens and their antibiotic susceptibility and prescribing practices of empirical antimicrobials in a cohort of adult in-patients with UTI, managed at a tertiary care hospital in Sri Lanka.

Methodology

Study subjects and Data collection

This descriptive observational study was conducted at Colombo North Teaching Hospital, Sri Lanka during the period 1st August 2009 to 31st October 2010. Ethical approval was granted for this study by the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya.

Consecutive adult (age ≥ 18 years) in-patients with a positive urine culture and clinical features compatible with UTI were enrolled after obtaining informed written consent. Out of a total of 745 culture positive samples, 724 were mid stream urine samples and the rest catheter samples. Data collection was done by MBBS qualified study coordinators. Details of urine culture and antibiotic sensitivity testing (ABST) results were extracted from the records maintained at the

Microbiology department of the Colombo North Teaching Hospital. Patients' demographic data, clinical data, past medical history, investigation findings (urine culture and ABST, imaging of the urinary tract, fasting / random blood sugar, serum creatinine) and details of prescribed empiric antimicrobial therapy were obtained via patient interviews and patients' medical records. Collected data were recorded in a pre-prepared and tested case record form and subsequently transferred to a computer data base (Epidata).

Definitions

Abnormal urinary tract (AUT): Structurally or functionally abnormal urinary tract which included calculi, strictures, hydronephrosis, scarred kidneys, polycystic kidney disease, simple cysts, tumours, bladder out-flow tract obstruction, an indwelling catheter in situ for ≥ 1 week and neurogenic bladder.

Hospital acquired infection: Infections acquired by patients during their stay in the hospital with clinical features of infection appearing 48 hours or more after hospital admission.[19]

Acute pyelonephritis (AP): Positive urine culture in the presence of ultrasound / CT scan evidence of acute pyelonephritis or loin pain/tenderness with fever $\geq 100^0$C.[20]

Recurrent UTI: At least 2 infections within 6 months or 3 infections within 1 year.[21]

Diabetes mellitus (DM): Already on treatment for diabetes mellitus or having a fasting blood glucose of ≥126mg/dl (7mmol/L) or random blood glucose of ≥200mg/dl (11.1mmol/L).[22]

Pregnancy: Pregnancy confirmed with urine human chorionic gonadotrophine test.

Chronic kidney disease (CKD): Serum creatinine >1.4mg/dl (123.8μmol/L) with a history of chronic renal impairment.

Laboratory Methods

Urine samples of adult patients received by the Microbiology department of the Colombo North Teaching Hospital for routine culture were included in the study. The laboratory methods followed during the study period are described below.

The urine samples were inoculated onto cystine lactose electrolyte deficient (CLED) medium using a 1 µl wire loop. Culture plates were incubated at 37^0C for 18-24 hours. A positive culture was defined as a urine sample containing $\geq 10^5$ colony-forming units/ml of an uropathogen. The isolated bacteria were identified by conventional methods.[23] Antibiotic sensitivity testing was done using the Joan Stokes method.[24] Ampicillin, cephalexin, co-amoxiclav, co-trimoxazole, gentamicin, nalidixic acid, nitrofurantoin and norfloxacin were used as first line antimicrobials and amikacin, cefuroxime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, imipenem, meropenem, netilmicin, and ticarcillin-clavulinic acid were used as second line antimicrobials. Amikacin, ceftazidime, ciprofloxacin, gentamicin, imipenem, meropenem and netilmicin were used for pseudomonas isolates.

Statistical analysis

The data was exported from Epidata to Stata and analysed using Stata version 8. Numerical data were summarized using the mean and standard deviation and categorical data were summarized using frequencies and percentages. The Chi squared test and fisher's exact test were used to assess the statistical significance of associations.

Results

Patient Demographics and Clinical Data

A total of 745 patients were studied. Four hundred and forty one (59.2%) were females and the mean age of the study population was 48.2 years with a standard deviation of 19 years. Hundred and seventy two (23.1%) patients were 65 years and above.

Hundred and ninety nine (26.7%) patients had abnormal urinary tracts and the commonest cause was calculi (62/199; 31.2%) followed by bladder outflow tract obstruction (41/199; 20.6%), hydronephrosis (35/199; 17.6%) and indwelling catheter for > 1 week (21/199;10.6%). Hundred and eighty two (24.4%) patients had DM. Hospital acquired infection was seen in 132 (17.7%). Acute pyelonephritis was diagnosed in 108 (14.5%). Recurrent UTI was reported in 77 (10.3%) while 71 (9.5%) had CKD. Fifty two (11.8%) of the females were pregnant.

Acute pyelonephritis and recurrent UTI were commoner among patients with diabetes (19.8% vs 12.8%, p = 0.020 and 14.8% vs 8.8%, p = 0.022 respectively). Recurrent UTI was also commoner among those with CKD (20% vs 9.5%, p = 0.010). Presence of an AUT was commoner among males (44.8% vs 14.74%, p <0.001) and those who were aged ≥ 65 years (41.3% vs 22.3%, p<0.001).

Isolated uropathogens

Coliforms were the commonest isolates (85.6%) followed by *Streptococcus* spp. (4.6%), *Candida* spp. (3.6%), *Staphylococcus* spp. (3.4%), and *Pseudomonas* spp. (2.8%). Further details regarding species identification was not available as it is not routinely carried out for urinary isolates due to resource constraints. The distribution of uropathogens according to age, gender, type and origin of UTI and other clinical data are given in Table 1.

Pseudomonas spp. was isolated from 9.1% of hospital acquired infections and 1.5% of community acquired infections (p<0.001). *Pseudomonas* spp. was also isolated significantly (p = 0.003) more often from patients with an AUT (7.0%) than from patients with a normal urinary tract (1.3%). *Candida* spp. was isolated in 7.7% of those with DM and 2.3% of those without DM (p = 0.025). A higher number of *Streptococcus* spp. was seen in pregnant females as compared to non-pregnant females (9.6% vs 4.4%) but this was not statistically significant.

Antimicrobial susceptibility patterns

Antibiotic susceptibility rates of different uropathogens are shown in table 2.
Overall, 76.8% of the isolates were susceptible to nitrofurantoin (coliforms 74.9%; *Streptococcus* spp. 100%; *Staphylococcus* spp. 95.6%). Overall susceptibility was <50% to most

Table 1: Isolated uropathogens according to age, gender, origin and type of UTI and the other relevant clinical data

		N n	Coliforms 638 (85.6%)	*Streptococcus* spp 34 (4.6%)	*Candida* spp. 27 (3.6%)	*Staphylococcus* spp. 25 (3.4%)	*Pseudomonas* spp. 21 (2.8%)	P value
Age	< 65 years	573	85.2 %	4.7 %	3.1 %	3.7 %	3.3 %	*0.353*
	≥ 65 years	172	87.2 %	4.1 %	5.2 %	2.3 %	1.2 %	
Gender	Female	441	87.1 %	5.0 %	3.4 %	3.2 %	1.4 %	*0.061*
	Male	304	83.6 %	4.0 %	4.0 %	3.6 %	4.9 %	
Origin	Community	613	87.6 %	4.2 %	3.3 %	3.4 %	**1.5 %**	***<0.001****
	Hospital	132	76.5 %	6.1 %	5.3 %	3.0 %	**9.1 %**	
Site	Cystitis	637	85.7 %	4.7 %	3.6 %	3.3 %	2.7 %	*0.930*
	Acute Pyelonephritis	108	85.2 %	3.7 %	3.7 %	3.7 %	3.7 %	
AUT	No	546	86.6 %	4.6 %	3.9 %	3.7 %	**1.3 %**	***0.003****
	Yes	199	82.9 %	4.5 %	3.0 %	2.5 %	**7.0 %**	
Recurrent	No	668	85.0%	4.5 %	4.0 %	3.7 %	2.7 %	*0.103*
UTI	Yes	77	91.0 %	5.2 %	0.0 %	0.0 %	3.9 %	
Diabetes	No	563	86.2 %	4.8 %	**2.3 %**	3.7 %	3.0 %	***0.025****
Mellitus	Yes	182	84.1 %	3.9 %	**7.7 %**	2.2 %	2.2 %	
CKD	No	674	85.9 %	4.8 %	3.3 %	3.6 %	2.5 %	*0.183*
	Yes	71	83.1 %	2.8 %	7.0 %	1.4 %	5.6 %	
Pregnancy	No	389	87.2 %	4.4 %	3.9 %	3.1 %	1.5 %	*0.268*
	Yes	52	86.5 %	9.6 %	0.0 %	3.9 %	0.0 %	

N = number of isolates; n=number of subjects; p value based on fisher's exact test; *p < 0.05
AP – Acute Pyelonephritis; AUT – Abnormal Urinary Tract; CKD – Chronic Kidney Disease

Table 2: Susceptibility rates (%) of isolated bacteria to antimicrobial agents in718[#] urine samples

Antibiotic	***N*** ***n***	**Overall**	**Coliforms** **638**	***Streptococcus spp*** **34**	***Staphylococcus spp*** **27**	***Pseudomonas spp*** **21**
Nitrofurantoin	667	76.8(512/667)	74.8(456/610)	100(34/34)	95.6(22/23)	**
Ampicillin	643	17.6(113/643)	13.4(81/607)	96.9(31/32)	25.0(1/4)	**
Nalidixic acid	594	34.7(206/594)	34.7(206/594)	**	**	**
Norfloxacin	585	43.6(255/585)	43.3(244/564)	**	52.4(11/21)	**
Co-trimoxazole	499	44.1(220/499)	43.3(208/481)	**	66.7(12/18)	**
Gentamicin	490	62.7(307/490)	63.0(291/462)	**	75.0(6/8)	50. 0(10/20)
Co-amoxiclav	271	20.7(56/271)	20.7(56/271)	**	**	**
Cephalexin	101	37.6(38/101)	37.6(38/101)	**	**	**
Ciprofloxacin	338	37.3(126/338)	37.7(118/313)	**	37.5(3/8)	29.4(5/17)
*Cefuroxime	298	46.3(138/298)	46.3(138/298)	**	**	**
Netilmicin	196	86.2(169/196)	85.9(152/177)	**	**	89.5(17/19)
*Cefotaxime / Ceftriaxone	188	35.6(67/188)	35.6(67/188)	**	**	**
Ceftazidime	154	42.2(65/154)	38.7(53/137)	**	**	70.6(12/17)
Amikacin	140	92.9(130/140)	93.1(121/130)	**	**	90.0(9/10)
Ticarcillin + clavulinic acid	92	38.0(35/92)	38.0(35/92)	**	**	**
Imipenam	83	90.4(75/83)	89.5(68/76)	**	**	100.0(7/7)
Meropenam	82	89.0(73/82)	89.6(69/77)	**	**	80.0(4/5)

N= number of isolates; [#]Candida isolates were not included; **not tested
n= number of isolates tested; resource constraints resulted in different numbers being tested for each antibiotic in the panel.
*Cefotaxime/ceftriaxone was tested for cefuroxime resistant coliforms or for isolates from patients who were already on cefotaxime/ceftriaxone

of the first line antimicrobials including ampicillin, cephalexin, co-amoxiclav, co-trimoxazole, nalidixic acid and norfloxacin. Amongst the second line antimicrobials, susceptibility was < 50% to ciprofloxacin, cefuroxime, ceftazidime, cefotaxime, and ceftriaxone. However susceptibility testing of ceftazidime, cefotaxime and ceftriaxone was carried out only for the isolates resistant to 2nd generation cephalosporins or for isolates from patients who were already on a 3rd generation cephalosporin. Susceptibility to ciprofloxacin was only 37.7% among coliforms and 29.4% among pseudomonas isolates. More than 70% of pseudomonas isolates were susceptible to amikacin, ceftazidime, imipenem, meropenem and netilmicin. Susceptibility rates of coliforms to different antimicrobials according to age, gender, type and origin of UTI and other clinical data are given in Table 3.

Table 3: Susceptibility rates (%) of coliforms according to age, gender, origin and site of UTI and other relevant clinical data

	Amp	Cefl	Coam	Cotr	Gen	Nal	Nit	Nor	Ami	Cefu	Cip	Mer	Net
Age													
< 65 years	14.4	42	22.1	44.4	64.1	38.2	77	48.1	95.9	52	41.4	91.1	90.1
≥ 65 years	9.9	20	16.4	39.6	59.2	24	68.1	29.4	84.8	29.3	25.7	85.7	73.9
P value[#]	0.178	0.069	0.322	0.370	0.37	**0.002**	**0.031**	**<0.001**	**0.031**	**0.001**	**0.015**	0.493	**0.007**
Gender													
Female	15.3	50	24.8	50.5	72.3	41.5	80.7	50.8	94.4	58.7	45.1	86.7	94.5
Male	10.4	19.5	16.1	32.1	49.7	24.4	66	33	92.1	30.5	28.6	91.5	79.8
P value[#]	0.084	**0.002**	0.078	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.605	**<0.001**	**0.003**	0.499	**0.006**
Origin													
Community	14.4	34.6	21.1	44	65.2	35.2	78.8	44.8	95.9	49.1	40.4	92.9	88.6
Hospital	7.4	50	18.9	39.7	50	31.9	53.2	34.6	84.4	35.5	22.9	80.9	75
P value[#]	0.067	0.202	0.719	0.484	**0.02**	0.539	**<0.001**	0.085	**0.026**	0.055	**0.022**	0.1127	**0.036**
Site													
Cystitis	13.5	39.4	22.3	43.5	63	34.5	73.1	42.7	92.9	44.9	35.8	88.4	84.6
AP	12.8	14.3	9.1	42.5	63.2	36	85.2	47.1	94.4	54.8	46.4	100	95.2
P value[#]	0.866	0.186	0.080	0.871	0.98	0.785	0.016	0.453	0.805	0.236	0.137	0.309	0.189
AUT													
No	15.9	45.2	24.3	45.5	68.3	39.2	77.8	49.4	93.5	55.7	43.2	85.1	85.8
Yes	5.9	17.9	13.8	37.3	47.9	21.9	66.5	27.8	92.4	26.3	24.7	96.7	85.9
P value[#]	**0.002**	**0.011**	**0.043**	0.112	**<0.001**	**<0.001**	**0.005**	**<0.001**	0.816	**<0.001**	**0.002**	0.105	0.986
Recurrent UTI	14												
No	7.7	42.3	20.8	44.6	64.7	36.5	74.7	45.6	94.2	48.5	39.8	87.9	86
Yes	0.155	12.5	20	32	50	20	76.1	26.1	88.5	31.6	20.6	100	85.2
P value[#]		**0.024**	0.917	0.088	**0.04**	**0.008**	0.804	**0.003**	0.300	0.051	**0.029**	0.223	0.911
DM	15												
No	7.8	39.8	20.2	42.9	63.5	637.5	74.5	46.9	92.1	49.8	40.9	90	86.3
Yes	**0.03**	27.8	22.1	44.7	61.3	25.9	76.1	32.1	96.4	34.8	28.4	88.3	84.8
P value[#]		0.341	0.743	0.729	0.69	**0.011**	0.711	**0.002**	0.430	**0.028**	**0.045**	0.833	0.805
CKD	14												
No	7.1	38.5	19.3	42.6	63.3	36.6	76	45.3	94.1	47.9	39.4	91.3	84.7
Yes	0.151	30	33.3	50	59.5	16.4	63.8	25.4	83.3	32.3	20.7	75	95
P value[#]		0.600	0.087	0.337	0.63	**0.003**	0.041	**0.005**	0.163	0.097	0.047	0.153	0.213

[e t#]p value based on chi squared test

Amp –Ampicillin; Cefl – Cefalexin; Coam – Coamoxiclav; Cotr - Cotrimoxazole; Gen – Gentamicin; Nal – Nalidixic acid; Nit – Nitrofurantoin; Nor – Norfloxacin; Ami – Amikacin; Cefu – Cefuroxime; Cip – Ciprofloxacin; Mer – Meropenem; Net - Netilmicin

AP – Acute Pyelonephritis; AUT – Abnormal Urinary Tract; CKD – Chronic Kidney Disease; DM – Diabetes Mellitus

Susceptibility rates of coliforms to nitrofurantoin, norfloxacin, nalidixic acid, ciprofloxacin, cefuroxime, amikacin and netilmicin in patients ≥65years of age were significantly lower as

compared with those aged <65years ($p<0.05$). Susceptibility rates to cephalexin, co-trimoxazole, gentamicin, nalidixic acid, nitrofurantoin, norfloxacin, ciprofloxacin and cefuroxime were lower among males ($p<0.01$). Susceptibility rates to nitrofurantoin, gentamicin, norfloxacin, ciprofloxacin and cefuroxime were significantly lower in the presence of an AUT ($p<0.005$). Significantly lower susceptibility rates ($p<0.05$) to nitrofurantoin, gentamicin, ciprofloxacin, amikacin and netilmicin were observed in hospital acquired infection. Lower susceptibility to nalidixic acid, norfloxacin, ciprofloxacin and cefuroxime was observed with diabetes ($p<0.05$). Susceptibility rates to cephalexin, gentamicin, nalidixic acid, norfloxacin and ciprofloxacin were lower in those with recurrent UTI ($p<0.05$). Once the urinary antiseptics (nitrofurantoin and nalidixic acid) which are inappropriate for acute pyelonephritis are disregarded, there was no significant difference in susceptibility rates of antibiotics among those with cystitis and acute pyelonephritis. Susceptibility rates to norfloxacin and nalidixic acid were significantly lower in those with CKD ($p<0.01$).

Empirical Antimicrobials

Among the 745 patients, 381(51.1%) received empirical antimicrobial therapy. Seventy five received more than one antimicrobial and the total number of antimicrobial prescriptions was 405 (Table 4). Ciprofloxacin was the most frequently prescribed empirical antimicrobial (208/381; 54.6%). Nitrofurantoin was prescribed in only 9.2% patients.

Table 4: Empirically prescribed antimicrobial agents

Antimicrobial agent	Number of Prescriptions (N=405)
Ciprofloxacin	208
Cefuroxime	50
Nitrofurantoin	35
Gentamicin	34
Co-amoxiclav	19
Amoxicillin	14
Ceftriaxone	14
Cefotaxime	10
Ceftazidime	9
Cephalexin	7
Meropenam	5

Prescription of empirical antibiotics differed significantly in some patient groups. Ciprofloxacin was given significantly more often ($p<0.001$) to patients with community acquired infection (60.8%) compared with hospital acquired infection (29.3%). Significant differences were also seen with cefuroxime and co-amoxiclav. However with regard to these two antibiotics, prescription rate was higher in hospital acquired infection than in community acquired infection (cefuroxime: 25.3% vs 10.2%, $p=0.001$; co-amoxiclav: 12% vs 3.3%, $p=0.002$). Prescription rates of ciprofloxacin in cystitis and acute pyelonephritis were 52.7% and 66.7% respectively ($p=0.063$).

Discussion

Our study shows the distribution of the aetiological uropathogens, antimicrobial susceptibility rates of these organisms and the empirical prescribing practices of antimicrobials in a cohort of adult in-patients with UTI managed at a tertiary care hospital in Sri Lanka. In addition, this study looks at the association between the antimicrobial susceptibility rates of coliforms - the commonest isolates - and a number of background variables like age, gender, origin of UTI, site and type of UTI and co-morbidities.

Local antimicrobial susceptibility patterns in UTI in Sri Lanka are an area where data is limited. Data gathered in this study would therefore be useful in guiding local antibiotic policies. The data related to prescribing practices is useful in identifying the shortcomings and initiating corrective measures required.

As has been previously described in several studies from different countries, the predominant group of uropathogens isolated in this study were coliforms.[3,4,5,8,9,10,11] The presence of a significantly higher number of pseudomonas isolates in those with hospital acquired infections and in those with abnormal urinary tracts highlight the need for considering anti-pseudomonal antibiotic cover for empirical therapy in these groups. The presence of a higher number of candida isolates in those with diabetes mellitus indicates the need for considering fungal infections also as an important cause of UTI in patients with diabetes. Even though the predominant group of uropathogens worldwide is coliforms, the antimicrobial susceptibility patterns vary amongst different regions, highlighting the need for local susceptibility data.

In the present study, coliforms showed highest susceptibility to nitrofurantoin (74.9%). In other studies, susceptibility rates to nitrofurantoin vary from 20% in India to 93.9% in the United Kingdom.[4,6] Low susceptibility rates to ampicillin have been reported in most studies from several countries.[3-11] However, the susceptibility rates reported in the current study (i.e.13.4%) is one of the lowest reported. For gentamicin, high susceptibility rates have been reported from several countries and our study too has shown a susceptibility rate of 62.7% which is reasonably high.[5,6,8,11] However the susceptibility rates reported from India were 36%.[4] Although susceptibility rates to co-amoxiclav reported from different countries varied from 40.8% to 86.3%.[4,6,8,9,11], it was very low (20.7%) in the current study. Even though rising resistance to ciprofloxacin is a problem except in India and Ruwanda, other countries have reported susceptibility rates of >70%. Susceptibility to ciprofloxacin was 37.7% in the present study. Susceptibility of coliforms to third generation cephalosporins varies in different countries and was less than 50% in our study. However it is difficult to arrive at a firm conclusion regarding susceptibility to third generation cephalosporins in this cohort as the number of samples tested was limited and further prospective studies will be useful. For carbapenems, high susceptibility rates were noted in the present study, similar to reports from different parts of the world. Different patterns of antimicrobial usage in different communities could have been responsible for all these observations.

Overall, in this population, nitrofurantoin was the only orally administered antimicrobial with >50% susceptibility rate. Gentamicin which needs parenteral administration also had a reasonably high overall susceptibility rate which dropped to 50% in males, in hospital acquired infection, in recurrent UTI and in the presence of an AUT. Amongst the second line antimicrobials, only amikacin, netilmicin, meropenem and imipenem showed an overall susceptibility rate of > 50%. These results clearly show that empirical treatment of urinary tract infection is a great challenge in the population studied.

Lower rates of susceptibility to almost all antimicrobials have been observed in males in a study carried out by Bean et al.[6] Similarly, susceptibility rates to most first line antimicrobials, ciprofloxacin and cefuroxime were lower among males ($p<0.01$) in the current study. This is likely to be due to the complicated nature of UTI in men where these antibiotics might have been used in the treatment of previous episodes. Susceptibility rates to several antimicrobials were significantly lower in the presence of an AUT in the present study, with AUT being

commoner among males. However, Randrianirina et al (2007) has reported that there was no difference in the resistance pattern according to gender in a group of patients with community acquired UTI in Madagascar.[8]

Age has previously been shown to have an impact on susceptibility rates of antimicrobials in UTI.[8,10,13,25] A significant proportion, almost one fourth of the subjects in our study, were elderly (65 years or more). According to our findings, structural or functional abnormalities of the urinary tract were commoner in this group. A number of first line as well as second line antimicrobials showed lower susceptibility rates in the elderly as well as in those with an AUT. These findings indicate that when treatment decisions are made it would be appropriate to consider the elderly as a separate group.

As discussed previously, there was a significant difference ($p<0.05$) in susceptibility of coliforms to nitrofurantoin, gentamicin, ciprofloxacin, amikacin and netilmicin in hospital acquired infections as compared with community acquired infections in the present study. Low susceptibility rates of Gram negative bacteria to many antimicrobials in hospital acquired infections has been previously reported by Benwan et al. (2010) and Bean et al. (2008).[5,6] The differences in antimicrobial susceptibility between isolates in community and hospital acquired infections is likely to be due to the presence of additional risk factors for antimicrobial resistance in the latter group and due to higher exposure of hospital acquired organisms to antimicrobials. We observed that a few antibiotics, especially norfloxacin and ciprofloxacin, had lower susceptibility rates in those with diabetes mellitus and recurrent UTI. As recurrent UTI is commoner among those with diabetes this shared pattern is expected. As ciprofloxacin is an antibiotic frequently used in Sri Lanka, those with recurrent UTI showing higher resistance is also not unexpected.

According to the findings of our study, susceptibility to nitrofurantoin was higher in those with acute pyelonephritis as compared to those with cystitis. However this is not clinically relevant because nitrofurantoin is a urinary antiseptic and therefore not suitable for treating acute pyelonephritis which needs systemic antibiotics. There was no significant difference in susceptibility rate of the other antimicrobials between those with cystitis and acute pyelonephritis. Previous local studies have not reported on this aspect.

Several studies have shown that previous antibiotic use and prescribing practices are important factors in the development of resistance to antibiotics in a given population.[13,14,26] Goossens et al. (2005) reported that resistance to fluoroquinolones is strongly associated with a high number of prescriptions for this group of antibiotics.[26] Pharmacological surveillance is therefore an important tool in studies on antimicrobial susceptibility. According to our study findings, ciprofloxacin was the most frequently prescribed empirical antimicrobial even though it should be a reserved drug due to its propensity for collateral damage. Similar results have been reported from Turkey.[3]

To our knowledge this is the first study in Sri Lanka that looked at empirical prescribing practices of antimicrobials in UTI. Since UTI is a common condition, inappropriate prescribing increases resistance among uropathogens. Susceptibility rates to ciprofloxacin reported in our study is comparable to the same reported from India[4] but much lower than the rates reported from a number of other countries including Turkey, United Kingdom, Russia and USA.[3,6,9,10] As shown by this study, ciprofloxacin is the preferred empirical antimicrobial in this group of Sri

Lankan patients which is likely to be the reason for the reportedly low susceptibility rates. Considering the low susceptibility rates observed ciprofloxacin is not appropriate as an empirical antimicrobial in this population. Furthermore if its use is continued, development of resistance is likely to become more widespread and collateral damage aggravated. Our study shows that the prescription rate of ciprofloxacin was higher in community acquired infection than in hospital acquired infection. This finding appears to be a paradox. The higher use in hospital acquired infections could have been explained by significantly higher pseudomonas isolates in in-patients with hospital acquired infections, with ciprofloxacin being an effective anti-pseudomonal antibiotic. On the other hand, prescription rates of cefuroxime and co-amoxiclav have been higher in hospital acquired infection than in community acquired infection. All these indicate that there is a need for improving existing prescribing practices.

Limitations of the study

Firstly the study sample may not be representative of the whole population of in-patients with urinary tract infections as only those who had a positive urine culture were studied. However, by examining the hospital medical records relevant to the study period, it was found that 80% of the adults who were discharged from the hospital with a diagnosis of UTI during the study period had a positive urine culture done in the hospital. Negative cultures could have been due to treatment with antimicrobials prior to hospital admission.

Secondly this study reports the sensitivity of the organisms isolated from routinely processed urine samples. Therefore the number of samples tested for different antibiotics is different. It would have been ideal if all the antibiotics were tested in a similar number of samples.

Thirdly, due to resource constraints, differentiation of coliforms as *Klebsiella* species and *E. coli* was not possible.

Another limitation is that the antibiotic susceptibility testing method used in this study is not widely used. However this study was done as an observational study of routine practice and at the time of the study, more current methods such as testing for minimum inhibitory concentration (MIC) by broth microdilution or disk diffusion were not available in the study centre.

Conclusions

Nitrofurantoin can be recommended as the empirical antimicrobial for uncomplicated community acquired cystitis in this population. Even though nitrofurantoin showed comparatively lower susceptibility in those aged $\geq$ 65 years and in males, even in these specific groups nitrofurantoin showed the highest susceptibility rates amongst antimicrobials that can be administered orally.

Considering the low susceptibility rates observed with many antimicrobials and the need for more aggressive parenteral therapy, amikacin, netilmicin and carbapenems may need to be considered as appropriate drugs for empirical therapy in hospital acquired UTI and in those with complicated UTI.

Even though the most frequently prescribed empirical antimicrobial was ciprofloxacin, the susceptibility data did not support this practice. Considering the extensive nature of the problem of resistance, antimicrobial therapy of UTI in in-patients should always be guided by culture and antibiotic sensitivity testing.

To optimize the use of empirical antimicrobial therapy, guidelines based on local surveillance data need to be incorporated into clinical practice. Regular communication to hospital staff regarding local susceptibility data will also be helpful in guiding empirical antimicrobial therapy.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
NW conceived the study, did the literature survey, collected data in collaboration with MD, participated in data interpretation, wrote the first draft and subsequent revisions, and wrote the final version of the manuscript. MD provided microbiological data, participated in data interpretation and in writing the revisions and the final version of the manuscript. AP did statistical analysis and participated in data interpretation and in writing the revisions and the final version of the manuscript. All authors contributed to the design and conduct of the study and approved the final version of the paper.

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