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MULTIPLE DRUG RESISTANCE IN URINARY PATHOGENS AT GONDAR COLLEGE OF MEDICAL SCIENCES HOSPITAL, ETHIOPIA
F. Moges, BSc, MSc, Lecturer, Department of Microbiology and Parasitology, G. Mengistu, MD, Assistant Professor, Department of Internal Medicine and A. Genetu, BSc, Assistant Lecturer, Department of Microbiology and Parasitology, Gondar College of Medical Sciences, P.O. Box 196, Gondar, Ethiopia

Request for reprints to: Dr. G. Mengistu, Department of Internal Medicine, Gondar College of Medical Sciences, P.O. Box 196, Gondar, Ethiopia

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F. MOGES, G. MENGISTU and A. GENETU

ABSTRACT

Objective: **To determine multiple drug resistance and its associated factors of urinary pathogens.**
Design: **cross-sectional study.**
Setting: **Gondar College of Medical Sciences teaching and Referral Hospital, Northwest Ethiopia, between January and October 2000.**
Subjects and Methods: **Mid stream urine samples from 420 subjects were studied by quantitative culture method. Designed Questionnaires were used for data collection on the previous use of antimicrobials, catheterisation and hospitalisation.**
Main outcome measures: **Rates of multiple drug resistance and the associated factors.**
Results: **Multiple drug resistance was common in the isolates tested against ten antibiotics showing more than 68% of the isolates being resistant to two or more antimicrobials. Significant variables associated with this were found to be urinary catheterisation, hospitalisation and previous use of antibiotics for urinary tract infection.**
Conclusion: **The rate of multiple drug resistance was very high in this study. Probable contributing factors were found to be previous antibiotic exposure, urinary catheterisation and hospitalisation. Reduction of hospital stays and catheterisation, aseptic care of catheterised patients and selective use of antibiotics and strict follow up of hospital disease controls are recommended.**

INTRODUCTION

Urinary tract infections (UTI) remains a major clinical problem over 50 years after the introduction of anti-microbial therapy. This is partly because of the emergence of increasing rate of drug resistance in UTI. Increasing prevalence of antibiotic resistance has been reported from various countries including Ethiopia(1-3). To cope up with this, culture and antibiotic sensitivity testing should be performed repeatedly for the proper management of bacterial infections. This is crucial for guiding empirical treatment in places where routine culture and sensitivity test is impossible. Among many others, one of the commonest infections both in out-patient and in-patient levels for which such information would be useful is UTI. Urinary tract pathogens, especially those from previous exposure of antimicrobials, catheterised and hospitalised patients have been known to include strains, which are resistant to many of the commonly used antibiotics.

The aim of this study was to determine the pattern of multiple drug resistance and its associated factors (such as previous exposure of antimicrobials, catheterisation and hospitalisation) in urinary tract infection among patients attending Gondar College of Medical Sciences (GCMS) teaching and referral hospital. It is one of the oldest hospitals of the country catering populated rural village for about 50 years.

MATERIALS AND METHODS

During a total period of 10 months from January to October 2000 four hundred and twenty mid stream urine samples from symptomatic in- and out-patients were collected. Of the study subjects, 227 were females and 193 were males. The age range was 1-90 years with a mean age of 33.5. All patients were clinically diagnosed as suffering from UTI. For data collection, questionnaires were designed. Previous history of UTI, antibiotic use, hospitalisation, urinary tract catetherisation were among the variables included. Samples were collected aseptically. Outpatients gave the samples in the laboratory. For in-patients no transport media was used since the wards are in proximity to the Microbiology laboratory.

Standard procedures of Finegold and Martin(4) and Cheesborough(5) were followed to isolate and identify the bacteria. Urine samples were cultured by the streak plate methods using standard 4mm internal diameter platinum wire loop. Blood agar (Oxoid) and MacConkey agar (Oxoid) plates were inoculated and incubated at 37°C aerobically for 24 hours. Cultures with colony counts above 100,000 per ml were considered to be of significant bacteruria.

Identification of Gram negative enteric rods was with the help of biochemical tests, which routinely included Triple sugar iron agar, Indole, Simmon's citrate agar, Lysine decarboxylase, Urease and Motility.

Sensitivity tests were done on Mueller- Hinton agar with commercial disc diffusion technique of Bauer *et al* (6) against Ampicillin (10 Mcg), Tetracycline (30 Mcg), Chloramphenicol (30 Mcg), Co-trimoxazole (25 Mcg), Gentamicin (10 Mcg), Ciprofloxacin (5 Mcg), Cefoxitin (30 Mcg) and PolymyxinB (300u). Penicillin G (10 Miu and Erytromycin (15 Mcg) were added for Gram-positive organisms only(6). *E. coli* and *S. aureus* strains susceptible to all antibiotics tested were used as controls. For data analysis Epi info version 6-software package was used.

RESULTS

Demographic data on the study subjects were reported previously by Moges *et al.* Out of 172 bacterial isolates of UTI tested against 10 antibiotics the susceptibility pattern using the disc diffusion method revealed high rate of multiple resistances to commonly used antibiotics.

Multiple drug resistance is shown in Tables 1 and 2. Extremely high resistance patterns were found in *Citrobacter spp.* for Ampicillin (100%), Co-trimoxazole (90%), Tetracycline (80%), Chloramphenicol (80%) and Gentamicin (50 %). The second high rates of drug resistance values were found in *Klebsiella spp.* for Ampicillin (94.4%), Tetracycline (77.8%), Chloramphenicol (77.8%), Co-trimoxazole (72.2%), and Gentamicin (33.3%). For *E. coli* the four high resistant levels were seen in Ampicillin (69.2%), Tetracycline (68%), Co-trimoxazole (56.4%) and Chloramphenicol (42.3%). In both cases sensitivity rate was above 84% for Cefoxtin and Polymyxin B except *Klebsiella spp* (66.6% for polymyxin B) and *Citrobacter spp.* (70% for Cefoxtin). Among Gram-positives *S. aureus* has high level of drug resistance for Tetracycline (71%), Chloramphenicol (51.6%), Co-trimoxazole (48.4%) and Penicillin (38.7%). On the other hand above 80% susceptibility was found for Ciprofloxacin, Polymyxin B and Erythromycin. Though the number of isolates was low, multiple drug resistances were high in *Proteus spp.*

Above 68% of the isolated pathogens showed resistance from two to nine antimicrobials and 15.7% were resistant to one antibiotic. Only 5.8% showed no resistance to the ten antibiotics.

Table 1

Sensitivity pattern of common urinary isolates

Organism	No. (%)	Pattern	AMP %	GEN %	SXT %	TTC %	CAF %	FOX %	CIP %	PB %	ERY %	PEN %
E. coli	78	S	24.4	83.3	39.7	26.9	56.4	84.6	100	84.6	-	-
	(45.3)	I	6.4	2.6	3.9	5.1	1.3	3.9	-	5.1	-	-
		R	69.2	14.1	56.4	68.0	42.3	11.5	-	10.3	-	-
S. aureus	31	S	67.7	77.4	48.4	16.1	41.9	77.4	93.5	87.0	80.6	45.2
	(18)	I	6.5	-	3.2	12.9	6.5	-	-	6.5	-	16.1
		R	25.8	22.6	48.4	71.0	51.6	22.6	6.5	6.5	19.4	38.7
Klebsiella spp.	18	S	5.6	61.1	27.8	11.1	22.2	88.9	100.0	66.6	-	-
	(10.5)	I	-	5.6	-	11.1	-	-	-	16.7	-	-
		R	94.4	33.3	72.2	77.8	77.8	11.1	-	16.7	-	-
Coagulase negative	14	S	64.3	78.6	42.9	28.6	35.7	71.4	100.0	85.8	71.5	57.1
Staphylococcus	(8.1)	I	14.3	-	-	-	14.3	-	-	7.1	7.1	-
spp.		R	21.4	21.4	57.1	71.4	50.0	28.6	-	7.1	21.4	42.9
Citrobacter spp.	10	S	-	50	10	20.0	20.0	70.0	100.0	90.0	-	-
	(5.8)	I	-	-	-	-	-	-	-	-	-	-
		R	100	50	90	80	80.0	30.0	-	10.0	-	-
Proteus spp.	7	S	28.6	57.1	28.6	-	28.6	57.1	100.0	57.1	-	-
	(4.1)	I	-	14.3	-	-	-	14.3	-	-	-	-
		R	71.4	28.6	71.4	100	71.4	28.6	-	42.9	-	-
Others*	14	S	21.4	71.4	7.1	28.6	21.4	57.1	85.7	78.6	75.0	50.0
	(8.1)	I	7.1	-	7.1	7.1	-	-	-	7.1	-	25.0
		R	71.4	28.6	85.8	64.3	78.6	42.9	14.3	14.3	25	25.0

AMP = Ampicillin, ERY = Erythromycin, CEN = Gentamicin, PEN = Penicillin, SXT = Co-trimoxazole, TTC = Tetracycline, CAF = Chloramphenicol, FOX = Cephoxitin, CIP = Ciprofloxacin, PB = Polymyxin B

S = Sensitive, I = Intermediate, R = Resistance

**Streptococci* (n = 4), *Enterobacter spp.* (n = 3) *Salmonella spp.* (n = 3), *Serratia spp.* (n = 2), *Pseudomonas species* (n = 1), *Hafinia alvei* (n = 1).

Table 2

Multiple resistance patterns in urinary pathogens

Organism	No	Antibiogram pattern (%)							
		Ro	R1	R2	R3	R4	R5	R6	≥R7
E Coli	78	10.3	10.3	6.4	24.4	17.9	14.1	1.3	1.3
S. aureus	31	3.2	32.3	3.2	9.7	22.6	6.5	6.5	9.7
Klebsiella spp.	18	0	11.1	5.6	5.6	38.9	27.8	0	0
Coagulase negative *Staphylococcus spp.*	14	0	35.7	14.3	21.4	7.1	0	7.1	7.1
Citrobacter spp.	10	0	0	10.0	10.0	20.0	50.0	0	0
Proteus spp.	7	0	28.8	0	0	0	57.1	14.3	0
Others*	14	7.1	0	7.1	7.1	21.4	35.7	7.1	14.3
Total	172	5.8	15.7	6.4	16.3	19.8	18.6	3.5	4.0

Ro = No Antibiotic resistance
RI-R6= Number of antibiotic resistance from 1 up to 6 respectively
≥ R7 = Resistant to 7 up to 10 antibiotics
**Streptococci* (n = 4), *Enterobacter spp.* (n = 3) *Salmonella spp.* (n = 3), *Serratia spp.* (n = 2), *Pseudomonas* species (n = 1), *Hafinia alvei* (n = 1).

Of the total patients 51 (12. 1 %) gave history of urinary catheterisation. Of these 3 6 (70.6%) were cultures positive (Table 3). This was statistically significant (P< 0.001 and OR = 4.4). Resistance was high among these patients. The highest resistance rates were observed in Tetracycline (87.2%), Ampicillin (84.6%), Chloramphenicol (79.5%) and Co-trimoxazole (79.5%) and relatively lower rates were observed in Gentamicin (35.9%), Cefoxitin (33.3%) and Polymyxin B (23.1%). The sensitivity for Ciprofloxacin was 100% (Table 4).

In-patients accounted for 70 (16.7%), of these 42 (60%) were culture positive (Table 3). This was statistically significant (P< 0.001). High resistance rates were observed in Tetracycline (80%), Ampicillin (80%), Co-trimoxazole (68.9%) and Chloramphenicol (66.7) and relatively lower rates were observed in Cefoxitin (37.8 %), Gentamicin (31.1%) and Polymyxin B (17.8%). Almost all organisms were sensitive to Ciprofloxacin except one isolate, which was *S. aureus* (Table 4).

Table 3

History of catheterisation and hospitalisation with culture positivity among UTI suspects

Category	Culture status		Total	Statistical test		
	Positive (%)	Negative (%)		X^2	P-value	OR
Catheterised	36 (70.6)	15 (29.4)	51	22	< 0.001	4.4
Non-catheterised	130 (35.2)	239 (64.8)	369			
In-patient	42 (60.0)	28 (40.0)	70	14	< 0.001	2.73
Out-patient	124 (35.4)	226(64.6)	350			

OR = Odds ratio

Table 4

Resistance pattern among UTI patients with history of catheterisation and hospital admission

Category		Antibiotics (%)							No Antibiotics (%)		
	No.	AMP	CAF	SXT	TTC	GEN	FOX	CIP	PB	ERY	PEN
Catheterised	39	84.6	79.5	79.5	87.2	35.9	33.3	0.0	23.1	4	0.0	50.0
Non-Catheterised	133	55.6	42.4	57.1	66.9	18.0	15.0	2.3	9.0	45	24.4	40.0
In-Patient	45	80.0	66.7	68.9	80.0	31.1	37.8	2.2	17.8	7	28.6	57.1
Out-patient	127	55.9	50.4	59.8	68.5	18.9	12.6	1.6	10.2	42	21.4	38.1

AMP = Ampicillin, CAF = Chloramphenicol, SXT = Co-trimoxazole, TTC = Tetracycline, ERY = Erythromycin, GEN = Gentamicin, FOX = Cefoxitin, CIP = Ciprofloxacin, PB = Polymyxin B, PEN = Penicillin

Table 5

Previous history of UTI and anti-biotic treatment versus culture positivity

Antibiotics	Culture positive	Culture negative	Total
AMP	7	15	22
CAF	-	1	1
CIP	1	-	1
GEN	1	3	4
PEN	1	1	2
SXT	13	10	23
TTC	2	1	3
NOR	-	2	2
AMP, AMOX	-	1	1
AMP, SXT	1	4	5
CAF, AMP	-	1	1
GEN, SXT	1	1	2
SXT, AMOX	-	2	2
SXT, CAF	-	1	1
SXT, PEN	1	-	1
AMP, GEN, TTC	1	-	1
AMP, SXT, GEN	-	2	2
AMP, CAF, TTC	-	1	1
GEN, TTC, CAF	1	-	1
TTC, SXT, AMP	1	-	1
UNSPECIFIED	23	34	57
TOTAL	54	80	134

AMP = Ampicillin, CAF = Chloramphenicol, CIP = Ciprofloxacin, GEN = Gentamicin, PEN = Penicillin, SXT = Co-trimoxazole, TTC = Tetracycline, NOR = Norfloxacin, AMOX = Amoxicillin

Out of 420 study subjects 134 (31.9%) gave history of previous urinary tract infections and usage of different antibiotics. Of these 54 (40.3%) were cultures positive (Table 5). Ampicillin was the most commonly used anti-microbial followed by Co-trimoxazole, Tetracycline, Chloramphenicol and Gentamicin. The Flouroquinolones were used only in four cases in which one case had significant bacteriuria.

DISCUSSION

The multiple drug resistance, which is extremely high to the commonly used antibiotics in this area, is frustrating. This may be explained by wide spread misuse of antibiotics, which can cause a shift to increase prevalence of resistant organisms in the community. This is shown by about 32 % of the subjects did use antibiotics previously for UTI and of these 54% of them were again culture positive. Moreover, the previously used antibiotics were found to have high multiple drug resistance rates (Tables 1, 2 and 5). Antibiotic resistance for Ampicillin, Co-trimoxazole, Tetracycline and Chloramphenicol was higher in both out- and in- patients. This may be explained by the fact that these antibiotics were most commonly used in this hospital hence drug resistant spp. may successfully grow around. This is in agreement with Amsalu (unpublished data) that the most commonly used antibiotics were found to be Ampicillin, Co-trimoxazole, Chloramphenicol and Penicillin G in GCMS teaching hospital.

Catheterisation predisposed patients 4.4 times in the development of UTI and hence resistance. The same holds true for hospitalisation hence nosocomial infections, which increased 2.73 times urinary tract infection. Both are statistically significant with $P<0.001$. The problem of resistant pathogens has become particularly important within the context of nosocomial infection of urinary tract(7). This is also in agreement with other previous findings(8-10). The rate of multiple drug resistance is high as compared to a previous study done in Addis Ababa(1) but is in line with that

of Gondar(11) in the same area and the blood culture sensitivity pattern in Addis Ababa(12). The sample size and patients setting could explain minor differences. But it is not surprising to see high percentage of urine culture isolates resistant to commonly used anti-microbial agents in this study. This may be due to the easy availability and indiscriminate use of these drugs. In Gondar people have easy access to most of the anti-microbial agents without prescription in the market, shops, pharmacies, clinics and drug vendors. Selective pressures of these commonly used antibiotics and probably of plasmid-coded resistance have contributed to the multiple drug resistance.

In conclusion, multiple drug resistance to the commonly used antibiotics in the area was very high. Significant factors associated with this were found to be previous drug exposure, catheterisation and hospital admission, reduction of hospital stay; aseptic catheter care and reducing catheter use, avoidance of bacterial resistance by selective use of antibiotics and strict follow up of hospital disease controls are recommended.

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REFERENCES

1. Messele, G. Urinary Tract infections; Etiologic patterns and resistance. *Ethiop. Med. J.* 1983; **21:** 3-13.
2. Dawit, W. and Worku, E. Increased incidence of resistance to Antimicrobial by urinary pathogens isolated at Tikur Anbessa hospital. *Ethiop. Med. J.* 1997; **35:** 127-135.
3. Lindtjorn, B., Setegne, D. and Niemi, M. Sensitivity pattern of bacterial isolates from patients at Sidamo Reginal Hospital. *Ethiop. Med. J.* 1988; **27:** 27-31.
4. Finegold, S.M. and Martin, W.J. *Diagnostic Microbiology* 6th ed. The C.V. Mosby Company Toronto, 1982.
5. Cheesbrough, M. *Medical Laboratory Manual for Tropical Countries.* V. II Tropical Health Technology, Doddington, 1984.
6. Bauer, A.W., Kirby, W.M.M., Sherirs, J.C. and Turck, M. Antibiotic susceptibility testing by standardized single disk method. *Amer. J. Clin. Pathol.* 1966; **45:** 433-496
7. Magoha, G.A.O. Nosocomial infection of the urinary tract: Pattern of antibiotics use and drug resistance. *E. Afri. Med. J.* 1997; **74:** 190-193.
8. Van Der Wall, E., Verkooyen, R. P., Groot, J.M., Oostinga, J., Dijk, A., Hustinx, W.N.M. and Verbrugh, H.A. Prophylactic Ciprofloxacin for catheter-associated urinary tract infection. *Lancet.* 1997; **339:** 946-951.
9. Willet, W.C. and Radojcic, V. Urinary tract pathogens and antibiotic sensitivity patterns in Dar es salaam. *E. Afri. Med. J.* 1976; **53:** 685-692.
10. Turck, M. and Stamm, W. Nosocomial infection of the urinary tract. *American J. Med.* 1981; **70:** 651-654.
11. Abrham, A. and Girmay, Y. Antibiotic sensitivity pattern of prevalent bacterial pathogens in Gondar, Ethiopia. *E. African Med. J.* 1996; **73:** 67-71.
12. Daniel Asrat and Yintubezenash Wolde Amanuel. Prevalence and antibiotics susceptibility pattern of bacterial isolates from blood culture in Tikur Anbessa Hospital, Addis Ababa, Ethiopia. *Ethiop. Med. J.* 2001; **39:** 97-104.