

Clinical and Lab-Assessed Antibiotic Resistance Pattern of Uropathogens among Women with Acute Uncomplicated Cystitis

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Abstract

Background: acute uncomplicated cystitis (AUC) in females is among the most frequent infections in community. Treatment of AUC in Egypt usually based on empirical therapy.

Objectives: To determine the most common uropathogens and their pattern of resistance to commonly used antimicrobials aiming at finding a proper antibiotic which can be used as effective empirical therapy in AUC.

Patients and Methods: Observational, hospital based, cross sectional study was performed. Three hundred and twelve female patients were recruited for the study with positive urine culture and clinical symptoms correlate with AUC during the period from December 2017 to August 2018.

Results: Eight organisms were isolated. E. coli was the most common uropathogen and was isolated from 231 cases (74%). The next most common was Pseudomonas which was detected in 41 cases (13.1%). Other organisms include MRSA (6.1%), Klebsiella (2.2%), Enterococcus spp. (1.9%), proteus (1.3%), Acinetobacter and Staph. aureus (0.6%) each. Isolated uropathogens in this study were least resistant to Nitrofurantoin (47.1%). The highest resistance rate was to TMP/SMZ (87.8%). Resistance pattern to quinolones were 64.1%, 67% and 60.6% to Ciprofloxacin, Norfloxacin and Levofloxacin respectively.

Conclusion: The most common cause of community acquired AUC was E. coli. Nitrofurantoin can be used as a first line empirical therapy for AUC as it showed the least resistance pattern (47.1%). Antimicrobial resistance is a crucial issue which evolves continuously and thus more studies must be carried out in different regions and constant time intervals.

Key words: Urinary tract infection, Acute uncomplicated cystitis, Antibiotic Resistance Pattern.

Introduction

Urinary tract infections are one of the most common infections in women⁽¹⁾. Acute uncomplicated cystitis refers to a bladder infection that occurs in women who have normal structure and function of the genitourinary tract⁽²⁾. 10% of women experience at least one episode of acute uncomplicated urinary infection in a year, and 60% have at least one episode during their lifetime⁽³⁾. The peak incidence of infection occurs in young, sexually active women aged 18 to 24 years⁽⁴⁾. E. coli accounts for 85% of community acquired and 50% of hospital acquired urinary tract infections. Gram-positive Enterococcus faecalis and Staphylococcus saprophyticus are causative agents for the remainder of community acquired infections⁽⁵⁾. Development of acute uncomplicated urinary infection follows colonization of the vagina and the periurethral area by uropathogenic E. coli⁽⁶⁾. Acute uncomplicated urinary infection has a

characteristic clinical presentation. New onset frequency, dysuria, and urgency, together with the absence of vaginal discharge or pain, has a positive predictive value of 90% for acute cystitis⁽⁷⁾. Diagnosis may be confirmed by urine analysis, urine culture and sensitivity test and may be pelvi-abdominal ultrasonography to exclude complicated cases. Significant bacteriuria refers to bacterial colonization $\geq 10^5$ cfu/ml⁽⁸⁾. The World Health Organization has named antibiotic resistance as one of the three most important public health threats of the 21st century⁽⁹⁾. It was estimated that at least 23,000 people die annually in the USA as a result of an infection with an antibiotic-resistant organism⁽¹⁰⁾. Antibiotic resistance is estimated to cause around 300 million premature deaths by 2050⁽¹¹⁾. Knowledge of the antimicrobial resistance patterns of common uropathogens is essential to provide an effective empirical therapy for AUC.

Patients and Methods

Patients:

The study was performed in Urology outpatient clinics of Al-Azhar University hospitals; 312 adult female patients presented with acute uncomplicated cystitis were recruited from December 2017 to August 2018. Patients were presented by one or more of the following symptoms; dysuria, frequency, urgency, incontinence, hematuria, suprapubic pain or loin pain. Patients with the following criteria were excluded; Recurrent UTI (three or more episodes of UTI in the past year), pregnancy, diabetes mellitus and other immune-compromised conditions, urinary tract anomalies (anatomical or functional disorders), urinary catheterization, current antibiotic use or history of neurological disorders.

Urine sample collection and processing:

After detailed medical and surgical history and once diagnosis of AUC was established, patients were informed and consented about the study and urine samples were collected. Every patient was carefully instructed about proper cleaning of external genitalia and collection of clean catch mid-stream urine sample. The urine samples were taken to the Microbiology laboratory, Faculty of Medicine, Al-Azhar University within two hours at most where they were examined microscopically for pus cells and inoculated immediately on blood agar and MacConkey's agar plates. Colony counting, isolation and identification of the urinary pathogens were done according to standard bacteriological techniques. Culture result with a bacterial growth of $\geq 10^5$ cfu/ml was considered as significant bacteruria⁽¹²⁾.

Antimicrobial susceptibility testing:

Antimicrobial susceptibility testing was performed using the disc diffusion method as described by the National Committee for

Clinical Laboratory Standards⁽¹³⁾. Antimicrobial agents discs tested and reported include, Norfloxacin (NOR10 μ g), Ciprofloxacin (CIP10 μ g), Ampicillin-Sulbactam (SAM 10/10 μ g), Amoxicillin/Clavulanic acid (AMC 20/10 μ g), Gentamicin(CN10 μ g), Cefotaxime (CTX30 μ g), Ceftriaxone(CRO30 μ g), Trimethoprim/Sulfamthoxazole (SXT 1.25/23.75 μ g) and Nitrofurantoin (F 300 μ g). Isolated organisms were tested for susceptibility on the following antimicrobials, Nitrofurantoin, Trimethoprim-Sulfamethoxazole (TMP-SMZ), Ciprofloxacin, Norfloxacin, Levofloxacin, Ceftriaxone, Cefotaxime, Amoxicillin/Clavulanic acid, Ampicillin/sulbactam and Gentamicin.

Antibiotic prescribed:

After collection of urine samples, patients were treated empirically with ciprofloxacin. TMP/SMZ was prescribed to cases (46 cases) who had history of ciprofloxacin hypersensitivity or others who can't tolerate ciprofloxacin due to GIT upsets. Patients were followed after one week for detection of clinical response.

Results

Out of 379 adult female patients recruited for the study, 312 patients were eligible for the study with a positive urine culture and clinical features compatible with AUC. Sixteen patients (4.2%) were discovered by completed assessment to have anatomic or functional abnormalities, 28 patients (7.3%) did not come for follow up and 23 patients (6%) their culture and sensitivity tests revealed no bacterial growth. The age of selected cases was classified into three categories. Most of cases, 218 patients (69.9 %), were below 40 years old, while 69 patients (22.1%) were found in the zone of 40 to 60 years old. Least cases, 25 patients (8%), were more than 60 years old.

Table (1): Age distribution in studied cases

Age groups	Frequency	Percent	Cumulative Percent
Less Than 40 years	218	69.9	69.9
40-60 years	69	22.1	92
More than 60 years	25	8	100
Total	312	100	

In studied cases, 233 cases (74.7%) were married while 79 (25.3%) were not.

Table (2): Marital status of studied cases

Marital status of selected cases				
Marital status	Frequency	Percent	Valid Percent	Cumulative Percent
Not Married	79	25.3	25.3	25.3
Married	233	74.7	74.7	100.0
Total	312	100.0	100.0	

By urine culture and sensitivity tests, eight species of bacteria were detected. The most common organism was E. coli which was detected in 231 cases (74%). The next most common was Pseudomonas which was detected in 41 cases (13.1%). Other organisms include; MRSA (6.1%), klebsiella (2.2%), enterococcus (1.9%), proteus (1.3), acinetobacter and Staph. aureus (0.6%) each.

Table (3): Bacterial species detected by culture and sensitivity tests of urine samples of studied cases.

Organisms				
Organism	Frequency	Percent	Valid Percent	Cumulative Percent
E. coli	231	74.0	74.0	74.7
Enterococcus	6	1.9	1.9	76.6
Klebsiella	7	2.2	2.2	78.8
MRSA	19	6.1	6.1	84.9
Proteus	4	1.3	1.3	86.2
Pseudomonas	41	13.1	13.1	99.4
Staph. aureus	2	0.6	0.6	100.0
Total	312	100.0	100.0	

The most common uropathogen in middle aged group (20-40 years old) was E. coli. Out of 202 cases at middle age, 144 E. coli isolates were detected (71.2%). Acinetobacter, klebsiella, MRSA, proteus and Staph. aureus were not detected at all below age of 20 years. Enterococcus and Staph. aureus were also absent above age of 40 years.

Table (4): Frequency of prevalent organisms in relation to patient's age

Organism		Acinetobacter	E. coli	Enterococcus	Klebsiella	MRSA	Proteus	Pseudomonas	Staph. aureus	Total (%)
Age (years)										
<20	Number	0	14	1	0	0	0	3	0	18
	Percentage	0.0	4.5	0.3	0.0	0.0	0.0	1.0	0.0	5.8
20-40	Number	1	144	5	4	13	3	30	2	202
	Percentage	0.3	46.2	1.6	1.3	4.2	1.0	9.6	0.6	64.7
>40	Number	1	73	0	3	6	1	8	0	92
	Percentage	0.3	23.4	0.0	1.0	1.9	0.3	2.6	0.0	29.5
Total	Number	2	231	6	7	19	4	41	2	312
	Percentage	0.6	74.0	1.9	2.2	6.1	1.3	13.1	0.6	100.0

Antibiotics sensitivity was tested against 10 antibiotics which are the commonly prescribed antibiotics in our society. These antibiotics are Nitrofurantoin, Ciprofloxacin, Norfloxacin, Levofloxacin, Trimethoprium/ sulfamethoxazole (TMP/SMZ), Ceftriaxone, Cefotaxime, Amoxicillin/ Clavulanic acid, Ampicillin/Sulbactam and Gentamicin.

Nitrofurantoin showed the least resistance pattern. Out of 312 cases, 165 cases were sensitive to Nitrofurantoin (52.9%) while 147 cases were resistant to it (47.1%).

Table (5): Sensitivity and resistance of Uropathogens to nitrofurantoin

Nitrofurantoin	Frequency	Percent	Valid Percent	Cumulative Percent
S	165	52.9	52.9	52.9
R	147	47.1	47.1	100.0
Total	312	100.0	100.0	

TMP/SMZ showed the least sensitivity pattern in selected cases. In 312 isolates, 38 cases (12.2%) were sensitive to TMP/SMZ while 274 cases (87.8%) were resistant.

Table (6): Sensitivity and resistance of TMP/SMZ in selected cases

TMP/SMZ	Frequency	Percent	Valid Percent	Cumulative Percent
S	38	12.2	12.2	12.2
R	274	87.8	87.8	100.0
Total	312	100.0	100.0	

Resistance and sensitivity pattern of antimicrobials to different Quinolones were quite similar. Ciprofloxacin showed sensitivity in 112 cases (35.9%) and resistance in 200 cases (64.1%). Norfloxacin showed sensitivity in 103 cases (33%) and resistance in 209 cases (67%). Levofloxacin showed sensitivity in 123 cases (39.4%) and resistance in 189 cases (60.6%).

Table (7): Sensitivity and resistance of uropathogens to ciprofloxacin

Ciprofloxacin	Frequency	Percent	Valid Percent	Cumulative Percent
S	112	35.9	35.9	35.9
R	200	64.1	64.1	100.0
Total	312	100.0	100.0	

Table (8): Sensitivity and resistance of uropathogens to norfloxacin

Norfloxacin	Frequency	Percent	Valid Percent	Cumulative Percent
S	103	33.0	33.0	33.0
R	209	67.0	67.0	100.0
Total	312	100.0	100.0	

Table (9): Sensitivity and resistance of uropathogens to Levofloxacin

Levofloxacin	Frequency	Percent	Valid Percent	Cumulative Percent
S	123	39.4	39.4	39.4
R	189	60.6	60.6	100.0
Total	312	100.0	100.0	

E. coli strains showed the least rate of resistance to Nitrofurantoin and the highest rate of resistance to TMP/SMZ. No organism were absolutely resistant to Nitrofurantoin while *Klebsiella*, *Enterococcus*, *Proteus*, *Staph. aureus* and *Acinetobacter* were absolutely resistant to TMP/SMZ.

Table (10): Overall resistance (%) of uropathogenes to antimicrobials in selected cases with acute uncomplicated cystitis

resistance organism	Nitrofurantoin	TMP-SMZ	Ciprofloxacin	Norfloxacin	Levofloxacin	Ceftriaxone	Cefotaxime	Amox/clav ¹	Amp/sulb ²	Gentamicin
E.coli	48.1	87.4	65.4	68.4	62.3	74.9	64.9	68.4	81.4	77.9
Pseudomonas	36.6	85.4	65.9	43.9	61	63.4	61	63.4	73.2	75.6
MRSA	57.9	84.2	52.6	57.9	31.6	57.9	57.9	73.7	94.7	89.5
Klebsiella	42.9	100	28.6	71.4	28.6	57.1	57.1	42.9	100	85.7
Enterococcus	33.3	100	50	83.3	83.3	83.3	83.3	50	66.7	100
Proteus	75	100	100	100	100	75	75	50	25	75
Staph aureus	50	100	50	50	50	50	50	50	100	50
Actinetobacter	50	100	100	100	100	100	100	50	50	50

*(1) Amoxicillin-clavulanicid, * (2) Ampicillin-sulbactam

MDR referred to uropathogens which were resistant to more than three groups of antimicrobials. Overall MDR were detected in 244 cases (78.2%). Out of 231 E. coli isolated strains, MDR were detected in 185 cases (80%) of all E. coli isolates which represent 59.3% of total MDR.

Table (11): Multidrug resistance of different uropathogens for the tested antimicrobials

Organisms		One drug resistance	Two drugs resistance	Three drugs resistance	More than three drug resistance	Total
Acinetobacter	Count	0	0	1	1	2
	percent	0.00	0.00	0.30	0.30	0.60
E. coli	Count	0	11	35	185	231
	percent	0.00	3.50	11.20	59.30	74.00
Enterococcus	Count	0	0	0	6	6
	percent	0.00	0.00	0.00	1.90	1.90
Klebsiella	Count	0	0	0	7	7
	percent	0.00	0.00	0.00	2.20	2.20
MRSA	Count	0	2	5	12	19
	percent	0.00	0.60	1.60	3.80	6.0
Proteus	Count	0	1	0	3	4
	percent	0.00	0.30	0.00	1.00	1.30
Pseudomonas	Count	0	4	7	30	41
	percent	0.00	1.30	2.20	9.60	13.10
Staph. aureus	Count	1	1	0	0	2
	percent	0.30	0.30	0.00	0.00	0.6
Total	Count	1	19	48	244	312
	percent	0.30	6.10	15.40	78.20	100.00

Ciprofloxacin was prescribed empirically in 266 cases (85.3%) while TMP/SMX was prescribed in 46 cases (14.7%).

Table (12): Empirical antibiotics prescribed for studied cases

Antibiotics prescribed				
Antibiotic	Frequency	Percent	Valid Percent	Cumulative Percent
Ciprofloxacin	266	85.3	85.3	85.3
TMP-SMZ	46	14.7	14.7	100.0
Total	312	100.0	100.0	

The clinical response of cases was determined after 7 days course of antibiotic. 279 cases improved (89.4%) while 33 cases didn't improve (10.6%).

Table (13): Clinical response of selected cases to empirical antibiotics prescribed

Clinical response				
Response	Frequency	Percent	Valid Percent	Cumulative Percent
Improved	279	89.4%	89.4%	89.4
Not improved	33	10.6%	10.6%	100.0
Total	312	100.0%	100.0%	

In cases treated empirically with ciprofloxacin, 237 cases improved clinically (89.1%) while 29 cases didn't improve (10.9%). In cases empirically treated with TMP/SMZ, 42 cases improved clinically (91.3%) while 4 cases didn't improve (8.7%).

Table (14): Clinical response of selected cases to ciprofloxacin and TMP/SMZ

Antibiotic	Response	Frequency	Percent	Valid Percent	Cumulative Percent
Ciprofloxacin	Improved	237	89.1	89.1	89.1
	Not improved	29	10.9	10.9	100.0
	Total	266	100.0	100.0	
TMP-SMZ	Improved	42	91.3	91.3	91.3
	Not improved	4	8.7	8.7	100.0
	Total	46	100.0	100.0	

In this study, 23 cases were excluded from the study after culture and sensitivity tests revealed no bacterial growth. Out of these cases, 21 cases received ciprofloxacin, while 2 cases received TMP/SMZ. On follow up, 19 cases (82.6%) improved while 4 cases (17.4%) didn't improve. Of ciprofloxacin prescribed cases 18 cases (85.7%) improved while 3 cases (14.3%) didn't. Of TMP/SMZ prescribed cases 1 case (50%) improved while 1 case (50%) didn't.

Discussion

This study included 312 patients with positive cultures, including total of eight species, three gram positive species; namely MRSA in 19 cases (6.1%), Enterococcus in 6 cases (1.9%), Staphylococcus aureus in 2 cases (0.6%) and five gram negative species; namely E coli presenting the most predominant species

in 231 cases(74%), pseudomonas in 41cases (13.1%), klebsiella in 7 cases (2.2%), proteus in 4 cases (1.3%), and Acinetobacter in 2 cases (0.6%).

Our results showed that E. coli was the most common bacterium that caused urinary tract infections (74 %), and this result agrees with previous studies both in Egypt and other countries^(14,15,16). In the current study, the most frequent uropathogens included in acute uncomplicated cystitis were E. coli (74%), Pseudomonas (13.1%), MRSA (6.1%), Klebsiella (2.2%) and Enterococcus (1.9%). In previous study done in Egypt, the prevalence of uropathogens was not the same. E. coli was found in 61.76%, Klebsiella 12.5%, Enterococcus 7.35%, Staphylococcus aureus 6.61% and Pseudomonas 3.76%⁽¹⁴⁾.

Although the demographic difference doesn't affect the fact that E. coli is the most

predominant organism causing acute uncomplicated cystitis, there were significant demographic changes regarding uropathogens other than *E. coli*. In a similar study performed at Saudia Arabia, *E. coli* represents 53% of the isolates while *Klebsiella* was 15%, *Pseudomonas* 12%, MRSA 3%, Enterococci 3%, Enterobacter 3% and *Proteus* 2%⁽¹⁵⁾. In an Indian study, *E. coli* represents 67.66% of isolates. The next most common uropathogen was *Klebsiella pneumoniae* (14%) followed by *Proteus sp.* (6%), *Pseudomonas* (8%), Enterococcus sp. (2%), and *Streptococcus agalactiae* (1%)⁽¹⁶⁾. In an Italian study, *E. coli* represents 85.3% of isolates, followed by *Klebsiella pneumoniae* (6%), *Staphylococcus saprophyticus* (3.2%), *Proteus Mirabilis* (2.3%), Enterococcus faecalis (1.7%)⁽¹⁷⁾. In a similar study performed at South Korea, *E. coli* represents 71.1% of isolates. The second most common uropathogen was Enterococci (13.0%) followed by *Klebsiella spp.* (3.7%) Enterobacter spp. (3.0%) Citrobacter spp. (3.0%) *Proteus spp.* (1.0%)⁽¹⁸⁾. In a Brazilian study, *E. coli* represents 64.7% of isolates. The second most common uropathogen was *Klebsiella sp.* (14.2%), Enterobacter sp. (7.1%) followed by *Proteus sp.* (4.8%), coagulase-negative staphylococcus (4.3%), Citrobacter sp. (2.4%), Enterococcus sp. (1.2%), Staph. aureus (0.8%) and *Pseudomonas sp.* (0.5%)⁽¹⁹⁾. In a study performed in USA, *E. coli* represents 68% of isolates. The second most common uropathogen was *Staphylococcus saprophyticus* (8%), followed by Group B streptococci (7%), *Proteus spp.* (6%), *Klebsiella spp.* (4%), Enterococcus (3%), and other organisms (4%)⁽²⁰⁾.

This study was concerned about detecting pattern of resistance of uropathogenes to antimicrobials which are commonly used in our society. These antimicrobials include: Nitrofurantoin, Trimethoprim/ sulfamethoxazole (TMP-SMZ), Ciprofloxacin, Levofloxacin, Norfloxacin, Ceftriaxone, Cefotaxime, Amoxicillin/Clavulanic acid, Ampicillin/Sulbactam and Gentamicin.

In this study, resistance to Nitrofurantoin was 47.1%, TMP-SMZ 87.8%, Ciprofloxacin 64.1%, Levofloxacin 60.6%, Norfloxacin 67%, ceftriaxone 72.1%, Cefotaxime 64.4%, Amoxicillin/Clavulanic acid 66.7%, Ampicillin/Sulbactam 79.8% and Gentamicin 78.5%. These data indicate that among common antibiotics tested in our study, only nitrofurantoin had less than 50% resistance (47.1%) which supports its recommendation as an effective

empiric therapy for AUC in our hospitalscommunity area. In an Egyptian study performed in 2009, resistance of *E. coli* was 17.4% to Nitrofurantoin, 60% to TMP-SMZ, 47.8% for Ciprofloxacin and Norfloxacin, 40.7% for Ceftriaxone, 39.1% for Cefotaxime, 68.1% for Amoxicillin/Clavulanic acid, 100% for Ampicillin/Sulbactam and 34.8% for Gentamicin⁽¹⁴⁾. In a study performed in Saudia Arabia, resistance to Nitrofurantoin was 22.4%, TMP-SMZ 59.5%, Ciprofloxacin 32.4%, Norfloxacin 46%, Ceftriaxone 32.2%, Amoxicillin/Clavulanic acid 51.6% and Gentamicin 32.3%⁽¹⁵⁾. In an Indian study, the pattern of resistance of *E. coli* was quite similar. Resistance of *E. coli* strains to Nitrofurantoin was 36.1%, TMP-SMZ 100%, Amoxicillin/Clavulanic acid 85%, Aminoglycosides 67%, Fluoroquinolones 75% and Ceftriaxone 65%⁽¹⁶⁾. In a Brazilian study, the pattern of resistance was quite different where resistance to Nitrofurantoin was 15.7%, TMP-SMZ 39.8%, Ciprofloxacin 10.2%, Norfloxacin 7.5%, Levofloxacin 18.2%, Ceftriaxone 4.9%, Amoxicillin/Clavulanic acid 17.4% and Gentamicin 3.5%⁽¹⁹⁾. In a similar study performed in Italy, resistant pattern was also different where Nitrofurantoin was 9.9%, TMP-SMX 30.2%, Ciprofloxacin 15%, levofloxacin 15% and amoxicillin/Clavulanic acid 11.7%⁽¹⁷⁾. In a similar study performed in South Korea, resistance to TMP-SMZ was 26.1%, Ciprofloxacin 21.1%, Ampicillin/Sulbactam 47.7% and Gentamicin 19.5%⁽¹⁸⁾.

In this study, multi-drug resistant *E. coli* strains represent 59.3%. In an Indian study, multi-drug resistant *E. coli* strains represent 65%⁽¹⁶⁾.

Out of 312 cases, Ciprofloxacin were prescribed empirically in 266 cases (85.3%) while TMP/SMZ was prescribed in 46 cases (14.7%). Out of 312 cases, 279 cases (89.4%) improved with empirical therapy while 33 cases (10.6%) didn't improve. Out of 266 cases ciprofloxacin was prescribed for, 237 cases improved clinically (89.1%) while 29 cases didn't improve (10.9%). Out of 46 cases TMP/SMZ was prescribed for, 42 cases improved clinically (91.3%) while 4 cases didn't improve (8.7%).

Conclusion

This study showed that *E. coli* is the most common pathogen involved in AUC. Antibiotic resistance is a worldwide problem threatening our ability to treat infections and

thus increase rate of treatment failure which in turn increases mortality, morbidity and economic costs. Isolated uropathogens in this study were least resistant to Nitrofurantoin (47.1%). The highest resistance rate was to TMP/SMZ (87.8%). Resistance pattern to quinolones were 64.1%, 67% and 60.6% to ciprofloxacin, norfloxacin and levofloxacin respectively.

Recommendations

From our study, we recommend that Nitrofurantoin is suitable to be the first line of empirical therapy for treating AUC as it shows the least resistance pattern among studied antibiotics. We also recommend that this study should be followed by similar community studies at different regions and constant intervals to detect pattern of uropathogens resistance to commonly used antimicrobials and whether it evolve or not. This will help clinicians to provide safe and effective empirical therapies with minimal therapeutic failures.

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