Microbial Uropathogens and Their Antibiotic Resistance Profile from Hospitalized Patients in Central Alabama

LI QIAN, TRACY CAMARA, J KYLE TAYLOR, KATHY W JONES

ABSTRACT

Urinary tract infections remain a common problem in inpatient care. They are highly challenging to provide effective initial therapy without sensitivity data. The purpose of this study was to survey the uropathogens and their sensitivity profile at a hospital in Central Alabama and to guide experiential antibiotic selection. This was the first reported study on bacterial uropathogens and their antibiotic resistance profile at this Central Alabama hospital. The survey period was between July 2009 and June 2010, a total of 473 urine cultures were reviewed and susceptibility testing was determined using the Clinical and Laboratory Standards Institute (CLSI) microdilution method. The results indicated that *Escherichia coli* (45.5%) was the most common organism, followed by *Klebsiella pneumoniae* (18.2%), *Pseudomonas aeruginosa* (10.1%), *Proteus mirabilis* (7.8%), *Enterobacter cloacae* (4.2%), methicillin-resistant *Staphylococcus aureus* (3.0%), *Klebsiella oxytoca* and *Citrobacter freundii* (1.5%), *Morganella morganii* (1.3%), and the other species (7.0%). For the 215 *E. coli* isolates, imipenem and cephalosporins (except for cefazolin) had the highest sensitivity (99-100%, $P<0.05$). In contrast, ampicillin had the highest resistance (57%, $P<0.05$) as compared to other antibiotics (about 30%) including ampicillin/sulbactam, ciprofloxacin, levofloxacin, tetracycline, and trimethoprim/sulfamethoxazole. The major finding of this study was that ciprofloxacin, levofloxacin and trimethoprim/sulfamethoxazole had comparable sensitivity patterns for *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae,* the most common uropathogens at this Central Alabama hospital. Additionally, this study found that *E. coli* had a resistant rate of 31% to ciprofloxacin and levofloxacin compared to the resistance rate of 28.4% and 15.8% in earlier reports (Lee et al. 2010; Rattanaumpawan et al. 2010), likely indicating the continuing evolution of resistance due to antibiotic exposure. It is imperative to monitor the resistance of *P. aeruginosa* considering their high resistance to imipenem found in this study.

ABBREVIATIONS

UTI-urinary tract infection, TMP/SXM-trimethoprim/sulfamethoxazole, Pip/Tazo-piperacillin/tazobactam, CLSI-Clinical and Laboratory Standards Institute, *E. coli-Escherichia coli, P. aeruginosa-Pseudomonas aeruginosa, K. pneumonia-Klebsiella pneumoniae, P. mirabilis-Proteus mirabilis, E. cloacae-Enterobacter cloacae,* MIC-minimum inhibitory concentration, IDSA-Infectious Disease Society of America, ESBL-extended spectrum beta-lactamase.

INDEX TERMS

Urinary tract infection, Antibiotic, Urinary pathogen

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INTRODUCTION

Urinary tract infections (UTI) remain common among clinic or medical center patients and continue to pose a serious challenge to effective chemotherapy. Approximately 50% of women report at least one UTI in their lifetime.[1] Moreover, UTIs are the most frequent cause of infection among nursing home residents and the most common documented source of bacteremia in the elderly population.[2,3] Each year, about 15% adult women and 3% adult men are diagnosed with UTI or cystitis. These diagnoses accounted for about 500,000 hospital admissions and more than 8 million outpatient visits each year.[4] Approximately 25% of patients already hospitalized with other medical and surgical conditions require endourological interventions (usually catheters) that could result in a nosocomial infection.[5] Among the hospitalized patients (over 1.5 million hospital case records), UTI's are the most common cause of bacteremic episodes and are associated with a high (10-23%) case fatality rate, prolonged hospital stay, and added health care costs.[6-8]

Treatment of UTI in the modern eras started in 1953 with the introduction of nitrofurantoin, a synthetic antibiotic that has been used for more than 50 years, which is safe to use, has a relatively low resistance and a high efficacy.[9] However, it does not penetrate urinary tract tissue very well, nor does it achieve bactericidal concentrations in blood. Hence, nitrofurantoin is not useful for treating complicated UTI and uncomplicated pyelonephritis. Nalidixic acid, the prototype of a new class of antimicrobials known as quinolones, readily penetrates urinary tract tissues and has been used as an effective treatment for complicated UTI and kidney infections.[10] β-lactams are a large family of antimicrobials that exert antibacterial activity by inhibiting cell wall synthesis. Some of the β-lactams such as amoxicillin and ampicillin used to be the preferred regimen for UTI, but many uropathogens have developed resistance to this class of agents.[9]

Trimethoprim/sulfamethoxazole (TMP/SMX) is active against most aerobic Gram-positive and Gram-negative organisms, but not against anaerobic bacteria or *Pseudomonas aeruginosa* (*P. aeruginosa*). The wide spread use of TMP/SMX has caused microbial resistance for this drug.[11] Fluoroquinolones exert bactericidal action by direct inhibition of DNA synthesis, leading to irreversible DNA damage and ultimately cell death.[12] Fluoroquinolones have potent activity against most etiological agents responsible for UTI. The most commonly used fluoroquinolones are Ciprofloxacin and Levofloxacin[13] and they still remain as the first line antibiotics for the empirical treatment of UTI in many parts of the world, including the US.

The pathogens responsible for UTI vary depending on gender, region, antibiotic use and other factors. Over the years, the patterns of uropathogen infections have shifted significantly, but *Escherichia coli* (*E.coli*) still remains the number one.[14-17] The initial treatment of UTI is always empirical before the identification and sensitivity results are available, which usually takes at least 24 hours. Hence, knowing the uropathogens and their resistance profile in a specific hospital is critical for effective management of UTI patients. To our knowledge, no study has been published in Central Alabama on this issue. Accordingly, this study was designed to survey the uropathogens and their sensitivity profile for inpatients in Central Alabama and to guide clinical practice for antibiotic selection.

MATERIALS AND METHODS

This study was performed at a teaching hospital in Central Alabama that has approximately 350 inpatients per day. Urine collected by indwelling catheterization, suprapubic aspiration, during cystoscopy or other surgical procedures was submitted to the hospital laboratory in Central Alabama from July 2009 to June 2010. The specified microbiology and antimicrobial susceptibility results (susceptibility category) were recorded according to the Clinical and Laboratory Standards Institute (CLSI) minimum inhibitory concentration (MIC) breakpoints.

Sixteen antimicrobials reported in this study included: ampicillin/sulbactam (Amp/sulbactam), ampicillin, ceftazidime, ceftriaxone, cefotaxime, cefazolin, ciprofloxacin, cefepime, nitrofurantoin, gentamicin, imipenem, levofloxacin, piperacillin/tazobactam (Pip/Tazo), TMP/SMX, tetracycline, and tobramycin. Quality control was performed weekly using the following test organisms *E. coli* ATCC 25922 and 35218, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 51299 and 29212, *P. aeruginosa* ATCC 27853, and *Klebsiella pneumoniae* (*K. pneumoniae*) ATCC 700603. CLSI (M100-S20)[18] contemporary documents served as the interpretive criteria for each

antimicrobial tested. The antimicrobials were categorized as cephalosporins, other β-lactams, aminoglycosides, fluoroquinolones, and others (e.g., TMP/SMX, tetracycline, and nitrofurantoin). Chi-square test or Fisher's exact *t*-test was used to determine the significant difference in resistance using IBM SPSS for Windows (version 19.0 software package; IMB Corp. Armonk, NY, USA). The significance level was defined at p less than or equal to 0.05.

RESULTS

From July 2009 to June 2010, 473 urine cultures were performed in Central Alabama hospital laboratory. The frequency of pathogen and rank order among the most prevalent pathogens are shown in Figure 1. *E. coli* accounted for approximately one-half of uropathogens (45.5%), followed by *K. pneumoniae* (18.2%), *P. aeruginosa* (10.1%), *Proteus mirabilis* (*P. mirabilis*) (7.8%), *Enterobacter cloacae* (*E. cloacae*) (4.2%), methicillin-resistant *Staphylococcus aureus* (3.0%), *Klebsiella oxytoca* (1.5%) and *Citrobacter freundii* (1.5%), *Morganella morganii* (1.3%), and the other species (7.0%).

Susceptibility testing results for the most common organisms in urine specimens are summarized in Table 1. Among the sixteen antibiotics tested, *E. coli* showed the highest sensitivity (99-100%) to imipenem and most cephalosporins excluding cefazolin ($P<0.05$), followed by Pip/Tazo (97%), aminoglycosides (92%), TMP/SMX (73%), levofloxacin (69%), tetracycline (69%), ciprofloxacin (68%), Amp/sulbactam (48%), and ampicillin (43%). It is interesting to note that *E. coli* had comparable sensitivity to ciprofloxacin, levofloxacin, TMP/SMX, and tetracycline in the range of 68%-73%.

K. pneumoniae had a high sensitivity (90%-100%) to cephalosporins, aminoglycosides, fluoroquinolones, TMP/SMX, tetracycline, imipenem, and Pip/Tazo. However, *K. pneumoniae* was highly resistant to ampicillin (100%) and relatively resistant to nitrofurantoin (36%).

For *P. aeruginosa*, the rank order of antimicrobial sensitivity was tobramycin (96%) > Pip/Tazo (92%) > ceftazidime (85%). The fluoroquinolones, including levofloxacin and ciprofloxacin, had a sensitivity in the range of 50-60%. Multidrug-resistant *P. aeruginosa* was detected in this central Alabama hospital as indicated by the resistance rate for ciprofloxacin and levofloxacin (42%) > cefotaxime (40%) > ceftriaxone (27%) >imipenem (19%).

P. mirabilis showed 100% susceptible rates to ceftriaxone, ceftazidime, cefotaxime, cefepime, Amp/sulbactam, and Pip/Tazo. This organism had a 100% resistant rate to tetracycline, followed by nitrofurantoin (95%), ciprofloxacin (43%).

E. cloacae did not show any resistance to imipenem. In addition, they were also very sensitive to aminoglycosides, fluoroquinolones, cefepime, TMP/SMX, and tetracycline (>80% susceptible). The *E. cloacae* were highly resistant to cefazolin and ampicillin ranging from 85% to 90%.

DISCUSSION

Urine culture is the gold standard diagnostic method for UTIs. However, obtaining reliable culture data can be challenging. The reliability of urine culture is directly related to the collection method employed. The collection method most commonly used in the outpatient setting is the midstream clean catch voiding method, although it is the most convenient, it is also the least reliable method.[1] Even when perineal cleaning is performed correctly, nearly one-third of these specimens can be contaminated.[19] Therefore, clinical practitioners prefer catheterized urine sample for UTI diagnosis, which contributed to catheterized urine specimens being the primary focus for this study.

Urinary tract infections are very common among hospitalized patients. The pathogen profiles are dependent on the patient profile and antibiotic usage. For instance, the pathogens for outpatient UTI are predominantly *E. coli* (more than 80%) while *E. coli* represented about 50% UTI for inpatients among many reported studies.[15-17] The top five uropathogens found in this study were similar to reported results by Jones et al.[14] in which *E. coli* was 48.6%, *Enterococcus* spp. 13.7%, *Klebsiella* spp. 12.0%, *P. aeruginosa* 6.2%, *Enterobacter* spp. 4.2%, *P. mirabilis* 3.8%. However, in the current study, *Klebsiella* spp. was 18.2%, ranked as the second most common pathogen. According to Norris et al.,[20] *Enterococcus* species infections tend to occur in old men with urinary tract abnormalities due to prostate gland. The different uropathogen profiles

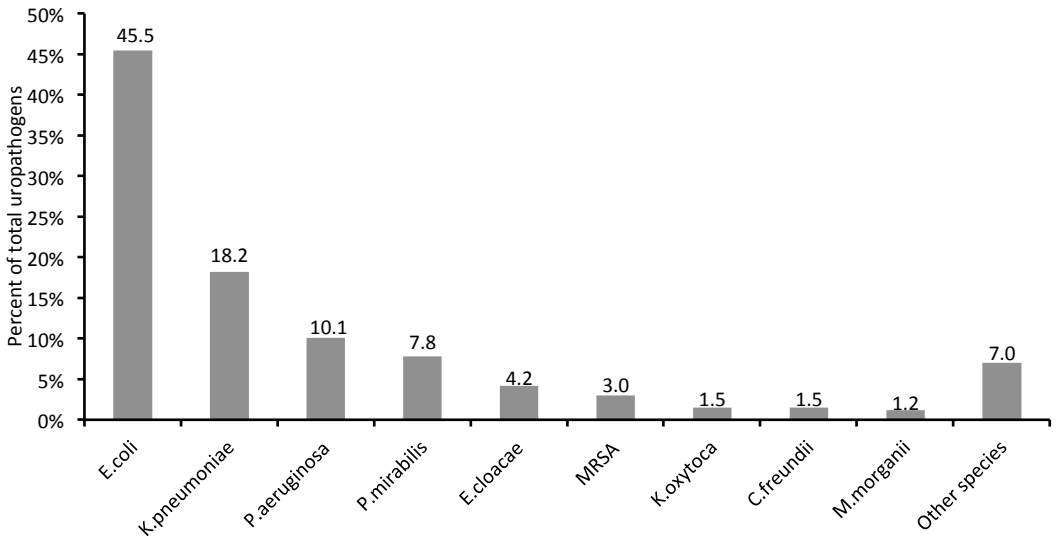

Figure 1. Frequency Distribution of Pathogens in Urine Culture from Hospitalized Patients in Central Alabama. July 2009 - June 2010

* Other species includes: *Acinetobacter lwoffii* (2), *Acinetobacter baumannii* (2), *Citrobacter amalonaticus* (2), *Citrobacter koseri* (4), *Enterobacter aerogenes* (4), *Proteus penneri* (1), *Proteus rettgeri* (1), *Proteus stuartii* (4), *Proteus* sp. (1), *Serratia liquefaciens* (1), *Serratia marcescens* (1),*Coagulase negative Staphylococcus* sp. (2), *Enterococcus* sp. (1), *Staphylococcus capitis* (1), *Staphylococcus aureus* (3), and *Enterococcus faecium* (3).

Table 1. The Susceptible Rates (%) of Sixteen Antibiotics against the Most Common Organisms in UTI from Catheterized Urine Samples

Antibiotic agent	E. coli			K. pneumoniae			P. aeroginosa			P. mirabilis			E. cloacae		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Cephalosporins															
Ceftriaxone	99	<1	<1	98	0	2	38*	35	27	100	0	0	65*	5	30
Ceftazidime	99	0	1	95	0	5	85	4	11	100	0	0	65*	0	35
Cefotaxime	99	0	1	98	0	2	15*	45	40	100	0	0	60*	10	30
Cefazolin	86*	7	7	92	1	7	-	-	-	95	5	0	10*	0	90
Cefepime	99	0	1	98	0	2	75*	15	10	100	0	0	90	5	5
Other β-lactams															
Amp/sulbactam	48*	20	33	85*	8	7	-	-	-	100	0	0	35*	5	60
Ampicillin	43*	0	57	0	0	100	-	-	-	97	0	3	10*	5	85
Imipenem	100	0	0	100	0	0	75*	6	19	97	0	3	100	0	0
Pip/Tazo	97	1	2	98	1	1	92	0	8	100	0	0	70	10	20
Aminoglycosides															
Gentamicin	92	0	8	95	0	5	69*	23	8	81	0	19	85	5	10
Tobramycin	92	2	7	95	2	3	96	2	2	81	11	8	80	20	0
Fluoroquinolones															
Ciprofloxacin	68*	1	31	95	2	3	56*	2	42	46*	11	43	80	0	20
Levofloxacin	69*	0	31	98		1	56*	2	42	62*	3	35	80	0	20
Others															
Trimeth/Sulfa	73*	0	27	92	0	8	-	-	-	62*	0	38	85	0	15
Tetracycline	69*	1	30	90	5	5	-	-	-	0	0	100	85	15	5
Nitrofurantoin	96	1	3	64*	29	7	-	-	-	0	5	95	40*	40	20

S=sensitive, I=intermediate, R=resistant, * $p < 0.05$

might indicate that the patient profiles are different between the two studies. Hence, clinical decisions should be made based on etiological pathogens and patient characteristics specific for each hospital Overall, *E. coli* showed satisfactory sensitivity (99%-100%) to most cephalosporins excluding cefazolin (86%, P<0.05),

imipenem, aminoglycosides, Pip/Tazo, and nitrofurantoin.

However, levofloxacin and ciprofloxacin, the current first line antibiotics, had sensitivity only around 70% that was below the recommended sensitivity of at least 80% for experiential treatment by Infectious Disease Society of America (IDSA).[21] This sensitivity was much lower than the 98% reported by Jones et al.[14] However, our results were similar to Lee et al.[22] (71.5%), but lower than Rattanaumpawan et al.[17] (84%). Based on data of the global inpatient urinary tract isolates of *E. coli*, Hoban et al.[23] reported that *E. coli* showed an increased resistance rate of 38% to quinolones including levofloxacin and ciprofloxacin; furthermore, for the extended spectrum beta-lactamase (ESBL) producers, the resistance rate was as high as 84.7%. The increased resistance to quinolones can be explained by their widespread use for UTI and other infections due to their broad spectrum of antimicrobial activity and convenient per oral regimen. The fluoroquinolones resistance noted among UTI pathogens in this study is of growing concern as these antimicrobial agents are usually important oral regimens for empiric treatment. Based on the data from this study, other less expensive antibiotics including aminoglycosides, tetracycline, nitrofurantoin, and TMP/SXM had better or similar activity for UTI as compared to quinolones. Overall, cephalosporins had better activity than quinolones. Hence, it might be a prudent approach to consider other antibiotics for future experiential treatment of UTI in a hospital setting other than quinolones in this Central Alabama hospital.

Although *K. pneumoniae* was the second most common uropathogen for UTI in this study, it was sensitive to most of the antibiotics tested (92%--100%) except for ampicillin (0%, $P<0.05$) and nitrofurantoin (64%, $P<0.05$), even with combination of sulbactam/ampicillin still had low activity against *K. pneumoniae*. The current finding of the resistance of *K. pneumoniae* to ampicillin (100%) supported the *Klebsiella* species intrinsic resistance to ampicillin.[24] The spectrums of the antibiotics of *K. pneumoniae* in this study agreed with most susceptibility patterns of *K. pneumoniae* reported.[15] Therefore, there is little concern about the coverage of this relatively common UTI pathogen in experiential treatment.

P. aeruginosa is notorious for its resistance to antimicrobial agents.[14,15] This study further confirmed this point. Tobramycin and Pip/Tazo showed the highest sensitivity of 96% and 92%, respectively. Ceftazidime showed sensitivity of 85%. Surprisingly, imipenem, an antibiotic reserved for resistant microbial infection, only had a sensitivity of 75%. This study did not agree with previous sensitive findings of 90%-100%.[14,23] However, it is similar to the result of the resistant rates of *P. aeruginosa* to imipenem in China (30.5%).[25] Hence, it is imperative to monitor the sensitivity trends of this organism to imipenem in this region.

E. cloacae, as expected, did not show any resistance to imipenem. Cefepime was also very active (90% susceptible) against *E. cloacae*. Aminoglycosides (>80%) and fluoroquinolones (80%) had relative high sensitivity against *E. cloacae*. This organism had 85 and 90% resistance rates to cefazolin and ampicillin, respectively. Overall, the sensitivity results of *E. cloacae* in this study were similar to those of previous results.[14,15] Hence, the data on *E. cloacae* from this study supported the current empirical therapy of this region.

CONCLUSIONS

E. coli was the most common uropathogen for hospitalized patients in the Central Alabama hospital. Excluding *P. aeruginosa and E. cloacae*, most uropathogens were sensitive to imipenem and cephalosporins except for cefazolin. The current first line experiential antibiotics for UTI, ciprofloxacin and levofloxacin, had sensitivity rates similar to tetracycline and TMP/SMX, all below the recommended threshold of 80% as experiential treatment by ISDA. It is imperative to monitor the sensitivity trends for *P. aeruginosa* considering their high resistance rate found in this study. Since treatment for UTI is usually initiated empirically, it is important to be familiar with local resistance patterns. Hopefully, findings from this study will provide evidence to improve the first 24-hour experiential treatment of UTI for the Central Alabama region.

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