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Alternative Antimicrobials for Treating Infections Caused by Drug-Resistant Uropathogens: An *In vitro* Laboratory-Based and Analytical Interpretation

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ABSTRACT

Objectives: *To determine the overall in vitro resistant rates among common uropathogens in order to indicate alternative antimicrobials for consideration in the future treatment of urinary tract infection (UTI).* ***Materials and methods:*** *Data included in this study were derived from 4 years (2013-2016) cross-sectional, a retrospective study carried out in Aseer Central Hospital, Saudi Arabia. Culture positives urine and other UT specimens (n=47193) obtained from patients suspected of having UTIs were identified and tested for antimicrobial assay using the VITEK 2 system. The analysis was done using SPSS software on culture positive samples against 39 antimicrobial agents and combinations of more than one agent.* ***Results:*** *Of the 47193 culture positive uropathogens, 51.5% were resistant to the 39 agents, whereas 48.5% were sensitive (p=0.7969). Antimicrobials with high sensitivity to all uropathogens were linezolid (99.1%), daptomycin (98.3%), vancomycin (86.7%), ertapenem (86.3%), teicoplanin (85.5%), tigecycline (85.3%), imipenem (82.4%), meropenem (79.6%), piperacillin/tazobactam (78.6%), and colistin (76.2%). In contrast, antimicrobials with high resistance were cephalothin (91.0%), nalidixic acid (86.7%), cefuroxime (79.6%), cefazolin (76.3%), mezlocillin (76.1%), piperacillin (73.6%), ceftriaxone (72.9%), norfloxacin (72.8%), ciprofloxacin (71.7%), and cefotaxime (69.7%).* ***Conclusions:*** *Empirically prescribed antimicrobials have displayed remarkable resistance in this survey. Information on the local antimicrobial trends is needed to plan evidence-based recommendations. Drugs such as linezolid, daptomycin, vancomycin, ertapenem, teicoplanin and tigecycline indicated good alternatives (≥ 85% sensitivity) for consideration in empirical UTI therapy. However, cephalothin, nalidixic acid, and cefuroxime revealed high resistance rates (≥ 80%).*

Keywords: Urinary tract infections (UTIs), *In vitro* assay, Drug resistance, Aseer, Saudi Arabia

INTRODUCTION

Urinary tract infection (UTI) is a significant cause of morbidity with high rates of incidence and up to 12-month recurrence episodes predominantly in a woman. UTI is an important medical illness among the community as well as hospital-based individuals. Nearby 150 million UTIs take place annually worldwide costing around $6 billion [1]. In primary care community-acquired urinary tract infection (UTI) is a widespread problem, accounting about 8 million annual medical visits in the United States [2]. UTI has several different clinical presentations which could be complicated or uncomplicated like urinary bladder infections cystitis or involving the kidney such as pyelonephritis [3]. UTI are among the highest complaints in adults that require antibiotics indications. Antibiotic resistance in uropathogens is a major burden worldwide. The most frequent empirically prescribed drugs in many hospital settings are under threat due to rising resistance trends. The crisis is being described trigger off by abuse of these medications and a lack of new drug development [4]. It is becoming a usual fact that people prescribed antibiotics for UTIs healthcare setting acquire resistant bacteria which makes their complaints continue for up to 12 months. UTI and resistant to its causal agents are widespread and important in everyday clinical routine, thus, a prompt and correct diagnosis is vital, and antibiotics should be prescribed rationally [5].

The spectrum of most common organisms causing UTI in healthy females includes *Escherichia coli* which are the

primary urinary tract pathogen of uncomplicated urinary tract isolates followed by *Staphylococcus saprophyticus*, *Klebsiella spp*, *Proteus spp* [6]. Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics. This crisis is global, reflecting the worldwide overuse of these drugs and the lack of development of new antibiotic agents by pharmaceutical companies to address the challenge. Antibiotic-resistant infections place a substantial health and economic burden on the U.S. health care system and population. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed [7].

The current treatment of UTI is empirical, based on the limited and predictable spectrum of etiological microorganisms, the recommended antimicrobial therapy for acute uncomplicated cystitis in healthy adults re fosfomycin nitrofurantoin for women, amoxicillin-clavulanate for men and ciprofloxacin and cephalosporin as alternatives [8]. However, as many community-acquired infections, resistance rates to antimicrobials which are commonly used in UTI is increasing and susceptibility of microorganisms shows significant geographical variations and shows geographical differences even in the same country [9,10].

The most important driving factor of resistance is overuse of antimicrobials. Increasing antimicrobial resistance complicates UTI treatment by increasing patient morbidity, costs of reassessment and re-treatment and use of broader spectrum antibiotics. Several studies have demonstrated increasing antibiotic resistance levels in *E. coli* causing community-acquired UTI, but most *in vitro* data come from laboratory-based surveys that often do not define the sex, age, clinical syndrome or other data of interest regarding the patients from whom the urine specimens were collected [10].

Our purpose in this study was to determine the overall *in vitro* resistant rates among common uropathogens in order to indicate alternative antimicrobials for consideration in the future treatment of urinary tract infection (UTI).

PATIENTS AND METHODS

Compliance with Ethics Guidelines

The study approval was obtained from the institutional review board of Aseer Central Hospital (ACH), Abha, Saudi Arabia and the Ethical Committee of King Khalid University (REC#2016-07-07). National data-protection rules were noted fall through. Patient-informed consent was not required due to the de-identified nature of the collected data.

Study Design and Data Extraction

This was a non-interventional, retrospective study done between January 2013 and June 2016. Patient and microbiological data were extracted from electronic medical records of Aseer Central Hospital (ACH), Abha, Saudi Arabia.

Patients

Diagnosis of UTI was established by the medical staff of ACH, on the basis of clinical symptoms. Multiple samples per patient were likely and repeat samples were done for many cases. These were according to clinical requests especially with a patient with a long hospital stay.

Laboratory Investigations

Laboratory investigations were done using selected conventional indicators. Urine samples were inoculated onto CLED (Cystine Lactose Electrolyte Deficient; BD, Becton Dickinson GmbH) agar by streak plate method following the standard microbiological procedures. A positive culture is defined as a clean catch midstream urine specimen with a growth of 105 CFU/mL of a single microorganism or mixed flora with a predominant species. Negative urine culture was defined as no growth, insufficient growth, or a mixed microbial flora with no predominant organism. The culture was identified and tested for antimicrobial assay using the VITEK 2 system (BioMérieux, Paris, France) following manufacturer instructions.

Antimicrobials in the original dataset with less than 100 reactions were excluded from the final data analysis Therefore, a total of 39 antimicrobial agents in susceptibility panel containing serial two-fold dilutions of each agent were tested (Table 1). Stock inoculum suspensions of the bacterial isolates were obtained from 24-hours cultures on blood agar plates at 37°C. Inoculum suspensions for the VITEK 2 system were prepared in sterile saline to turbidity equal to a 0.5 McFarland standard.

Statistical Analysis

The analysis was done using SPSS software (SPSS version 16.0) on proven culture positive samples (n=47193) against 39 antimicrobial agents and combinations of more than one agent. Descriptive statistics were calculated for all variables as means with standard deviation or percentages where appropriate. Continuous variables were analyzed using t-tests for independent samples, and categorical variables were analyzed using a Chi-squared test. The results were evaluated with 95% confidence intervals. A p-value of <0.05 was considered significant.

RESULTS

Out of the 47193 culture positive uropathogens, 51.5% were resistant to the 39 agents, whereas 48.5% were sensitive (p=0.7969). The overall difference between percentage sensitive and resistant was not significant (p=0.5873) (Figure 1). Out of these 47193 culture positive samples, 28269 were males (59.9%) and 18924 were females (40.1%) (p=0.0001).

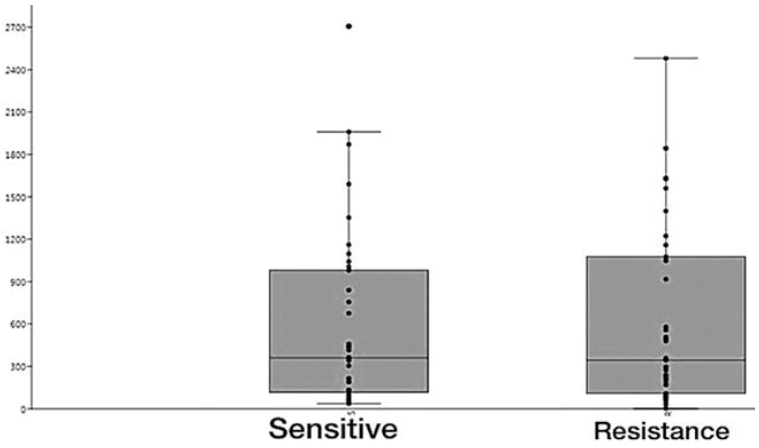

Figure 1 Boxer jitter plot of a number of sensitive and resistant uropathogens (n=46793) bacteria to 39 antimicrobial

Most common bacterial species causing UTIs in Aseer region and their sensitivity (%) to some empiric antimicrobial agents are shown in Figure 2.

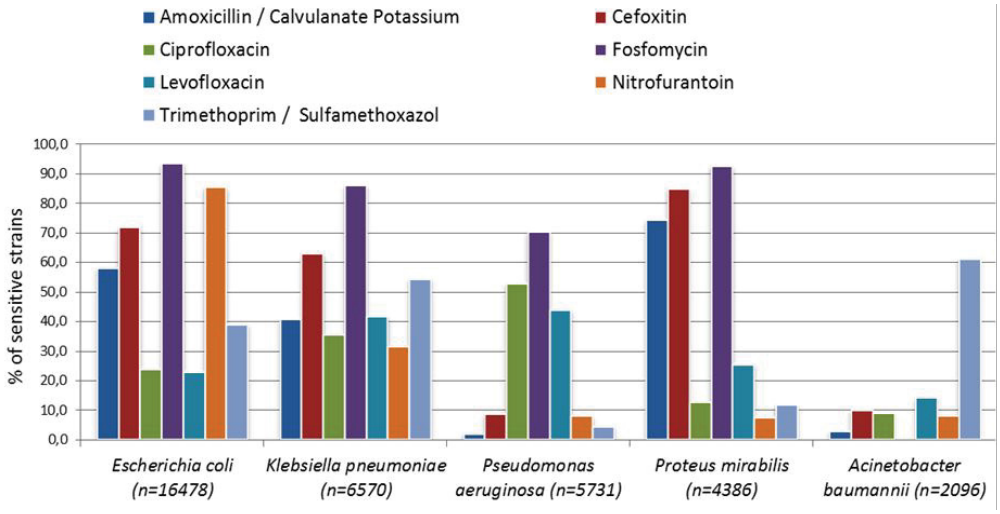

Figure 2 Most common bacterial species causing UTIs in Aseer region and their sensitivity (%) to some empiric antimicrobial agents

Percentage of sensitive and resistant uropathogens accounted in Aseer Central Hospital (2013-2016) is shown in Figure 3. Antimicrobials with high sensitivity to uropathogens were linezolid (99.1%), daptomycin (98.3%), vancomycin (86.7%), ertapenem (86.3%), teicoplanin (85.5%), tigecycline (85.3%), imipenem (82.4%), meropenem (79.6%), piperacillin/tazobactam (78.6%), and colistin (76.2%).

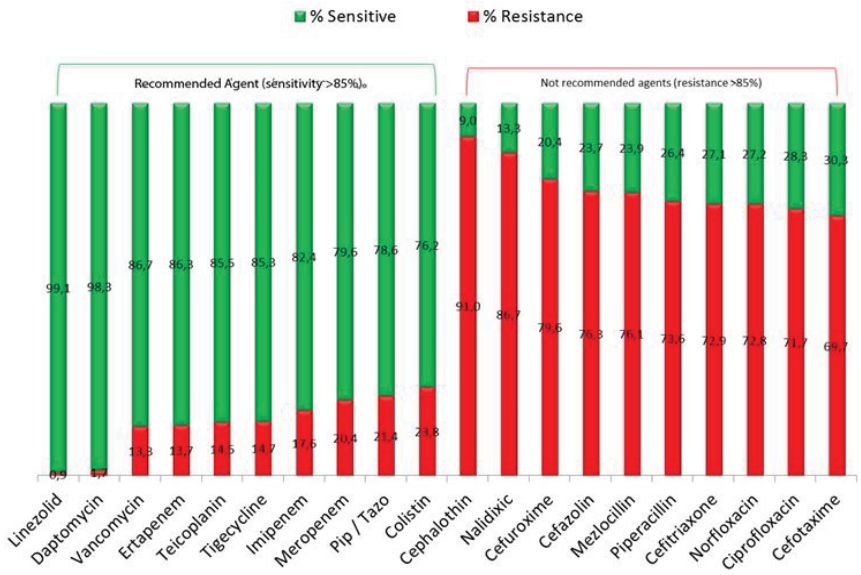

Figure 3 Percentage of sensitive and resistant uropathogens accounted n Aseer central Hospital (2013-2016)

In contrast, antimicrobials with high resistance were cephalothin (91.0%), nalidixic acid (86.7%), cefuroxime (79.6%), cefazolin (76.3%), mezlocillin (76.1%), piperacillin (73.6%), cefitriaxone (72.9%), norfloxacin (72.8%), ciprofloxacin (71.7%), and cefotaxime (69.7%) (Table 1).

Table 1 Percentage of sensitive and resistant of each antimicrobial in Aseer Central Hospital, Aseer region, Saudi Arabia

Antibiotic	Resistant (%)	Sensitive (%)
Amikacin	31.9%	68.1%
Amox/K Clav	55.5%	44.5%
Amp/Subactam	69.2%	30.8%
Ampicillin	82.1%	17.9%
Aztreonam	64.1%	35.9%
Cefazolin	76.3%	23.7%
Cefepime	61.8%	38.2%
Ceftriaxone	72.9%	27.1%
Cefotaxime	69.7%	30.3%
Cefoxitin	39.6%	60.4%
Ceftazidime	63.9%	36.1%
Cefuroxime	79.6%	20.4%
Cephalothin	91.0%	9.0%
Ciprofloxacin	71.7%	28.3%
Colistin	23.8%	76.2%
Cotrimox	67.2%	32.8%
Daptomycin	1.7%	98.3%
Ertapenem	13.7%	86.3%
Fosfomycin	17.9%	82.1%
Gent. Synergy	61.5%	38.5%
Gentamicin	50.7%	49.3%
Imipenem	17.6%	82.4%
Levofloxacin	69.8%	30.2%
Linezolid	0.9%	99.1%
Meropenem	20.4%	79.6%
Mezlocillin	76.1%	23.9%
Nalidixic	86.7%	13.3%

Nitrofurantoin	44.3%	55.7%
Norfloxacin	72.8%	27.2%
penicillin	45.0%	55.0%
Pip/Tazo	21.4%	78.6%
Piperacillin	73.6%	26.4%
Teicoplanin	14.5%	85.5%
Tetracycline	69.2%	30.8%
Tigecycline	14.7%	85.3%
Tobramycin	56.8%	43.2%
Trimethoprim/Sulfa	62.7%	37.3%
Trimethoprim	56.1%	43.9%
Vancomycin	13.3%	86.7%

DISCUSSION

High resistance to broad-spectrum antibiotics, especially to extended-spectrum beta-lactams, carbapenems, and fluoroquinolones among uropathogens emerges as a critical problem in many countries. Appropriate antimicrobial stewardship and continuous surveillance are necessary to monitor the trends of susceptibility for main pathogens. For these MDR uropathogens, polymyxin, fosfomycin, tigecycline, nitrofurantoin, linezolid, and daptomycin might be potential treatments for patients with uncomplicated and complicated UTIs in some countries, although they might not be approved by their regulation. However, more clinical evidence and more extensive meta-analyses are needed to evaluate and confirm the effectiveness of their usage in countries with a high prevalence of multidrug resistance [11].

The overall difference between percentage sensitive and resistant uropathogens in this study was not significant ($p=0.5873$). This means that the random chance of treating or not treating is almost similar, implying the seriousness of drug-resistant in the region.

Antimicrobial resistance (%) for *E. coli* in urine samples from patients with urinary tract infections, in 6 European countries, was found variable. Croatia in 2009 recorded 2% resistance to nitrofurantoin and 24% resistance to sulfamethizole-trimethoprim; Denmark in 2009, 0-5% resistance to nitrofurantoin and 10-28 to sulfamethizole-trimethoprim; Germany in 2006, 1-2% resistance to nitrofurantoin and 25-26% to co-trimoxazole; Scotland in 2000, 0% resistance to nitrofurantoin and 16-17% to co-trimoxazole; Sweden in 2007, 1% resistance to nitrofurantoin and 15% to co-trimoxazole [12].

Trimethoprim-sulfamethoxazole or trimethoprim should be used as first-line therapy because of its low cost and efficacy for uncomplicated urinary tract infections in women unless the prevalence of resistance to these agents among uropathogens in the community is greater than 10% to 20% [13]. Practitioners in the clinical setting who are treating patients with complicated, hospital-acquired, gram-negative IAIs and UTIs need to consider the possibility of polymicrobial infections, antibiotic-resistant organisms, and/or severely ill patients with multiple comorbidities. There is a severe shortage of evidence-based research to guide the selection of empiric antibiotic therapy for many patients in this setting. New therapies recently approved or in late-stage development promise to expand the number of options available for empiric therapy of these hospital-acquired, gram-negative infections [14]. The treatment of UTI is empirical on the basis of the limited and predictable spectrum of etiological microorganisms and their susceptibility *in vitro* sensitivities [15]. In Turkey, the resistance rates of *E.coli,* with some agents such as ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, cefuroxime, ceftriaxone, fluoroquinolones, co-trimoxazole and gentamicin were found 55.1%, 32.7%, 32.7%, 23.4%, 15.9%, 25.2%, 41.1%, 6.1% respectively. Fluoroquinolones were the most common prescribed antibiotics (77.9%) ($p<0.001$), followed by co-trimoxazole (10.7%), fosfomycin (9.2%), nitrofurantoin (2.1%). Treatment durations were statistically longer than the recommended 3-day course ($p<0.001$). These authors discouraged the empirical use of fluoroquinolones in treating uncomplicated UTI because of increased antimicrobial resistance rates [10].

CONCLUSION

- Empirically prescribed antimicrobial agents for these studies such as fluoroquinolones (ciprofloxacin, levofloxacin) co-trimoxazole, levofloxacin, fosfomycin or nitrofurantoin has displayed remarkably high resistant rates in this study [10-12]

- Accurate information regarding local antimicrobial trends is needed to plan evidence-based recommendations for the empirical therapy for UTIs
- Drugs such as ertapenem, tigecycline, imipenem, and meropenem revealed well *in vitro* alternatives for empirical UTI therapy. Drugs such as linezolid, daptomycin, vancomycin, teicoplanin, revealed well *in vitro* alternatives for gram-positive bacteria, they showed high sensitivity to more than 80% of the tested uropathogens
- An overall high resistance rate (>80%) was noticed among cephalothin, nalidixic acid, and cefuroxime

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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