Original Article

Relationship Between Antimicrobial Prescribing and Antimicrobial Resistance Among UTI Patients at Buraidah Central Hospital, Saudi Arabia

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Abstract

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Introduction

Most of the decisions regarding diagnosis and treatment are based on laboratory test results. Urinary tract infections (UTIs) are among the most common infections in humans. The changing antimicrobial sensitivity in UTI requires appropriate antibiotics. Antimicrobial resistance is an emerging problem in the Kingdom of Saudi Arabia where the complete reversal of antimicrobial resistance is difficult due to irrational use of antibiotics. Objectives: This study aimed to determine the most common bacterial agents causing UTI in different seasons among patients who were admitted to Buraidah Central Hospital (BCH), Saudi Arabia. The study also evaluated the link between prescribing and resistance toward antimicrobials. Materials and Methods: A 6-month retrospective study was conducted among adult patients who were admitted to the inpatient department at BCH. A total of 379 files were collected from microbiological laboratory for inpatients. Results: Most UTI-causing bacteria prevailed in the same season. Of 15 bacterial strains, 12 were significantly correlated with 20 (of a total of 40) antibiotics that were used. Most bacteria were gram-negative. Gram-negative bacilli including Escherichia coli, Klebsiella spp., and Pseudomonadaceae and gram-positive Enterococcus faecalis were most frequently causing UTIs. Conclusion: Overall prevalence of antibiotic resistance was negative in bacterial isolates. However, the relationship between antimicrobial prescribing and antimicrobial resistance was significantly negative among UTI patients in BCH, Saudi Arabia.

Keywords: Antimicrobials, bacterial isolates, resistance, Saudi Arabia, urinary tract infections

Introduction

Bacterial strains are found in almost every part of the globe.[1] They have the ability to survive in harsh environments and colonize almost all habitats by adopting to environment. Due to this adoption, there are diverse strains and types of bacteria. Urinary tract infection (UTI) is common in both men and women. However, the incidence is higher among women due to female anatomy.[2,3] It is a condition where one or several parts of the urinary system such as urethra, kidney, or bladder become infected. It may occur at any particular period of life.[2,3] Moreover, it is one of the most frequently occurring infection reported in both inpatients and outpatients, and may lead to mortality.[4] UTIs may not occur if bacteria are introduced into the bladder due to body’s immune defense that helps protecting the urinary tract.

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UTIs are classified as complicated or uncomplicated (i.e., those that depend on trigger factors) and recurrent or primary (i.e., those that depend on the type of infection that occurred for the first time or a reinfection). Evidence indicates that UTIs are the common cause of hospital-acquired infections and account for approximately 40% of all infections.[7] There is a plethora of evidence regarding impact of seasonal variation on diseases and bacteria commonly associated with seasonal disease incidence; the understanding of epidemiological consequences of seasonality remains poor.[8,9] Humidity, changes in temperature and rainfall are associated with prevalence of diseases.[10-12]

Literature reports that UTIs may be seasonal.[13-15] Antibiotics have been the primary means of curing UTIs. However, due to increasing resistance to first-line antibiotic therapies, UTIs are becoming untreatable.[16-18] The use of antibiotics in UTIs is based on certain considerations such as gender, age, and health condition of patient. Antibiotic usage in this condition has faced resistance from *Escherichia coli* strains. Moreover, the microbial flora colonizing vaginal cavity as well as gastrointestinal tract could be affected by short antibiotic courses.[19,20] Initial use of an antibiotic is a major determinant of antibiotic-resistant UTIs.[21,22] Several studies have reported *E. coli*, *Klebsiella* spp., *Enterococcus faecalis*, and *Pseudomonadaceae* as most common bacteria causing UTIs.[23-27]

Bacterial resistance to antibiotics, especially in UTI, has been on the rise globally owing to its excessive use.[28,29] Resistance to an antibiotic may be acquired by a bacterium by horizontal gene transfer mechanism. This resistance may also apply simultaneously to different classes of antibiotics. Despite the resistance to antibiotics that is reported from economically developing countries in particular, they are invariably used for the treatment of UTIs.[30,31] Moreover, some resistance mechanisms have been proven to result into resistance of many other antibiotics’ classes.[32-35] Although the antimicrobial-resistant pathogens are increasing, the pattern of bacterial resistance has not been adequately investigated, especially in Saudi Arabia.[36,37]

Hence, the aims of this study were to determine the most frequently found bacteria that cause UTIs and to investigate the relationship between antimicrobial prescribing and antimicrobial resistance in this population.

**Materials and Methods**

A 6-month retrospective study was carried out among adult patients admitted to inpatient department at Buraidah Central Hospital (BCH), Saudi Arabia. The inclusion criteria were age above 18 years and all types of the laboratory reports of inpatients with suspected bacterial infection admitted to BCH. The exclusion criteria were any culture reporting any other infection except bacteria, pregnancy, or a severe disease such as HIV and tuberculosis. The data were collected from the microbiology laboratory at BCH, Saudi Arabia.

Of more than 6000 (95% confidence interval) isolated culture specimens, 379 were collected from patients at the microbiology laboratory at BCH, Saudi Arabia.[38] Isolates were collected for a period of 6 months (August 2016 to January 2017) from urine, blood, and stool. This collection included 32 gram-negative bacilli (GNB), 18 *Klebsiella pneumoniae*, 16 *Staphylococcus aureus*, 15 *Pseudomonas aeruginosa*, 13 *E. coli*, 13 *Enterococcus faecium*, 10 *Acinetobacter* spp., 7 *Providencia stuartii*, 7 *Staphylococcus epidermidis*, 2 *Staphylococcus haemolyticus*, 2 *Streptococcus agalactiae*, and 1 coagulase-negative *Staphylococcus*. Consecutive clinical isolates from blood, urine, or stool specimens collected during 6 months from clinical microbiology laboratories in BCH. A total of 44 antibiotic drugs were used among these 379 UTI inpatients. The most commonly used drugs were ciprofloxacin (25.9%), gentamicin (25.3%), amoxicillin/clavulanic acid (23%), cefoxitin (20.6%), and levofloxacin (20.1%). However, the less commonly used drugs were polymyxin B (0.3%), neomycin (0.3%), bacitracin (0.5%), methicillin (1.1%), and chloramphenicol (1.6%).

Ethical approval was obtained from the General Directorate of Health Affairs and Ethics Committee of Ministry of Health of the Kingdom of Saudi Arabia (45/44/1458). The lab reports and patient files were collected, and data was recorded.

Data were sought from patient files at BCH. Patient name and gender were kept anonymous. Information related to use of antibiotics and hospitalizations was collected from follow-up record. Data analysis was conducted through SPSS, version 21, software package (IBM Corporation, NY).

**Results**

A total of 379 samples of UTI inpatients were collected during the study period. Among 379 cases, there were 133 infected cases (35.1%). Table 1 shows that most gram-negative bacteria occurred in winter season. However, positive isolates of GNB were mostly in the months of November (3.2%) and December (2.4%); *K. pneumoniae* was mostly in January (3.4%) and December (1.1%); *S. aureus* was mostly in August.
(1.6%), September (0.8%) and October (0.8%), as well; *P. aeruginosa* was mostly in December (1.6%) and January (1.1%); *E. coli* was mostly in August (1.3%) and January (1.1%); *E. faecium* was mostly in January (1.6%) and December (1.4%); *Acinetobacter* spp. were mostly in September (0.6%), August (0.8%) and January (0.8%); *P. stuartii* was mostly in September (0.6%), October (0.5%) and December (0.5%); *S. epidermidis* was mostly in August (0.8%) and December (0.5%); and *S. haemolyticus*, *S. agalactiae*, and coagulase-negative *Staphylococcus* were in October (0.2%).

A total of 44 antibiotics were used in 379 UTI patients. In addition, a total of 15 bacterial cultures were isolated in these patients. However, 12 bacterial strains significantly (*P* < 0.05) correlated with 20 antibiotics that were used. The results indicated that it was unlikely that these variables were independent of each other. Thus, we can conclude that there was a relationship between the bacterium and the antibiotic used. These bacteria were *Citrobacter koseri* (gram-negative), *staphylococci* (gram-positive), and *Staphylococcus capitis* (gram-positive).

In addition, the most commonly used antibiotics were ciprofloxacin (25.9%), gentamicin (25.3%), amoxicillin/clavulanic acid (23.0%), and ampicillin (20.6%). The less commonly used antibiotics were neomycin (0.3%), polymyxin B (0.3%), bacitracin, (0.5%) and methicillin (1.1%). Tables 2–5 indicate that *E. coli* (gram-negative) and *E. faecium* (gram-positive) were the most common isolated bacteria that significantly correlated with seven antibiotics. Tables 1–4 reflect that amikacin was the most significant antibiotic used, whereas mupirocin, tetracycline, and levofloxacin were the second most significant antibiotic drugs used. In addition, the bacteria *S. aureus* (gram-positive), *S. haemolyticus* (gram-positive), and *S. agalactiae* (gram-positive) were significantly correlated with one antibiotic use, i.e., gentamicin, mupirocin, and amikacin, respectively.

**DISCUSSION**

Urinalysis and blood and stool cultures on different microbiological media have been the cornerstone of diagnosing and detecting bacterial strains that caused UTIs. Gram staining, biochemical tests, and direct microscopy observation are common means of detecting bacterial strains and diagnosing infections. On the basis of exclusion criteria, data pertaining to age, risk factors, and molecular biology diagnosis were excluded. Available data reported determinants that were surgery, diabetes mellitus, immunosuppression, transplantation, pregnancy, hypertension, stone formation, hospitalization, and catheterization.

### Table 1: Name and percentage of bacterial pathogens during different seasons

| Bacteria                  | August 2016 (%) | September 2016 (%) | October 2016 (%) | November 2016 (%) | December 2016 (%) | January 2017 (%) |
|---------------------------|-----------------|--------------------|------------------|-------------------|-------------------|------------------|
| **GNB (gram-negative bacilli)** |                 |                    |                  |                   |                   |                  |
| Negative                  | 16.9            | 15.0               | 9.5              | 14.2              | 16.9              | 19.0             |
| Positive                  | 0.5             | 0.6                | 1.8              | 3.2               | 2.4               | 0.0              |
| **Klebsiella pneumoniae** |                 |                    |                  |                   |                   |                  |
| Negative                  | 17.4            | 15.6               | 11.3             | 17.2              | 18.2              | 15.6             |
| Positive                  | 0.0             | 0.0                | 0.0              | 0.2               | 1.1               | 3.4              |
| **Staphylococcus aureus** |                 |                    |                  |                   |                   |                  |
| Negative                  | 15.8            | 14.8               | 10.6             | 16.9              | 18.7              | 19.0             |
| Positive                  | 1.6             | 0.8                | 0.8              | 0.5               | 0.5               | 0.0              |
| **Pseudomonas aeruginosa**|                 |                    |                  |                   |                   |                  |
| Negative                  | 17.2            | 15.0               | 11.1             | 17.2              | 17.7              | 17.9             |
| Positive                  | 0.2             | 0.6                | 0.2              | 0.2               | 1.6               | 1.1              |
| **Escherichia coli**      |                 |                    |                  |                   |                   |                  |
| Negative                  | 16.1            | 15.0               | 11.3             | 17.4              | 18.7              | 17.9             |
| Positive                  | 1.3             | 0.6                | 0.0              | 0.0               | 0.6               | 1.1              |
| **Enterococcus faecium**  |                 |                    |                  |                   |                   |                  |
| Negative                  | 17.4            | 15.6               | 11.3             | 16.9              | 17.9              | 17.4             |
| Positive                  | 0.0             | 0.0                | 0.0              | 0.5               | 1.4               | 1.6              |
| **Acinetobacter species**|                 |                    |                  |                   |                   |                  |
| Negative                  | 16.6            | 15.0               | 11.3             | 17.2              | 19.0              | 18.2             |
| Positive                  | 0.8             | 0.6                | 0.0              | 0.2               | 0.3               | 0.8              |
| **Providencia stuartii**  |                 |                    |                  |                   |                   |                  |
| Negative                  | 17.2            | 15.0               | 10.8             | 17.4              | 18.7              | 19.0             |
| Positive                  | 0.2             | 0.6                | 0.5              | 0.0               | 0.5               | 0.0              |
| **Staphylococcus epidermidis**|              |                    |                  |                   |                   |                  |
| Negative                  | 16.6            | 15.3               | 11.1             | 17.4              | 18.7              | 19.0             |
| Positive                  | 0.8             | 0.3                | 0.2              | 0.0               | 0.5               | 0.0              |
| **Staphylococcus haemolyticus**|            |                    |                  |                   |                   |                  |
| Negative                  | 17.4            | 15.6               | 11.1             | 17.4              | 19.0              | 19.0             |
| Positive                  | 0.0             | 0.0                | 0.2              | 0.0               | 0.3               | 0.0              |
| **Streptococcus agalactiae**|              |                    |                  |                   |                   |                  |
| Negative                  | 17.4            | 15.6               | 11.1             | 17.4              | 19.0              | 19.0             |
| Positive                  | 0.0             | 0.0                | 0.2              | 0.0               | 0.3               | 0.0              |
| **Coagulase-negative**    |                 |                    |                  |                   |                   |                  |
| Negative                  | 17.4            | 15.6               | 11.1             | 17.4              | 19.0              | 19.0             |
| Positive                  | 0.0             | 0.0                | 0.2              | 0.0               | 0.3               | 0.0              |
| **Staphylococcus**        |                 |                    |                  |                   |                   |                  |
| Negative                  | 0.0             | 0.0                | 0.2              | 0.0               | 0.3               | 0.0              |
| Positive                  | 0.0             | 0.0                | 0.2              | 0.0               | 0.3               | 0.0              |
The age-wise seasonal intensity of infection among males and females is undocumented. These triggers vary with respect to gender. Considering the impact of dehydration on UTI incidence, and possible link between hydration and climate variability, this notion highlights temperature as a determinant of UTI seasonality.

The extent and severity of disease caused by multiresistant bacteria vary institutionally and the population affected. However, the control and prevention of these multiresistant bacteria should be a national priority. Therefore, a periodic evaluation of antibiotic use and its subsequent resistance is critical. Negative outcomes as a result of inappropriate and inadequate antimicrobial treatment resulting in resistance have been reported in previously published studies. This indicates that increasing resistance may precipitate a treatment failure with antibiotic and would require shifting of care from outpatient to inpatient settings. This highlights the increase in incidence of UTI-related extended hospital stay.

In this study, we reported extensive resistance pattern among bacterial isolates obtained from inpatient department. The results of our study demonstrate the degree of contamination with multiresistant/sensitivity

| Antibiotic | Escherichia coli | Staphylococcus aureus | Staphylococcus pneumoniae |
|------------|------------------|-----------------------|--------------------------|
|            | S (%)            | R (%)                 | S (%)                    | R (%)             | S (%)          | R (%)         |
| Gentamicin | Negative         | 39 (40.6)             | 47 (60.3)                | 38 (39.6)         | 46 (47.9)      |
|            | Positive         | 9 (9.4)               | 2 (2.1)                  | 10 (10.4)         | 2 (2.1)        |
| Cefoxitin  | Negative         | 10 (13.2)             | 54 (71.1)                | 7 (41.2)          | 5 (8.5)        |
|            | Positive         | 7 (41.2)              | 5 (8.5)                  | 10 (14.3)         | 1 (1.4)        |
| Tienam     | Negative         | 29 (41.4)             | 30 (42.9)                | 10 (14.3)         | 1 (1.4)        |
|            | Positive         | 10 (14.3)             | 1 (1.4)                  | 10 (14.3)         | 1 (1.4)        |
| Cefuroxime | Negative         | 9 (14.1)              | 44 (68.8)                | 9 (14.1)          | 6 (9.4)        |
|            | Positive         | 5 (7.8)               | 6 (9.4)                  | 5 (7.8)           | 6 (9.4)        |
| Cefotaxime | Negative         | 8 (15.1)              | 37 (69.8)                | 6 (11.3)          | 2 (3.8)        |
|            | Positive         | 6 (11.3)              | 2 (3.8)                  | 6 (11.3)          | 2 (3.8)        |
| Ceftriocine| Negative         | 7 (14.6)              | 37 (71.1)                | 3 (6.3)           | 1 (2.1)        |
|            | Positive         | 3 (6.3)               | 1 (2.1)                  | 3 (6.3)           | 1 (2.1)        |
| Amikacin   | Negative         | 23 (46.0)             | 15 (30.0)                | 10 (18.9)         | 37 (69.8)      |
|            | Positive         | 12 (24.0)             | 0 (0.0)                  | 12 (24.0)         | 0 (0.0)        |

R = resistance, S = sensitivity
gram-negative and gram-positive pathogens, which was higher with gram-negative pathogens. In contrast, Lemmen et al.\textsuperscript{[46]} in 2004 reported that the contamination of multiresistant gram-positive pathogens was higher than that of multiresistant gram-negative pathogens.

The most resistant bacteria found in our study were \textit{E. coli} (gram-negative) = 54 (71.1\%) against cefoxitin, and \textit{E. coli} (gram-negative) and \textit{S. aureus} (gram-positive) = 47 (60.3\%) and 46 (47.9\%) against gentamicin, respectively, \textit{Acinetobacter} spp. (gram-negative) = 52 (53.1\%) against ciprofloxacin, and \textit{E. faecium} (gram-positive) and \textit{S. agalactiae} (gram-positive) = 58 (74.4\%) and 61 (78.2\%) against ampicillin, respectively.

This study demonstrated that gram-positive bacteria (\textit{E. faecium} and \textit{S. agalactiae}) were negatively resistant to ampicillin alone. Moreover, most gram-negative bacteria were sensitive to gentamicin, ciprofloxacin, and cefoxitin. Nevertheless, most gram-negative bacteria isolated were resistant to ampicillin. These outcomes are similar to the study reported by Seppälä et al.\textsuperscript{[47]} in 1992.

A multihospital study on resistance and antimicrobial usage has emphasized a close coordination between microbiology department and infection control committee. It further stresses on the need to ensure appropriate use of antibiotics by pharmacists.

### Table 4: Resistance and sensitivity pattern of significant most bacteria among antibiotics used (\(n = 44\))

| Antibiotic                  | \textit{Acinetobacter} species | \textit{Streptococcus agalactiae} | \textit{Staphylococcus haemolyticus} | \textit{Providencia stuartii} |
|-----------------------------|-------------------------------|----------------------------------|--------------------------------------|-------------------------------|
|                             | S (%)                         | R (%)                            | S (%)                                | R (%)                         |
| Ciprofloxacin               | 38 (38.8)                     | 52 (53.1)                        | 39 (84.8)                            | 4 (8.7)                       |
| Mupirocin                   | 22 (88.0)                     | 1 (4.0)                          | 0 (0.0)                              | 2 (8.0)                       |
| Tetracycline                | 31 (42.9)                     | 27 (42.9)                        | 9 (18.0)                             | 61 (78.2)                     |
| Amikacin                    | 35 (70.0)                     | 15 (19.2)                        | 61 (78.2)                            | 0 (0.0)                       |
| Levofoxacin                 | 35 (46.1)                     | 36 (47.4)                        | 22 (91.7)                            | 0 (0.0)                       |
| Vancomycin                  | 19 (76.0)                     | 6 (24.0)                         | 1 (4.2)                              | 1 (4.2)                       |

\(R = \text{resistance}, S = \text{sensitivity}\)

### Table 5: Resistance and sensitivity pattern of significant most bacteria among antibiotics used (\(n = 44\))

| Antibiotic                  | Gram-negative bacilli | Pseudomonas aeruginosa |
|-----------------------------|-----------------------|------------------------|
|                             | S (%)                 | R (%)                  | S (%)                 | R (%)                  |
| Ceftazidime                 | 10 (22.2)             | 18 (40.0)              | 22 (88.0)             | 2 (8.0)                |
| Cefoxitin                   | 16 (21.1)             | 37 (48.7)              | 0 (0.0)               | 1 (4.0)                |
| Ampicillin                  | 16 (20.5)             | 39 (50.0)              | 4 (6.5)               | 0 (0.0)                |
| Cefotaxime                  | 12 (22.6)             | 20 (37.7)              | 4 (6.5)               | 0 (0.0)                |
| Trimethoprim/Sulfamethoxazole | 25 (40.3)             | 33 (53.2)              | 22 (91.7)             | 1 (4.2)                |
| Amikacin                    | 33 (66.0)             | 11 (22.0)              | 0 (0.0)               | 2 (8.0)                |
| Mupirocin                   | 22 (88.0)             | 2 (8.0)                | 0 (0.0)               | 1 (4.0)                |
| Fosfomycin                  | 49 (80.3)             | 6 (9.8)                | 3 (4.9)               | 3 (4.9)                |

\(R = \text{resistance}, S = \text{sensitivity}\)
Moreover, it entails that multihospital study may not identify the relationship between antimicrobial resistance and antimicrobial usage.[48] Available literature reports that antibiotic use has a significant relationship with antimicrobial resistance.[49-52] This resistance might be developed as a result of misuse of antibiotics. Several studies have reported that the antimicrobial prescribing pattern of physicians is a determinant of increasing resistance to antibiotics.[53-55]

**CONCLUSION**

Urinalysis may be required for majority of patients with uncomplicated acute cystitis. Though, physical examination and history may not be sufficient to diagnose UTI. Laboratory tests are essential in diagnosing the ailment and providing details about the pathogen and its susceptibility toward antibiotics. Both the laboratory diagnosis and clinical diagnosis of laboratory test results must be made in light of the method of collection used and clinicians should specify the method of collection on test requisition forms.

A urinalysis is helpful primarily as a means of excluding bacteriuria, but it is not a surrogate for culture. Although cultures identify pathogens, the accurate interpretation of culture results requires clinical information that is usually available only to the clinician. Climate change has an impact on incidence of many infections. In spite of the extensive knowledge and experience regarding infections, the epidemiological implications of climate change are not properly interpreted. The effect of climate change on observed UTI incidence was also explored. UTI at most times is a mild infection that can be easily treated in outpatients using oral antibiotics. Only a small number of these patients are actually hospitalized. Moreover, UTI is one of the most common infectious diseases that has been extensively studied in clinical practice.[56]

In this study, we found that the GNB was the most frequently occurring bacteria. UTI was usually caused by E. coli, Klebsiella spp., E. faecalis, and Pseudomonadaceae. Studies have reported an increase in antibiotic resistance of these bacteria in invasive infections such as UTIs.[23-27,57,58] UTI may be caused by coliforms and Enterococcus spp. because of their presence on perineum.[24-29] In this study, GNB, E. coli, Klebsiella spp., E. faecalis, and Pseudomonadaceae were reported as most common uropathogens in different seasons. Our study demonstrated that the relationship between antimicrobial prescribing and antimicrobial resistance was significant, and negatively resistant.

Despite the fact that we could not evaluate the correlation between antibiotic usage and resistance, our study showed that there is a possibility for isolates to have multiple drug resistance. The results encourage further evaluation of relationship between antimicrobial usage and resistance. These data would be useful in developing guidelines and policies for appropriate use of antibiotics particularly in BCH as well as in Saudi Arabia.

It is recommended that researchers now study the modalities that could enhance the treatment actions of antimicrobial agents. Further studies on this topic are required. Although the data used in these analyses were much more diverse with regard to climate and demographics, a limitation is the unavailability of information about the resistance profiles of UTI patients.

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**Conflicts of interest**

There are no conflicts of interest.

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