Antibacterial Resistance Patterns Among Common Infections in a Tertiary Care Hospital in Saudi Arabia

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Abstract

Background

The rapid emergence of antibiotic-resistant bacteria threatens the control of infectious diseases by reducing treatment effectiveness, prolonging illness duration, and increasing healthcare costs. This study aimed to identify the common rate of bacterial resistance against antibacterial agents in tertiary healthcare providers in Saudi Arabia.

Methodology

This retrospective cross-sectional observational study was conducted from May 2016 to December 2019 on 1,151 urinary tract infection (UTI) and respiratory tract infection (RTI) positive cultures collected from participants aged 15 years or older who received antibiotic treatment. The obtained variables included age, gender, diagnosis, antibiotic type, specimen source, culture results, and sensitivity test results.

Results

The most common bacteria in UTI were Escherichia coli (46.7%), followed by Klebsiella pneumoniae (30.5%). Moreover, E. coli was most resistant to ampicillin (56.4%), followed by ceftriaxone (33.8%). Among the respiratory cultures, the most frequently isolated pathogen was Pseudomonas aeruginosa (28.5%), followed by K. pneumoniae (17.6%). The 162 respiratory P. aeruginosa isolates were most resistant to piperacillin/tazobactam (51.9%), followed by ciprofloxacin (25%) and ampicillin (10.6%).

Conclusion

High levels of antibiotic resistance were observed in both Gram-negative and Gram-positive bacteria. This indicates a need for better implementation of antibacterial stewardship and increased awareness of appropriate antibiotic use to limit the rapid spread of antibacterial resistance.

Keywords: klebsiella pneumoniae, pseudomonas aeruginosa, antibiotic-resistant bacteria, escherichia coli, e.coli, urinary tract infection, respiratory tract infection, resistance, antibiotics

Introduction

The introduction of antibiotics to the medical field was one of the greatest discoveries in the history of medicine. When penicillin was introduced in the 1940s by Alexander Fleming, a new era of therapeutic medicine was established [1]. The outcomes of bacterial infections saw a great turnaround as fatal and severe infections became easily treatable. However, the efficiency of antibiotics has decreased as many available antibiotics are no longer effective along with the emergence of antibiotic-resistant (ABR) strains. Importantly, antibiotic resistance discovery is related to resistance detection in clinical samples; however, the resistance might be discovered earlier according to the observation from laboratory samples.

Globally, it is estimated that ABR infections are responsible for approximately 700,000 deaths per year [2,3]. If no preventative actions are taken, it is predicted that infections caused by ABR bacteria will have a mortality rate exceeding that of cancer and become the most common cause of death by the end of 2050 [2,3]. According to the Centers for Disease Control and Prevention (CDC), approximately 35,900 deaths out of 2,868,700 ABR cases are expected to be reported annually in the United States [2]. In 2012, Aly et al. investigated antimicrobial resistance in 37,295 bacterial isolates collected from different hospitals in the Gulf region. Within this sample, the most prevalent microorganism was Escherichia coli, followed by Klebsiella pneumoniae, Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus (MRSA),
Acinetobacter, Clostridium difficile, and Enterococcus [4]. In addition, a study conducted by the Saudi national surveillance on Gram-positive cocci revealed that 32% of S. aureus belonged to MRSA, 33% of S. pneumoniae were resistant to penicillin G, and 26% of S. pneumoniae were resistant to erythromycin [3]. In the western region of Saudi Arabia, Alam et al. reported bacterial resistance to trimethoprim/sulfamethoxazole (48.6%), ampicillin (49.3%), piperacillin (59.3%), and methicillin (50.3%) [5].

Bacteria have the unique ability to lower or eliminate the antimicrobial efficacy of drugs and chemical agents [6]. This may occur through natural resistance (e.g., β-lactamase production) or acquired resistance [7,8]. Acquired bacterial resistance may occur through four mechanisms. One of these mechanisms is the production of enzymes that modify or inhibit antibiotic action [7-9]. Another mechanism is through changes in the permeability of bacterial cell walls [7]. Bacteria can also acquire resistance through disruptions in protein synthesis [7], alterations in metabolic pathways, or genetic mutations [8]. Finally, bacteria can acquire resistance from the transferred copy of the plasmid (R-plasmid genes) of a previously resistant bacteria [7-9].

The development of antibiotic resistance appears to be inevitable [10]. However, the overuse and misuse of antibiotics are accelerating this process [11]. The misuse of antibiotics is a complex problem driven by several factors related to patients, healthcare providers, and institutional healthcare regulations [12]. Public knowledge, awareness, and attitudes regarding antibiotic use are strong determinants of antibiotic misuse [13]. In a systematic review conducted by Alhommad et al. in 2017 and demonstrated the use of antibiotics in the Middle East, the overall prevalence of participants who used antibiotics as self-prescription ranged from 19% to 82% [14]. The highest prevalence of self-prescription antibiotics was reported in Yemen and Oman followed by Saudi Arabia [14]. Access to antibiotics without a prescription and gaps in knowledge and safe practices regarding antibiotics' use (e.g., keeping leftover antibiotics from an uncompleted course for future use and sharing antibiotics with others) were among the reported reasons for self-medication with antibiotics [14]. Furthermore, prescribers’ knowledge and attitudes regarding antibiotic use and resistance have been reported to determine the quality of antibiotic prescriptions [15]. One core problem underlying improper antibiotic prescription is the lack of sufficient diagnostic tests to rapidly identify pathogens and their antibiotic susceptibility profiles [16]. Another proven risk factor for antibiotic resistance is travel, specifically during the Hajj season, when the acquisition and transmission of infectious diseases (including those caused by ABR bacteria) are common occurrences [17].

The topic of antibiotic resistance has been approached from many perspectives for a wide variety of clinical and social practices and implications. However, the present research specifically aimed to assess the prevalence of ABR infections in Ministry of National Guard-Health Affairs (MNGHA), Jeddah, Saudi Arabia. In a study conducted in the western region of Saudi Arabia, pneumonia was the most prevalent infectious disease reported in patients aged 26-45 years [18]. Additionally, pneumonia and urinary tract infections (UTIs) were the most prevalent forms of infectious diseases among female patients [18]. In the central region of Saudi Arabia, respiratory tract infections (RTIs) and UTIs have been found to be the most frequent complaints, encountered in emergency departments [19]. The availability of updated epidemiological data from a given region or community is important not only for the optimization of empirical therapies but also for the implementation of an effective antimicrobial stewardship program in hospitals [20].

**Materials And Methods**

**Selection criteria**

An observational cross-sectional quantitative study (with non-probability convenience sampling) was conducted in the MNGHA, Jeddah, Saudi Arabia. For this study, patients were selected according to the following criteria: male and female Saudi inpatients and outpatients aged 15 years or older who had received antibiotic treatments prior to the initiation of the study for UTIs and/or RTIs. This sample excluded the oncology department, patients infected with tuberculosis (TB), and patients infected with human immunodeficiency virus (HIV).

**Sample size calculation**

The sample size was calculated using Raosoft® software (Raosoft Inc., Seattle, United States). Approximately 231,000 patients received antibiotic treatments in MNGHA, Jeddah, between May 2016 and December 2019. At a 95% confidence level, an estimated 59.1% prevalence of ABR patients, and a 5% margin of error, the required minimum sample size was estimated at 371 samples. All patients who met the sample criteria from May 2016 to December 2019 were included in the study.

Data were obtained from the BESTCare system (ezCaretech, Torrance, California, United States) using a data collection sheet. The collected numerical variables included age and date of diagnosis, and the collected categorical/nominal variables included gender, hospital setting, diagnosis, antibiotic type, specimen source, culture results, and sensitivity test results.

**Data analysis**

Parametric and non-parametric approaches were used to describe the numerical data (age and date of...
diagnosis). Percentages were used to describe the categorical variables (gender, hospital setting, diagnosis, antibiotic type, specimen source, type of organism, and sensitivity test results). Chi-square or Fisher exact test was used to compare categorical data, while t-test and ANOVA were used to make comparisons between categorical and numerical variables. A p-value of less than 0.05 was statistically significant. All data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (Released 2011; IBM Corp., Armonk, New York, United States).

**Ethical approval**

The study was carried out in line with the Helsinki protocol and ethical approval from the Institutional Review Board of King Abdullah International Medical Research Centre, Jeddah, Saudi Arabia, was duly acquired prior to conducting this study (approval number: SP20/050/1, dated April 22, 2020). No names and Identities (IDs) were collected from the participants, and the data were stored within 64-bit encrypted software on the work computer of the primary investigator that was not liable to be breached by nonauthorized persons.

**Results**

A total of 1,151 isolates were obtained from the BESTCare system in MNGHA, Jeddah, Saudi Arabia, between May 2016 and December 2019. These samples were categorized into age groups. Overall, 52.7% (n = 607) of these samples were collected from female patients, and 78.2% (n = 900) and 21.8% (n = 251) were collected from inpatients and outpatients, respectively. Data regarding patient demographics, hospital settings, and specimen types are displayed in Table 1.
# TABLE 1: Participants’ demographic data.

Regarding specimen sources, 49.3% (n = 568) of the samples were obtained from respiratory specimens, 50.7% (n = 583) were obtained from urine specimens, and the sources of seven specimens were not documented; thus, the total number of specimens was 1,144 (Table 2).
| Specimen source                      | n=1144 | %    |
|--------------------------------------|--------|------|
| Urine                                | 578    | 50.5 |
| Sputum                               | 397    | 34.7 |
| Endotracheal aspiration              | 62     | 5.4  |
| Tracheal aspiration                  | 51     | 4.5  |
| Nasal swab                           | 21     | 1.8  |
| Urinary catheter                     | 13     | 1.1  |
| MRSA culture                         | 10     | .9   |
| Bronchoalveolar lavage               | 5      | .4   |
| Nasopharyngeal airway (NPA)          | 3      | .3   |
| Bronchial biopsy                     | 1      | .1   |
| Bronchial wash                       | 1      | .1   |
| Pleural fluid                        | 1      | .1   |
| Tissue culture                       | 1      | .1   |

**TABLE 2: Specimen source.**

MRSA: methicillin-resistant *Staphylococcus aureus*

The top 10 most common causative agents of UTIs and RTIs were *E. coli* (26.4%; n = 304), *K. pneumoniae* (24.2%; n = 278), *P. aeruginosa* (16.9%; n = 194), *Acinetobacter baumannii* (8.4%; n = 97), MRSA (5.6%; n = 42), *Enterococcus faecalis* (5%; n = 35), *S. aureus* (2.9%; n = 33), *Proteus mirabilis* (2.1%; n = 24), *Haemophilus influenzae* (2%; n = 23), and *S. pneumoniae* (1.8%; n = 21) (Figure 1, Table 3).
FIGURE 1: Bacterial composition: comparison between common bacterial isolates in urinary tract infections (UTIs) and respiratory tract infections (RTIs) during the study period.

In ascending order, this figure lists the bacterial isolates (x-axis) most commonly found in UTIs and RTIs with their percentages (y-axis) in each type of infection. The line graph represents changes in these bacterial isolates that occurred in 2016 (blue line), 2017 (red line), 2018 (green line), and 2019 (purple line).

The percentages in RTIs were as follows: Pseudomonas aeruginosa 36% (2016), 25.7% (2017), 28.2% (2018), and 27.7% (2019); Acinetobacter baumannii 28.1% (2016), 21.2% (2017), and 0% (2018 and 2019); Klebsiella pneumoniae 9% (2016), 17.3% (2017), 17.8% (2018), and 23.4% (2019); methicillin-resistant Staphylococcus aureus (MRSA) 5.6% (2016), 6.7% (2017), 11% (2018), and 8.8% (2019); Escherichia coli 4.5% (2016 and 2017), 7.4% (2018), and 5.8% (2019).

The percentages in UTIs were as follows: E. coli 49.4% (2016), 52.6% (2017), 42.8% (2018), and 42.7% (2019); K. pneumoniae 22.4% (2016), 24.3% (2017), 37.5% (2018), and 33.3% (2019); P. aeruginosa 4.7% (2016), 5.2% (2017), 4.8% (2018), and 7.7% (2019); Enterococcus faecalis 10.6% (2016), 5.2% (2017), 4.8% (2018), and 6% (2019); Proteus mirabilis 3.5% (2016), 2.3% (2017), 1.9% (2018), and 2.6% (2019).

| Bacteria                                      | n=1151 | %  |
|-----------------------------------------------|--------|----|
| *Escherichia coli*                            | 304    | 26.4|
| *Klebsiella pneumoniae*                       | 278    | 24.2|
| *Pseudomonas aeruginosa*                      | 194    | 16.9|
| *Acinetobacter baumannii*                     | 97     | 8.4 |
| Methicillin-resistant *Staphylococcus aureus*  | 42     | 3.6 |
| *Enterococcus faecalis*                       | 35     | 3.0 |
| *Staphylococcus aureus*                       | 33     | 2.9 |
| *Proteus mirabilis*                           | 24     | 2.1 |
| *Haemophilus influenzae*                      | 23     | 2.0 |
| *Streptococcus pneumoniae*                    | 21     | 1.8 |
| *Serratia marcescens*                         | 18     | 1.6 |
| *Stenotrophomonas maltophilia*                | 16     | 1.4 |
| *Enterobacter cloacae*                        | 9      | .8 |
| *Citrobacter koseri*                          | 8      | .7 |
| *Providencia stuartii*                        | 7      | .6 |
| Microorganism                       | Count | %  |
|------------------------------------|-------|----|
| Enterobacter aerogenes             | 7     | .6|
| Enterococcus faecium               | 5     | .4|
| Burkholderia cepacia               | 5     | .4|
| Klebsiella oxytoca                 | 4     | .3|
| Citrobacter freundii               | 2     | .2|
| Salmonella                         | 2     | .2|
| Elizabethkingia meningoseptica     | 2     | .2|
| Alcaligenes faecalis               | 2     | .2|
| Serratia liquefaciens              | 1     | .1|
| Bacillus anthracis                 | 1     | .1|
| Moraxella catarrhalis              | 1     | .1|
| Serratia fonticola                 | 1     | .1|
| Morganella morganii                | 1     | .1|
| Sphingobacteris capsulusing        | 1     | .1|
| Cedecea lapagei                    | 1     | .1|
| Pseudomonas putida                 | 1     | .1|
| Providencia rettgeri               | 1     | .1|
| Achromobacter xylosoxidans        | 1     | .1|
| Cronobacter sakazakii              | 1     | .1|
| Haemophilus parainfluenza          | 1     | .1|
| Pantoea species                    | 1     | .1|

**TABLE 3: Causative agents of urinary tract infections (UTIs) and respiratory tract infections (RTIs).**

The most common microbial causative agent of UTIs was *E. coli* (46.7%; n = 272), followed by *K. pneumoniae* (30.5%; n = 178), *E. faecalis* (6%; n = 35), *P. aeruginosa* (5.5%; n = 32), and *P. mirabilis* (2.2%; n = 13) (Table 4).
TABLE 4: Bacteria isolated from urine specimen sources.

Furthermore, *E. coli* was most resistant to ampicillin (56.4%), followed by ceftriaxone (35.8%), ciprofloxacin (3.8%), amoxicillin (2.6%), and trimethoprim/sulfamethoxazole (1.7%; p = 0.014). Similarly, *K. pneumoniae* was most resistant to ampicillin (69.7%), followed by ceftriaxone (23.9%), amoxicillin-clavulanate (2.8%), amoxicillin (1.7%), and ciprofloxacin (0.6%; p < 0.001). Meanwhile, *E. faecalis* was most resistant to ciprofloxacin (28.6%), followed by ampicillin (21.4%), erythromycin and clindamycin (14.5%), and vancomycin (7.1%; p = 0.619). The *P. aeruginosa* isolates were most resistant to piperacillin/tazobactam (53.8%), followed by ciprofloxacin and ampicillin/sulbactam (15.4%) and cefazolin and trimethoprim/sulfamethoxazole (7.7%; p = 0.025). Finally, *P. mirabilis* was most resistant to ampicillin (53.8%), followed by ciprofloxacin (23.1%), nitrofurantoin (15.4%), and trimethoprim/sulfamethoxazole (7.7%; p = 0.860). The complete results are illustrated in Table 5 and Table 6.
| Antibiotic              | Klebsiella pneumoniae | Enterococcus faecalis | Pseudomonas aeruginosa | Proteus mirabilis |
|------------------------|-----------------------|-----------------------|-----------------------|-------------------|
|                        | n=19 | % | n=42 | % | n=77 | % | n=38 | % |
| Ceftriaxone            | 13   | 41.9 | 30   | 37.0 | 23   | 27.7 | 13   | 33.3 |
| Piperacillin/tazobactam| 0    | 0.0 | 0    | 0.0 | 1    | 1.2 | 0    | 0.0 |
| Amoxicillin-clavulanate| 0    | 0.0 | 0    | 0.0 | 0    | 0.0 | 1    | 2.6 |
| Cefazolin              | 0    | 0.0 | 1    | 1.2 | 0    | 0.0 | 0    | 0.0 |
| Nitrofurantoin         | 1    | 3.2 | 4    | 4.9 | 1    | 1.2 | 0    | 0.0 |
| Amoxicillin            | 17   | 54.8 | 43   | 53.1 | 51   | 61.4 | 21   | 53.8 |
| Ampicillin             | 0    | 0.0 | 0    | 0.0 | 2    | 2.4 | 2    | 5.1 |
| Trime-thoprim/sulfamethoxazole| 0 | 0.0 | 0    | 0.0 | 2    | 2.4 | 2    | 5.1 |
|                        | n=19 | % | n=42 | % | n=77 | % | n=38 | % |
|                        | 0.209 | | | | | | |
| Ciprofloxacin          | 0    | 0.0 | 0    | 0.0 | 0    | 0.0 | 1    | 2.6 |
| Ceftriaxone            | 2    | 10.5 | 13   | 31.0 | 18   | 23.4 | 9    | 23.7 |
| Piperacillin/tazobactam| 0    | 0.0 | 1    | 2.4 | 0    | 0.0 | 0    | 0.0 |
| Amoxicillin-clavulanate| 0    | 0.0 | 0    | 0.0 | 2    | 2.6 | 3    | 7.9 |
| Nitrofurantoin         | 0    | 0.0 | 1    | 2.4 | 0    | 0.0 | 0    | 0.0 |
| Amoxicillin            | 1    | 5.3 | 0    | 0.0 | 1    | 1.3 | 1    | 2.6 |
| Ampicillin             | 16   | 84.2 | 27   | 64.3 | 56   | 72.7 | 24   | 63.2 |
|                        | n=5  | % | n=4  | % | n=2  | % | n=3  | % |
|                        | 0.412 | | | | | | |
| Ciprofloxacin          | 3    | 60.0 | 0    | 0.0 | 1    | 50.0 | 0    | 0.0 |
| Vancomycin             | 0    | 0.0 | 1    | 25.0 | 0    | 0.0 | 0    | 0.0 |
| Erythromycin           | 0    | 0.0 | 1    | 25.0 | 0    | 0.0 | 1    | 33.3 |
| Gentamicin             | 1    | 20.0 | 0    | 0.0 | 0    | 0.0 | 0    | 0.0 |
| Nitrofurantoin         | 0    | 0.0 | 0    | 0.0 | 0    | 0.0 | 1    | 33.3 |
| Clindamycin            | 1    | 20.0 | 1    | 25.0 | 0    | 0.0 | 0    | 0.0 |
| Ampicillin             | 0    | 0.0 | 1    | 25.0 | 1    | 50.0 | 1    | 33.3 |
|                        | n=4  | % | n=5  | % | n=2  | % | n=3  | % |
|                        | 0.911 | | | | | | |
| Ciprofloxacin          | 1    | 25.0 | 0    | 0.0 | 0    | 0.0 | 1    | 50.0 |
| Piperacillin/tazobactam| 2    | 50.0 | 3    | 60.0 | 1    | 50.0 | 1    | 50.0 |
| Cefazolin              | 0    | 0.0 | 0    | 0.0 | 1    | 50.0 | 0    | 0.0 |
| Ampicillin/Sulbactam   | 1    | 25.0 | 1    | 20.0 | 0    | 0.0 | 0    | 0.0 |
| Trime-thoprim/sulfamethoxazole| 0 | 0.0 | 1    | 20.0 | 0    | 0.0 | 0    | 0.0 |
|                        | n=3  | % | n=3  | % | n=4  | % | n=3  | % |
|                        | 0.666 | | | | | | |
| Ciprofloxacin          | 1    | 33.3 | 0    | 0.0 | 2    | 50.0 | 0    | 0.0 |
| Nitrofurantoin         | 0    | 0.0 | 1    | 33.3 | 0    | 0.0 | 1    | 33.3 |
| Ampicillin             | 1    | 33.3 | 2    | 66.7 | 2    | 50.0 | 2    | 66.7 |
| Trime-thoprim/sulfamethoxazole| 1 | 33.3 | 0    | 0.0 | 0    | 0.0 | 0    | 0.0 |
# TABLE 5: Resistance rate changes over the study period among urinary tract bacteria.

| Urinary tract infection bacteria (resistant) |   |   |
|---------------------------------------------|---|---|
| **Escherichia coli**                       | n | % |
| Ampicillin                                  | 132 | 56.4 |
| Ceftriaxone                                  | 79 | 33.8 |
| Ciprofloxacin                                | 9 | 3.8 |
| Amoxicillin                                  | 6 | 2.6 |
| Trimethoprim/sulfamethoxazol                 | 4 | 1.7 |
| Piperacillin/tazobactam                      | 1 | .4 |
| Amoxicillin/clavulanate                      | 1 | .4 |
| Cefazolin                                    | 1 | .4 |
| Nitrofurantoin                               | 1 | .4 |
| **Total**                                    | 234 | 100.0 |
| **Klebsiella pneumoniae**                    | n | % |
| Ampicillin                                  | 123 | 69.9 |
| Ceftriaxone                                  | 42 | 23.9 |
| Amoxicillin/clavulanate                      | 5 | 2.8 |
| Amoxicillin                                  | 3 | 1.7 |
| Ciprofloxacin                                | 1 | .6 |
| Piperacillin/tazobactam                      | 1 | .6 |
| Nitrofurantoin                               | 1 | .6 |
| **Total**                                    | 176 | 100.0 |
| **Enterococcus faecalis**                    | n | % |
| Ciprofloxacin                                | 4 | 28.6 |
| Ampicillin                                   | 3 | 21.4 |
| Erythromycin                                 | 2 | 14.3 |
| Clindamycin                                  | 2 | 14.3 |
| Vancomycin                                   | 1 | 7.1 |
| Gentamicin                                   | 1 | 7.1 |
| Nitrofurantoin                               | 1 | 7.1 |
| **Total**                                    | 14 | 100.0 |
| **Pseudomonas aeruginosa**                   | n | % |
| Piperacillin/tazobactam                      | 7 | 53.8 |
| Ciprofloxacin                                | 2 | 15.4 |
| Amoxicillin/sulbactam                        | 2 | 15.4 |
| Cefazolin                                    | 1 | 7.7 |
| Trimethoprim/sulfamethoxazol                 | 1 | 7.7 |

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## Table 6: Urine isolated bacterial resistance rate.

Regarding the isolates from respiratory sources, the most frequently isolated pathogen was *P. aeruginosa* (28.5%), followed by *K. pneumoniae* (17.6%), *A. baumannii* (15.1%), MRSA (7.2%), and *E. coli* (5.6%) (Table 7).

| Isolate                  | n  | %     |
|--------------------------|----|-------|
| **Total**                | 13 | 100.0 |
| **Proteus mirabilis**    |    |       |
| Ampicillin               | 7  | 53.8  |
| Ciprofloxacin            | 3  | 23.1  |
| Nitrofurantoin           | 2  | 15.4  |
| Trimethoprim/sulfamethoxazol | 1 | 7.7   |
| **Total**                | 13 | 100.0 |
| **Acinetobacter baumannii** | 10 | 100.0 |
| Piperacillin/tazobactam  | 9  | 90.0  |
| Ampicillin               | 1  | 10.0  |
| **Total**                | 10 | 100.0 |
| **Citrobacter koseri**   |    |       |
| Piperacillin/tazobactam  | 2  | 33.3  |
| Amoxicillin/clavulanate  | 2  | 33.3  |
| Ciprofloxacin            | 1  | 16.7  |
| Cefazolin                | 1  | 16.7  |
| **Total**                | 6  | 100.0 |
| **Enterobacter cloacae** |    |       |
| Amoxicillin/clavulanate  | 5  | 100.0 |
| **Enterococcus faecium** |    |       |
| Ampicillin               | 4  | 80.0  |
| Nitrofurantoin           | 1  | 20.0  |
| **Total**                | 5  | 100.0 |
| **Providencia stuartii** |    |       |
| Ampicillin               | 3  | 60.0  |
| Ceftriaxone              | 2  | 40.0  |
| **Total**                | 5  | 100.0 |
| **Enterobacter aerogenes** |    |       |
| Amoxicillin/clavulanate  | 3  | 75.0  |
| Amoxicillin              | 1  | 25.0  |
| **Total**                | 4  | 100.0 |
### TABLE 7: Bacteria isolated from respiratory specimen sources.

| Bacteria                                    | n=568 | %  |
|---------------------------------------------|-------|----|
| Pseudomonas aeruginosa                      | 162   | 28.5 |
| Klebsiella pneumoniae                       | 100   | 17.6 |
| Acinetobacter baumannii                     | 86    | 15.1 |
| Methicillin-resistant Staphylococcus aureus | 41    | 7.2  |
| Escherichia coli                            | 32    | 5.6  |
| Staphylococcus aureus                       | 31    | 5.5  |
| Haemophilus influenzae                      | 22    | 3.9  |
| Streptococcus pneumoniae                    | 20    | 3.5  |
| Serratia marcescens                         | 15    | 2.6  |
| Stenotrophomonas maltophilia                | 14    | 2.5  |
| Proteus mirabilis                           | 11    | 1.9  |
| Burkholderia cepacia                        | 5     | 0.9  |
| Enterobacter cloacae                        | 4     | 0.7  |
| Klebsiella oxytocta                         | 4     | 0.7  |
| Enterobacter aerogenes                      | 3     | 0.5  |
| Citrobacter koseri                          | 2     | 0.4  |
| Providencia stuartii                        | 2     | 0.4  |
| Elizabethkingia meningoseptica              | 2     | 0.4  |
| Alcaligenes faealalis                       | 2     | 0.4  |
| Serratia liquefaciens                       | 1     | 0.2  |
| Bacillus anthracis                          | 1     | 0.2  |
| Moraxella catarrhalis                       | 1     | 0.2  |
| Morganella morganii                         | 1     | 0.2  |
| Citrobacter freundii                        | 1     | 0.2  |
| Staphylococcus capitis                      | 1     | 0.2  |
| Providencia rettgeri                        | 1     | 0.2  |
| Achromobacter xylosoxidans                  | 1     | 0.2  |
| Cronobacter sakazakii                       | 1     | 0.2  |
| Haemophilus parainfluenza                   | 1     | 0.2  |

Regarding the 162 respiratory P. aeruginosa isolates, most (51.9%) were resistant to piperacillin/tazobactam, followed by ciprofloxacin (25%), ampicillin (10.6%), ampicillin/sulbactam (5.8%), and meropenem (2.9%; p < 0.001). Meanwhile, K. pneumoniae was most resistant to ampicillin (82.7%), followed by ceftriaxone (9.2%), piperacillin/tazobactam (7.1%), and amoxicillin (1%; p = 0.153). Finally, the A. baumannii isolates were most resistant to piperacillin/tazobactam (52.6%; p = 0.520). Table 8 and Table 9 give details of respiratory infection bacterial resistance.
| Pseudomonas aeruginosa     | n  | %  |
|---------------------------|----|----|
| Piperacillin/tazobactam   | 54 | 51.9 |
| Ciprofloxacin             | 26 | 25.0 |
| Ampicillin                | 11 | 10.6 |
| Ampicillin/sulbactam      | 4  | 3.8  |
| Meropenem                 | 3  | 2.9  |
| Imipenem                  | 2  | 1.9  |
| Cefazidim                 | 2  | 1.9  |
| Cefepime                  | 1  | 1.0  |
| Tigecycline               | 1  | 1.0  |
| Total                     | 104| 100.0 |

| Klebsiella pneumoniae     | n  | %  |
|---------------------------|----|----|
| Ampicillin                | 81 | 82.7 |
| Ceftriaxone               | 9  | 9.2  |
| Piperacillin/tazobactam   | 7  | 7.1  |
| Amoxicillin               | 1  | 1.0  |
| Total                     | 98 | 100.0 |

| Acinetobacter baumannii   | n  | %  |
|---------------------------|----|----|
| Piperacillin/tazobactam   | 41 | 52.6 |
| Ampicillin                | 30 | 38.5 |
| Ciprofloxacin             | 4  | 5.1  |
| Meropenem                 | 1  | 1.3  |
| Ceftriaxone               | 1  | 1.3  |
| Amoxicillin/clavulanate   | 1  | 1.3  |
| Total                     | 78 | 100.0 |

| Methicillin-resistant Staphylococcus aureus | n | %  |
|--------------------------------------------|---|----|
| Cefazolin                                  | 8 | 72.7 |
| Clindamycin                                | 2 | 18.2 |
| Piperacillin/tazobactam                    | 1 | 9.1  |
| Total                                      | 11 | 100.0 |

| Escherichia coli                      | n | %  |
|---------------------------------------|---|----|
| Ampicillin                            | 16| 59.3 |
| Ceftriaxone                           | 10| 37.0 |
| Amoxicillin                           | 1 | 3.7  |
| Total                                 | 27| 100.0 |

| Staphylococcus aureus                 | n | %  |
|---------------------------------------|---|----|
| Clindamycin                           | 4 | 40.0 |
| Erythromycin                          | 3 | 30.0 |
| Trimethoprim/sulfamethoxazol          | 2 | 20.0 |
| Cefazolin                             | 1 | 10.0 |
### TABLE 8: Respiratory tract bacterial resistance rate.

| Respiratory infection bacteria (Resistant) | Year of diagnosis | p-value |
|------------------------------------------|-------------------|---------|
|                                          | 2016 | 2017 | 2018 | 2019 |       |
|                                          | n=25 | n=35 | n=26 | n=18 |       |
|                                          | %    | %    | %    | %    |       |
| **Pseudomonas aeruginosa**                |      |      |      |      | <0.001|
| Meropenem                                | 2    |     | 1    |     |       |
|                                         | 8.0  | 1.0 | 2.9  | 0.0  | 0.0    |
| Ciprofloxacin                            | 2    | 8.0 | 2.0  | 5.7  | 16.5  |
|                                         | 8.0  | 2.0 | 5.7  | 16.5 | 33.3  |
| Piperacillin/tazobactam                   | 8    | 32.0| 27.1 | 77.1 | 34.6  |
|                                         | 8.0  | 32.0| 27.1 | 77.1 | 55.6  |
| Imipenem                                 | 0    | 0.0 | 1.0  | 2.9  | 3.8   |
|                                         | 0.0  | 0.0 | 1.0  | 2.9  | 3.8   |
| Cefazidim                                 | 2    | 8.0 | 0.0  | 0.0  | 0.0   |
|                                         | 8.0  | 0.0 | 0.0  | 0.0  | 0.0   |
| Cefepime                                 | 0    | 0.0 | 0.0  | 0.0  | 0.0   |
|                                         | 0.0  | 0.0 | 0.0  | 0.0  | 0.0   |
| Tigecycline                               | 0    | 0.0 | 0.0  | 0.0  | 0.0   |
|                                         | 0.0  | 0.0 | 0.0  | 0.0  | 0.0   |

| **Haemophilus influenzae**                |      |      |      |      |       |
|                                          | n    | %    | %    | %    |       |
| Ciprofloxacin                            | 1    | 50.0 |      |      |       |
| Ampicillin                                | 1    | 50.0 |      |      |       |
| **Total**                                 | 2    | 100.0|      |      |       |

| **Streptococcus pneumoniae**              |      |      |      |      |       |
|                                          | n    | %    | %    | %    |       |
| Ceftriaxone                               | 2    | 20.0 |      |      |       |
| Erythromycin                              | 2    | 20.0 |      |      |       |
| Clindamycin                               | 2    | 20.0 |      |      |       |
| Penicillin                                | 2    | 20.0 |      |      |       |
| Vancomycin                                | 1    | 10.0 |      |      |       |
| Levofoxacin                               | 1    | 10.0 |      |      |       |
| **Total**                                 | 10   | 100.0|      |      |       |

| **Serratia marcescens**                   |      |      |      |      |       |
|                                          | n    | %    | %    | %    |       |
| Amoxicillin/clavulanate                   | 10   | 76.9 |      |      |       |
| Ciprofloxacin                            | 1    | 7.7  |      |      |       |
| Cefazolin                                 | 1    | 7.7  |      |      |       |
| Cefazidim                                 | 1    | 7.7  |      |      |       |
| **Total**                                 | 13   | 100.0|      |      |       |

| **Stenotrophomonas maltophilia**          |      |      |      |      |       |
|                                          | n    | %    | %    | %    |       |
| Trimethoprim/sulfamethoxazol              | 2    | 40.0 |      |      |       |
| Ciprofloxacin                            | 1    | 20.0 |      |      |       |
| Piperacillin/tazobactam                   | 1    | 20.0 |      |      |       |
| Levofloxacin                              | 1    | 20.0 |      |      |       |
| **Total**                                 | 5    | 100.0|      |      |       |
TABLE 9: Resistance rate changes over the study period among respiratory tract bacteria.

|                          | 1  | 4.0 | 3  | 8.6 | 0  | 0.0 | 0  | 0.0 |
|--------------------------|----|-----|----|-----|----|-----|----|-----|
| **Ampicillin/sulbactam** |    |     |    |     |    |     |    |     |
| **Ampicillin**           | 10 | 40.0| 1  | 2.9 | 0  | 0.0 | 0  | 0.0 |
| **Klebsiella pneumoniae**|    |     |    |     |    |     |    |     |
| Ceftriaxone              | 1  | 12.5| 3  | 9.7 | 2  | 7.1 | 3  | 9.7 |
| Piperacillin/tazobactam  | 0  | 0.0 | 6  | 19.4| 1  | 3.6 | 0  | 0.0 |
| Amoxicillin              | 0  | 0.0 | 0  | 0.0 | 0  | 0.0 | 0  | 1.0 |
| Ampicillin               | 7  | 87.5| 22 | 71.0| 25 | 89.3| 27 | 87.1|
| **Acinetobacter baumannii**|   |     |    |     |    |     |    |     |
| Meropenem                | 0  | 0.0 | 1  | 2.9 | 0  | 0.0 | 0  | 0.0 |
| Ciprofloxacin            | 2  | 9.1 | 1  | 2.9 | 1  | 10.0| 0  | 0.0 |
| Ceftriaxone              | 0  | 0.0 | 1  | 2.9 | 0  | 0.0 | 0  | 0.0 |
| Piperacillin/tazobactam  | 9  | 40.9| 19 | 54.3| 5  | 50.0| 8  | 72.7|
| Amoxicillin/clavulanate  | 0  | 0.0 | 0  | 0.0 | 0  | 0.0 | 1  | 9.1 |
| Ampicillin               | 11 | 50.0| 13 | 37.1| 4  | 40.0| 2  | 18.2|
| **Methicillin-resistant Staphylococcus aureus** |    |     |    |     |    |     |    |     |
| Piperacillin/tazobactam  | 0  | 0.0 | 0  | 0.0 | 1  | 16.7| 0  | 0.0 |
| Cefazolin                | 0  | 0.0 | 2  | 100.0| 4 | 66.7| 2  | 100.0|
| Clindamycin              | 1  | 100.0| 0  | 0.0 | 1  | 16.7| 0  | 0.0 |
| **Escherichia coli**     |    |     |    |     |    |     |    |     |
| Ceftriaxone              | 1  | 25.0| 2  | 28.6| 5  | 45.5| 2  | 40.0|
| Amoxicillin              | 0  | 0.0 | 1  | 14.3| 0  | 0.0 | 0  | 0.0 |
| Ampicillin               | 3  | 75.0| 4  | 57.1| 6  | 54.5| 3  | 60.0|

Discussion

The growing incidence of antibiotic resistance is a substantial concern globally and is considered the main hurdle to the effectiveness of treating bacterial infection. Table 10 shows the list of antibiotic resistance over time. Importantly, the resistance discovery dates in Table 10 are according to the observations during clinical practice, however, the resistance might have appeared earlier based on the findings from laboratory-based experiments.
The growing prevalence of ABR bacteria may affect the capability to control infectious diseases by reducing treatment effectiveness, prolonging illness duration, raising mortality rates, and increasing healthcare costs. This study aimed to identify the common rate of bacterial resistance against antibacterial agents in MNGHA, Jeddah, Saudi Arabia, and to assess the practice of appropriate antibiotic treatment.

In this study, the top 10 most common causative agents of UTIs and RTIs were *E. coli* (26.4%), *K. pneumoniae* (24.2%), *P. aeruginosa* (10.9%), *A. baumannii* (8.4%), MRSA (5.6%), *E. faecalis* (5%), *S. aureus* (2.9%), *P. mirabilis* (2.1%), *H. influenzae* (2%), and *S. pneumoniae* (1.8%). Despite the lack of significant differences between isolated organisms across age groups, most of the causative organisms identified in this study were more prevalent (25.5%) in the group aged 76-85 years than in other age groups.

The most common causative agent of UTIs in this study was *E. coli* (46.7%), followed by *K. pneumoniae* (30.5%), *E. faecalis* (6%), *P. aeruginosa* (5.5%), and *P. mirabilis* (2.2%). These findings are consistent with local and global epidemiological data. In 2012, the most frequently identified bacteria in urinary isolates from female outpatients in the United States was *E. coli* (64.9%), followed by *K. pneumonia* (10.1%), *P. mirabilis* (5%), *E. faecalis* (4.1%), and *P. aeruginosa* (2.7%) [21]. In 2018, the most common microbial causative agent of UTIs in isolates collected from major tertiary hospitals in Riyadh, Saudi Arabia, was *E. coli* (52%), followed by *K. pneumoniae* (15%), *P. aeruginosa* (8%), *S. agalactiae* (7%), and *E. faecalis* (5%) [22].

Among the most commonly prescribed antibiotics for UTI management, the most commonly identified uropathogen in the present study (*E. coli*) was most resistant to ampicillin (56.4%), followed by ceftriaxone (33.8%), ciprofloxacin (3.8%), amoxicillin (2.6%), and sulfamethoxazole/trimethoprim (1.7%). A similar result was reported in a study of three governmental hospitals (Najran General Hospital, Khalid Hospital, and Najran University Hospital) in the Najran region of Saudi Arabia, which aimed to investigate the antimicrobial resistance patterns of 136 outpatient urine samples. In this prior study, *E. coli* (58.5%) was the most common causative agent of UTIs, with an ampicillin resistance rate of 56.94% [23]. Although the emergence of antibiotic resistance may vary regionally and geographically, the present results regarding UTIs appear to be consistent with global antibiotic resistance data. In a multinational, multicenter study of 19,756 urine samples collected from 2003 to 2010, *E. coli* showed aminopenicillin antibiotic resistance rates of 42% in Northern Europe, 59% in Southern Europe, 60% in Asia, and 55% in South America and Africa [24].

Among the isolates from respiratory sources, the most common bacterial pathogen was *P. aeruginosa*, totaling 162 isolates (28.5%). Of these *P. aeruginosa* isolates, most (51.9%) were resistant to piperacillin/tazobactam, followed by ciprofloxacin (25%), ampicillin (10.6%), ampicillin/sulbactam (3.8%),

### TABLE 10: Selected germs showing resistance over time.

| Antibiotic Approved or Released | Year Released | Resistant Germ Identified                                                                 | Year Identified |
|---------------------------------|---------------|------------------------------------------------------------------------------------------|----------------|
| Penicillin                       | 1943          | Penicillin-resistant *Streptococcus pneumonia*; Penicillinase-producing *Neisseria gonorrhoeae* | 1967, 1976     |
| Vancomycin                      | 1958          | Plasmid-mediated vancomycin-resistant *Enterococcus faecium*; Vancomycin-resistant *Staphylococcus aureus* | 1988 [22], 2002 [23] |
| Amphotericin B                  | 1959          | Amphotericin B-resistant *Candida auris*                                                  | 2016 [24]      |
| Methicillin                     | 1960          | Methicillin-resistant *Staphylococcus aureus*                                              | 1960 [25]      |
| Extended-spectrum cephalosporins | 1980 (Cefotaxime) | Extended-spectrum beta-lactamase-producing *Escherichia coli*                              | 1983 [26]      |
| Azithromycin                    | 1980          | Azithromycin-resistant *Neisseria gonorrhoeae*                                             | 2011 [27]      |
| Imipenem                        | 1985          | *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*               | 1996 [28]      |
| Ciprofloxacin                   | 1987          | Ciprofloxacin-resistant *Neisseria gonorrhoeae*                                            | 2007 [29]      |
| Fluconazole                     | 1990 (FDA approved) | Fluconazole-resistant *Candida*                                                              | 1988 [30]      |
| Caspofungin                     | 2001          | Caspofungin-resistant *Candida*                                                             | 2004 [31]      |
| Daptomycin                      | 2003          | Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*                          | 2004 [32]      |
| Ceftazidime-avibactam           | 2015          | Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*                      | 2015 [33]      |
and meropenem (2.9%). Similarly, in a study of 10 medical centers from all regions of Canada, the P. aeruginosa isolate was the predominant respiratory organism (26.2%; 423/1,612 isolates) [25]. These findings are also consistent with those of a more recent study in which more than 20% of P. aeruginosa isolates were resistant to piperacillin/tazobactam [26]. In the present study, K. pneumoniae was the second-most prevalent bacteria (17.6%) in the isolates from respiratory sources. Regarding the 100 K. pneumoniae isolates, ampicillin resistance was highest (82.7%), followed by ceftriaxone (9.2%) and piperacillin/tazobactam (7.1%) resistance. This is contrary to the study by Al-Zalabani et al., in which the overall resistance found in 11,507 K. pneumoniae isolates was 61.7%, with remarkably high resistance rates of 80.4% and 58.7% to piperacillin and piperacillin/tazobactam, respectively [34]. There have been varied reports on the prevalence of Klebsiella species in different parts of the world [25].

The present study revealed high resistance rates for commonly used antibiotics, including ampicillin, amoxicillin/clavulanic acid, and sulfamethoxazole/trimethoprim. It has been suggested that the high rate of resistance to first-line therapies is due to several factors, including antibiotic misuse or self-medication and the ongoing unlawful dispensing of antibiotics in community pharmacies [27], despite the regulations and efforts applied by the Saudi Ministry of Health to alleviate emerging antibiotic resistance. The prescription of antibiotics in dentistry is of particular concern, as it has been reported that general dental practitioners are lacking knowledge regarding prescription of antibiotics in endodontic treatment and situations requiring prophylactic antibiotics [28]. Further investigation is needed to assess these concerns.

Importantly, an initiative strategy by the CDC known as the Antimicrobial Stewardship Programs (ASPs), which was developed as a preventive measure for increased resistance, outlined a set of seven integrated elements to be used by medical care providers globally: leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, and education [35]. Thus, the Saudi Ministry of Health has put efforts into implementing the ASPs in healthcare facilities [36].

**Limitations**

The population in our study is limited to one particular tertiary healthcare center in Jeddah, Saudi Arabia and this may not represent the antimicrobial resistance trends in another region within the same country. Additionally, the present study was based on information from patients’ files. The BESTCare patient data documentation system, which enabled physicians to monitor each patient’s course of antibiotics and guide them through proper and reliable antibiotic management, helped the researchers track patient records. However, incomplete documentation of certain prescribed antibiotics and their impacts on patient outcomes was considered a limitation. Also, communication with infectious disease specialists could have helped in understanding the hospital’s protocol regarding antibiotic resistance.

**Conclusions**

In this study, high levels of antibiotic resistance were observed in both Gram-negative and Gram-positive bacteria. For better implementation of antibacterial stewardship and the optimization of empirical therapies, updated epidemiological data from a given community is necessary to determine the actual pattern of bacterial resistance within that community. Moreover, future studies should assess the impact of maternal antibiotic administration on newborns and the spread of ABR bacteria.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC), Jeddah, Saudi Arabia issued approval SP20/050/J dated April 22, 2020. The study was conducted in accordance with the Declaration of Helsinki. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**References**

1. Gaynes R: The discovery of penicillin—new insights after more than 75 years of clinical use. Emerg Infect Dis. 2017, 23:849-53. 10.3201/eid2305.161556
2. Kadri SS: Key takeaways from the U.S. CDC’s 2019 antibiotic resistance threats report for frontline providers. Crit Care Med. 2020, 48:939-45. 10.1097/CCM.0000000000004571
3. Almaziad S, Bosaeed M: Current state of antimicrobial stewardship and organ transplantation in Saudi Arabia. Transpl Infect Dis. 2022, 24:e13891. 10.1111/tid.13891
4. Aly M, Balkhy HH: The prevalence of antimicrobial resistance in clinical isolates from Gulf Corporation Council countries. Antimicrob Resist Infect Control. 2012, 1:26. 10.1186/2047-2994-1-26
5. Alam MZ, Alam Q, Jiman-Fatani AA, Shukri HA, Haque A: A surveillance study on the prevalence and...
antimicrobial resistance pattern among different groups of bacteria isolated from Western province of Saudi Arabia. Biomed Res. 2017, 28:

6. Li J, Xie S, Ahmed S, et al.: Antimicrobial activity and resistance: influencing factors. Front Pharmacol. 2017, 8:564. 10.3389/fphar.2017.00564

7. Ambroggio I, Tabb LP, O’Meara T, Sheffler-Collins S, McGowan KL, Shah SS: Influence of antibiotic susceptibility patterns on empiric antibiotic prescribing for children hospitalized with community-acquired pneumonia. Pediatr Infect Dis J. 2012, 31:531-6. 10.1097/INF.0b013e3182489c4

8. Reyyaert WC: An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018, 4:482-501. 10.3954/microbiol.2018.3.482

9. Peerey S, Goret J, Bébéar C: Mycoplasma pneumoniae: current knowledge on macrolide resistance and treatment. Front Microbiol. 2016, 7:574. 10.3389/fmicb.2016.00574

10. Davies J, Davies D: Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010, 74:417-33. 10.1128/MMBR.00016-10

11. Aiken AM, Allegrenzi B, Scott JA, Mehtar S, Pittet D, Grundmann H: Antibiotic resistance needs global solutions. Lancet Infect Dis. 2014, 14:550-1. 10.1016/S1473-3099(14)70709-1

12. Mohamadool A, Ramazankhani A, Zarein-Dolah S, Salamzadeh J, Mohamadool F: A systematic review of main factors leading to irrational prescription of medicine. Iran J Psychiatry Behav Sci. 2017, 11:e10242. 10.5144/0268-10242

13. Alumran A, Hurst C, Hou XY: Antibiotics overuse in children with upper respiratory tract infections in Saudi Arabia: risk factors and potential interventions. Clin Med Diagn. 2011, 1:8-16. 10.5925/j.cimd.20110102

14. Alhomoud F, Aijamea Z, Almahasnah R, Alkhalifah K, Basalelah L, Alhomoud FK: Self-medication and self-prescription with antibiotics in the Middle East–do they really happen? A systematic review of the prevalence, possible reasons, and outcomes. Int J Infect Dis. 2017, 57:5-12. 10.1016/j.ijid.2017.01.014

15. Machowska A, Stålsby Lundborg C: Drivers of irrational use of antibiotics in Europe. Int J Environ Res Public Health. 2018, 16:272. 10.3390/ijerph16010027

16. Harbarth S, Samore MH: Antimicrobial resistance determinants and future control. Emerg Infect Dis. 2005, 11:794-801. 10.3201/eid1106.050167

17. Zowawi HM: Antimicrobial resistance in Saudi Arabia. An urgent call for an immediate action. Saudi Med J. 2016, 37:955-960. 10.15577/smj.2016.9.16159

18. Alghamdi AA: Pattern of infectious diseases in the western region of Saudi Arabia; a study of 495 hospitalized patients. Med Sci. 2009, 16:16-2.

19. Hameed T, Al Nafeesah S, Chiisti S, Al Shaalan M, Al Fakheeb K: Community-acquired urinary tract infections in children: resistance patterns of uropathogens in a tertiary care center in Saudi Arabia. Int J Pediatr Adolesc Med. 2019, 6:51-4. 10.1016/j.ipam.2019.02.010

20. Amer MR, Akhras NS, Mahmoud WA, Al-Jazairi AS: Antimicrobial stewardship program implementation in a medical intensive care unit at a tertiary care hospital in Saudi Arabia. Ann Saudi Med. 2015, 35:547-54. 10.5144/0256-4947.2013.547

21. Rammelkamp CH, Maxon T: Resistance of Staphylococcus aureus to the action of penicillin. Proceedings of the Society for Experimental Biology and Medicine. 1942, 386-9. 10.1893/00379727-51-1358

22. Cetinkaya Y, Falk P, Mayhall CG: Vancomycin-resistant enterococci. Clin Microbiol Rev. 2000, 13:686-707. 10.1128/CMR.13.5.486

23. Goldrick B: First reported case of VRSA in the United States. Am J Nurs. 2002, 102:17. 10.1097/00000446-200211000-00015

24. Lockhart SR: Candida auris and multidrug resistance: defining the new normal. Fungal Genet Biol. 2019, 131:103243. 10.1016/j.fgb.2019.103243

25. Enright MC, Robinson DA, Randle G, Feil EJ, Grundmann H, Spratt BG: The evolutionary history of methicillin-resistant Staphylococcus aureus (MRSA). Proc Natl Acad Sci U S A. 2002, 99:7687-92. 10.1073/pnas.122108599

26. Neu HC: Trends in the development of beta-lactam antibiotics. Scand J Infect Dis Suppl. 1984, 42:7-16.

27. Katz AR, Komeya AY, Soge OO, et al.: Neisseria gonorrhoeae with high-level resistance to azithromycin: case report of the first isolate identified in the United States. Clin Infect Dis. 2012, 54:841-3. 10.1093/infdis/cir929

28. Norström P, Cuzon G, Naas T: The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. Lancet Infect Dis. 2009, 9:328-36. 10.1016/S1473-3099(09)70054-4

29. Newman LM, Moran JS, Workowski KA: Update on the management of gonorrhea in adults in the United States. Clin Infect Dis. 2007, 44:S84-101. 10.1086/511422

30. Warnock DW, Burke J, Cope NJ, Johnson EM, von Fraunhofer NA, Williams EW: Fluconazole resistance in Candida glabrata. Lancet. 1988, 2:1310. 10.1016/s0140-6736(88)92919-4

31. Hernandez S, López-Ribot JL, Najvar LR, McCarthy DI, Bocanegra R, Graybill JR: Caspofungin resistance in Candida albicans: correlating clinical outcome with laboratory susceptibility testing of three isogenic isolates serially obtained from a patient with progressive Candida esophagitis. Antimicrob Agents Chemother. 2004, 48:1582-3. 10.1128/AAC.48.4.1582-1583.2004

32. Martý FM, Yeh WW, Wenersteen CB, et al.: Emergence of a clinical daptomycin-resistant Staphylococcus aureus isolate during treatment of methicillin-resistant Staphylococcus aureus bacteremia and osteomyelitis. J Clin Microbiol. 2006, 44:595-7. 10.1128/JCM.44.2.595-597.2006

33. Humphries RM, Yang S, Hemarajata P, Ward KW, Hindler JA, Miller SA, Gregson A: First report of ceftazidime-avibactam resistance in a KPC-3-expressing Klebsiella pneumoniae isolate. Antimicrob Agents Chemother. 2015, 59:6605-7. 10.1128/AAC.00166-15

34. Al-Zalabani A, AlThubayne OA, Alshehri AO, Namankan MO, Aljafri OH: Prevalence of Klebsiella pneumoniae antibiotic resistance in Medina, Saudi Arabia, 2014-2018. Cureus. 2020, 12:e9714. 10.7759/cureus.9714

35. Hwang S, Kwon KT: Core elements for successful implementation of antimicrobial stewardship programs. Infect Chemother. 2021, 53:421-35. 10.3947/ic.2021.0095
56. Haseeb A, Faidah HS, Al-Gethamy M, et al.: Evaluation of antimicrobial stewardship programs (ASPs) and their perceived level of success at Makkah region hospitals, Kingdom of Saudi Arabia. Saudi Pharm J. 2020, 28:1166-71. 10.1016/j.jsps.2020.08.005