

# ANTIBIOTIC-RESISTANT BACTERIA IN INTENSIVE CARE UNITS IN THE KINGDOM OF SAUDI ARABIA: A SYSTEMATIC REVIEW

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## Abstract

**Background:** The emergence of bacterial pathogens and their associated resistance to antibiotic therapy is one of the most serious public health concerns threatening today's society, including Saudi Arabia's intensive care units (ICUs).

**Aim:** This study used a systematic review to explore the antibiotic-resistant bacteria in the intensive care units (ICUs) in Saudi Arabia.

**Methods:** The review adhered to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 guidelines. The search was limited to studies published within 13 years between 2010 and 2023 through CINAHL, Web of Knowledge, PubMed, Science Direct, and Google Scholar.

**Results:** Fifteen studies were reviewed: 12 were retrospective, 1 was comparative historical, 1 was descriptive epidemiologic and 1 was a surveillance study. Most frequently isolated antibiotic-resistant bacteria were *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, and *Enterobacter*. These pathogens were found resistant to various antibiotics including methicillin, tazobactam, cilastatin, meropenem, tigecycline, imipenem, meropenem, piperacillin, colistin, penicillin, ampicillin, oxacillin, vancomycin, carbapenems,

amoxicillin, ceftriaxone, amikacin, gentamicin, clindamycin, azithromycin, levofloxacin, nitrofurantoin, trimethoprim, cefuroxime, ciprofloxacin, aztreonam, and cefotaxime.

**Conclusion:** To eradicate future infection outbreaks of *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and other antibiotic-resistant pathogens in Saudi Arabia's ICUs, comprehensive surveillance programs, strict infection control and prevention guidelines, and stringent implementation of proactive antimicrobial stewardship program are warranted.

**Keywords:** antibiotic; antibiotic-resistant bacteria; intensive care unit; Saudi Arabia

## Introduction

Antibiotics are one of the most frequently used medications worldwide [1], and these drugs reduce mortality rates among critically ill patients [2]. However, the use of any antibiotic drug produces unwanted adverse events, and it is the main driver for the increasing problems with antibiotic resistance [3]. Specifically, intensive care units (ICUs) provide care for vulnerable and critically ill patients by using varied invasive devices; ICUs have encountered increased antibiotic resistance, leading to high nosocomial infection burden [4,5]. In addition, the most essential issue facing ICUs is the spread of nosocomial infections caused by antibiotic resistance [6,7]. Infections with antibiotic-resistant bacteria in ICUs lead to increased negative effects on morbidity and mortality and patients' survival, prolonged hospitalization, and elevated healthcare costs [5,7,8,9]. Thus, the emergence and spread of antibiotic resistance have become a public health priority in healthcare settings, primarily in ICUs, where it may become the leading cause of death by the year 2050 [8,10].

Globally, numerous investigations in ICUs have explored bacterial pathogens and their resistance to antibiotic therapy as one of the most serious health concerns threatening today's society [11]. In Saudi Arabia, a substantial number of studies have investigated the antibiotic-resistant incidences of bacteria in ICUs [4-9,12-18]. With this synopsis about the antibiotic resistance of bacteria, this review presents trends in ICU settings in the Kingdom of Saudi Arabia (KSA). This work may add to the existing knowledge on how to implement control and interventions geared toward reducing morbidity and mortality, decreasing healthcare costs and hospital stay, and improving survival rates of critically ill patients infected with antibiotic-resistant bacteria. The results of this review may reveal the need for continued and vigilant national monitoring for antibiotic-resistant bacteria to reduce the risk of new resistant isolates and avoid complications in ICU settings. Thus, the current study aimed to review the antibiotic-resistant bacteria in the ICUs in KSA between January 2010 and December 2023.

## Methods

### Design

A systematic review of literature was conducted in this study. The review adhered to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 checklist.

### Search strategy

The literature search of studies that investigated the antibiotic resistance of bacteria in the ICUs in KSA was performed online and manually using the following electronic databases: CINAHL, Web of Knowledge, PubMed, Science Direct, and Google Scholar. The search terms used were "antibiotic-resistant bacteria," "antibiotic-resistant pathogens," "intensive care units," "critically ill patients," and "Saudi Arabia." The electronic search was accomplished by limiting studies only to the last 13 years (January 2010–December 2023) to include contemporary studies on antibiotic resistance of bacteria in the ICUs in KSA. The studies included in the review were those that 1) focused on the antibiotic resistance of bacteria; 2) were conducted in the ICUs either in general or sub-units, or in other hospital units that included the ICU; 3) were published in English and in peer-reviewed journals; and 4) were full-text articles with an abstract. Studies without an abstract, not full text, not carried out in the ICU, and not conducted in KSA were excluded from the review.

### Outcomes and data extraction

Initially, the search retrieved 2,670 hits in all electronic databases, as shown in Figure 1. Most of the articles were conducted not in the ICU and outside KSA. Filtered screening through reading of titles and abstracts from these articles resulted in the selection of 21 articles based on the inclusion and exclusion criteria. After the final review and analysis of the author, 15 articles were selected. Details of the author of the study, year of publication, aim of the study, location of the study in KSA, sample (antibiotic-resistant bacteria), design used, and major findings as remarks were extracted from each study (Refer to Table 1).

## Results

This systematic review involved 15 studies conducted in different regions in KSA including two in the western region, three in the eastern region, two in the southwest region, and most (8) in the central region. Surprisingly, no study was conducted in the northern regions of the kingdom. Among those studies, 12 were retrospective, 1 was comparative historical, 1 was descriptive epidemiologic, and 1 was a surveillance study. The most frequently isolated antibiotic-resistant bacteria in this review were *Klebsiella pneumoniae* described in 11 studies, *Pseudomonas aeruginosa* investigated in 9 studies, *Acinetobacter baumannii* reported in 8 studies, *Escherichia coli* studied in 5 studies, *Enterobacter* stated in 5 studies, and others included *Providencia* spp., *Citrobacter* spp., *Serratia* spp., *Proteus mirabilis*, *Staphylococcus aureus*, *Candida albicans*, and *Clostridium difficile*. Finally, most of the pathogens presented above were resistant to various antibiotics including methicillin, tazobactam, cilastatin, meropenem, tigecycline, imipenem, meropenem, piperacillin, colistin, penicillins, ampicillin, oxacillin, vancomycin, carbapenems, amoxicillin, ceftriaxone, amikacin, gentamicin, clindamycin, azithromycin, levofloxacin, nitrofurantoin, trimethoprim, cefuroxime, ciprofloxacin, aztreonam, and cefotaxime.

## Discussion

This study reviewed related literature about antibiotic-resistant bacteria in ICUs in Saudi Arabia. After an extensive search, most of the studies were conducted in tertiary hospitals in the central region of the kingdom [4-5,7,11,13,15-17], and few were carried out in the eastern [8,9,14], southwest regions [6,18], and western region [19,20]. However, no work was conducted in the western and northern regions of the kingdom. This does not mean that there were no investigations about antibiotic-resistant pathogens in these regions; studies may have been conducted in different hospital units, and researchers possibly did not focus on ICUs, such as in the work of Alam et al. [21] and Yagoub et al. [22]. Another reason could be that reports were submitted to the Ministry of Health but not published in journals. Nonetheless, most of the studies were retrospective in design [4-7,9,12-13,16-20], and others were comparative historically controlled studies [15], descriptive epidemiologic hospital-based case-control studies [14], and surveillance studies [8]. These studies were mostly conducted in general ICUs, and few were performed in specific sub-units such as coronary, neonatal, and adult ICUs.

The most frequently isolated antibiotic-resistant bacteria in this review were (1) *K. pneumoniae* [4-9,11,13,17-19], (2) *P. aeruginosa* [4-7,9,11,13,16,18], (3) *A. baumannii* [4-7,9,11,16,18], (4) *E. coli* [4,6,7,11,18], (5) other *Enterobacter* species [4-5,13,14,18], and (6) others, including *Stenotrophomonas maltophilia*, *Providencia* spp., *Citrobacter* spp., *Serratia* spp., *P. mirabilis*, *S. aureus*, *C. albicans*, and *C. difficile*. Therefore, this study revealed that the top three antibiotic-resistant

bacteria isolated in the ICUs in Saudi Arabia were *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*, which are all categorized as Gram-negative bacteria.

Among those above-identified pathogens in ICUs, the susceptibility patterns of antibiotics significantly decreased with *E. coli*, *A. baumannii*, *Enterobacter*, and *Serratia marcescens* [4]. Specifically, *A. baumannii* showed high resistance with ventilator-associated pneumonia patients in the ICU [16]. In terms of samples collected for antibiotic susceptibility, respiratory samples, blood samples, and urinary samples [4-5,11] were the three specimens most frequently indicative of multidrug-resistant bacteria typically found in general ICUs [11,18]. Factors that were identified to be associated with vancomycin-resistant enterococci included multi-organ failure admission, gastrointestinal oral contrast procedure, chronic renal failure, hemodialysis, and prior use of antimicrobial drugs in the past 3 months and before admission in the ICU [14]. Moreover, being admitted in the ICU, including mechanical ventilation and parenteral feeding, was revealed to be a marginally significant risk factor for susceptibility to antibiotic-resistant pathogens [8,17].

Most of these pathogens, particularly *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*, show resistance to methicillin [11], tazobactam, cilastatin, meropenem, tigecycline [15], imipenem, meropenem, piperacillin [6,15], colistin [9,13], penicillin [16,18], ampicillin, oxacillin [16], vancomycin [14-17], carbapenems [5], amoxicillin, ceftriaxone, amikacin, gentamicin, clindamycin, azithromycin, levofloxacin, nitrofurantoin, [18], trimethoprim, cefuroxime, ciprofloxacin [6,18,19], aztreonam and cefotaxime [6,20]. In particular, with low dose of colistin, the incremental costs per nephrotoxicity case can be avoided [9]. With the call for stringent implementation of proactive antimicrobial stewardship programs as a vital approach to prevent the emergence of antibiotic resistance [13,15], antibiotic use was lessened and unfitting, leading to reduced direct cost [9,15].

## Conclusions

*K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* were the three most frequently isolated Gram-negative bacteria in the ICUs in Saudi Arabia. Comprehensive surveillance programs, strict infection control and prevention guidelines, and stringent implementation of a proactive ASP are warranted to eliminate future infection outbreaks with these antibiotic-resistant pathogens.

## Conflict of Interest

No conflict of interest has been declared by the author.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Figure 1: PRISMA flow chart of the review

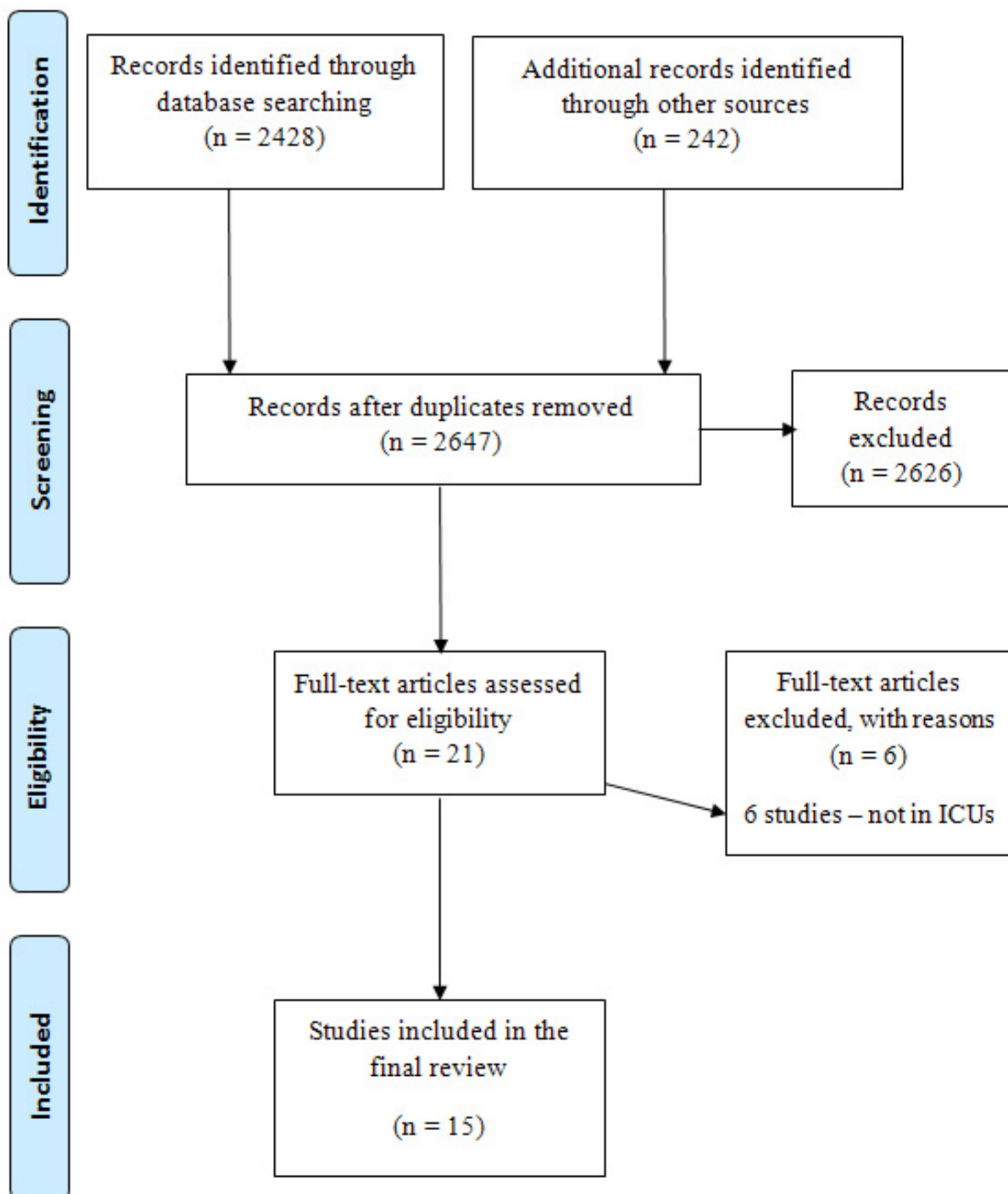


Table 1. Study Characteristics

Author/s & Year	Purpose	Design and Location	Findings
Al Johani et al. (2010)	To examine patterns of antimicrobial susceptibility in gram-negative isolates to commonly used drugs in an adult intensive care unit (ICU)	A retrospective study in adult ICU at King Fahad National Guard Hospital (KFNGH) in Riyadh, Central Kingdom of Saudi Arabia (KSA)	<ul style="list-style-type: none"> <li>- Acinetobacter baumannii was the most frequently isolated organism.</li> <li>- Others were Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Stenotrophomonas maltophilia, and Enterobacter.</li> <li>- Antibiotic susceptibility patterns significantly declined in many organisms, especially A baumannii, E coli, S marcescens, and Enterobacter.</li> <li>- Respiratory samples were the most frequently indicative of multidrug-resistant pathogens followed by urinary samples.</li> </ul>
Saeed et al. (2010)	To assess the prevalence of multi-drug resistant (MDR) bacteria causing infections in patients as well as their antimicrobial resistance patterns for one year	A retrospective, cohort investigation at the intensive care units (ICUs) of Riyadh Military Hospital (RMH), Central KSA	<ul style="list-style-type: none"> <li>- Acinetobacter baumannii (A. baumannii) comprised 40.9%, Klebsiella pneumonia (K. pneumonia) - 19.4%, while Pseudomonas aeruginosa (P. aeruginosa) formed 16.3% of these isolates.</li> <li>- A total of 1210 isolates were collected from various specimens such as: respiratory (469), blood (400), wound/ tissue (235), urinary (56), nasal swabs (35), and cerebro-spinal fluid (15).</li> <li>- Regardless of the specimen, there was a high rate of nosocomial MDR organisms isolated from patients enrolled in the General ICU (GICU) in Riyadh.</li> </ul>
Amer et al. (2013)	To compare the prescribing appropriateness rate of the empirical antibiotic therapy before and after the antimicrobial stewardship programs (ASP) implementation in a tertiary care hospital	A comparative, historically controlled study involving Clostridium difficile bacteria in the medical ICU at KCUH, Riyadh, Central KSA	<ul style="list-style-type: none"> <li>- A total of 73 subjects were recruited, 49 in historical control and 24 in the active arm where for the ASP group, initial uses of antibiotic were inappropriate and diminished by ASPs to 0% on the recommendations implementation with a reduction in antibiotics utilization and direct cost were also noticed in the ASP arm.</li> <li>- A proactive ASP is a vital approach in optimizing the appropriate empirical antibiotics utilization in an ICU setting in tertiary care hospitals.</li> </ul>
Garbati et al. (2013)	To highlight the growing prevalence of infections with colistin-resistant Enterobacteriaceae in response to the rising incidence of drug resistance	A retrospective observational study was conducted in the ICU of King Fahad Medical City, Riyadh, Central KSA	<ul style="list-style-type: none"> <li>- Nine episodes of infection with colistin-resistant Enterobacteriaceae were recorded in seven patients.</li> <li>- In five of the episodes, Klebsiella pneumoniae was responsible, Serratia marcescens was reported in two, while Enterobacter aerogenes and Providencia stuartii were responsible for one episode of infection each.</li> </ul>

Shorman & Al-Tawfiq (2013)	To determine the risk factors associated with vancomycin-resistant enterococci (VRE) infection or colonization in intensive care unit (ICU) settings	A descriptive, epidemiologic hospital-based case-control study at King Fahad Specialist Hospital in Dammam, Eastern KSA	<ul style="list-style-type: none"> <li>- Factors associated with VRE included ICU admission for multi-organ failure, chronic renal failure, prior use of antimicrobial agents in the past three months and before ICU admission, gastrointestinal oral contrast procedure, and hemodialysis which are often complex and may be confounded by local variables.</li> </ul>
Balkhy et al. (2014)	To examine the extent of multiple-drug resistance among common microbial causes of ventilator-associated pneumonia (VAP).	A retrospective susceptibility study in the adult ICU at King Abdulaziz Medical City, Riyadh, Central KSA	<ul style="list-style-type: none"> <li>- A total of 248 isolates including 9 different pathogens were included.</li> <li>- Acinetobacter species were highly resistant to all tested antimicrobials.</li> <li>- Acinetobacter in the current study was an increasingly resistant VAP-associated pathogen.</li> </ul>
Somily et al. (2014)	To determine possible risk factors for infection or colonization with extended spectrum- $\beta$ -lactamase-producing Klebsiella pneumoniae (ESBLKp) during an outbreak in the NICU	A retrospective cohort study in NICU in KFSHRC, Riyadh, Central KSA	<ul style="list-style-type: none"> <li>- Out of 118 neonates, 4 became infected, and 8 were colonized with ESBLKp.</li> <li>- Among 14 neonates who were treated with vancomycin, 9 developed infection or colonization with ESBLKp, whereas, among 104 neonates who were not treated with vancomycin, 3 were affected.</li> <li>- Parenteral feeding and mechanical ventilation were found to be marginally significant risk factors.</li> </ul>
Al Yousef (2016)	To study epidemiology and resistant pattern of bacteria causing infection in different hospital units including ICUs.	A surveillance method was carried out at King Khalid Hospital in Hafr Al-Batin, Eastern KSA	<ul style="list-style-type: none"> <li>- Escherichia coli, Klebsiella pneumonia, and Pseudomonas aeruginosa were the commonly identified Gram-negative bacteria where Staphylococcus aureus was the only identified Gram-positive bacterium.</li> <li>- The most common antibiotic-resistant bacteria were found on female surgical ward followed by ICU and male surgical ward.</li> </ul>

<p>Abujheisha et al. (2017)</p>	<p>To explore the multidrug-resistant bacteria, Extended Spectrum <math>\beta</math>- lactamase bacteria [ESBLs] and the possibility of carbapenems resistant bacteria isolated from clinical samples of patients</p>	<p>A retrospective study of 317 samples for cultivation and antibiogram according to Clinical and laboratory standard institute (CLSI) guidelines in ICUs at King Khalid Hospital, Al-Kharj, Central KSA</p>	<ul style="list-style-type: none"> <li>- Out of 317 total samples processed, significant growth was shown in 62 samples where respiratory samples showed the highest rate of positive growth followed by urine samples.</li> <li>- Fifty-seven isolates were gram-negative and five isolates were gram-positive.</li> <li>- K. pneumoniae was the most frequently isolated among Gram-negative with 16 isolates followed by P. aeruginosa.</li> <li>- All isolates of P. aeruginosa, Acinetobacter spp., Providencia spp., Enterobacter spp., Citrobacter spp., Serratia spp. were MDR while five isolates of Proteus mirabilis, and 11 of K. pneumoniae were MDR.</li> <li>- ESBLs were confirmed in 39 isolates out of 47 MDR gram-negatives; among them, 11 were K. pneumoniae and 10 isolates of P. aeruginosa.</li> <li>- Resistance to carbapenems was detected in 23 isolates of MDR gram-negative bacteria; among them, 10 isolates of P. aeruginosa, and 6 isolates each of Acinetobacter spp. and K. pneumoniae.</li> </ul>
<p>Alavudeen et al. (2017)</p>	<p>. To determine the prevalence of bacterial pathogens and to assess the multi-drug resistant (MDR) strains to different antibiotics in Aseer Region, Southwest KSA</p>	<p>A retrospective analysis of 163 subjects diagnosed with variable infections</p>	<ul style="list-style-type: none"> <li>- A total of 15 different strains of gram positive and negative were isolated where, a urine specimen was found to have the highest number of bacterial isolates and intensive care unit (ICU) had higher number of isolates.</li> <li>- Among 46 antibiotics tested, only 12 antibiotics were included in the analysis.</li> <li>- Almost, the majority of the gram positive and gram negative bacterial isolates had resistance to more than three antimicrobials, which satisfies the criteria to call them multidrug resistant bacterial isolates.</li> </ul>
<p>Cara et al. (2018)</p>	<p>To evaluate the cost effectiveness of low versus high dose colistin in the treatment of Pneumonia caused by colistin-only sensitive gram negative bacteria</p>	<p>A retrospective review was conducted in ICU and non-ICU at King Abdulaziz Hospital in AlHasa, Eastern KSA</p>	<ul style="list-style-type: none"> <li>- The main outcomes were cure, nephrotoxicity, total direct costs per episode, cost per additional cure and cost per nephrotoxicity avoided.</li> <li>- No significant difference between high and low dose colistin with regards to clinical cure.</li> <li>- Significantly more patients experienced nephrotoxicity with high versus low dose colistin.</li> <li>- With low dose colistin, the incremental costs per nephrotoxicity were avoided.</li> </ul>
<p>Ibrahim (2018)</p>	<p>To determine the distribution and resistance profiles of Gram-negative bacteria (GNB) in intensive care units (ICUs)</p>	<p>A record based retrospective study at King Abdullah Hospital in Bisha, Southwest KSA</p>	<ul style="list-style-type: none"> <li>- Of 3,736 specimens, 358 were positive for pathogens and GNB constituted the majority.</li> <li>- Increased antimicrobial resistance with high proportions of multidrug resistant patterns was found among GNB from ICUs.</li> </ul>

Azim et al. (2019)	To investigate the widespread multidrug resistance (MDR) gram-negative bacterial pathogens isolated from ICUs	A retrospective study at King Khalid University Hospital (KKUH), Riyadh, Central KSA	<ul style="list-style-type: none"> <li>- A total of 70 MDR isolates from different body sites comprised <i>P. aeruginosa</i>, <i>K. pneumoniae</i>, <i>E. coli</i>, and <i>A. baumannii</i>.</li> <li>- The essential resistance mechanisms in the evaluated strains were extended spectrum-<math>\beta</math>-lactamase (ESBL) and Metallo-<math>\beta</math>-lactamase (MBL).</li> <li>- Molecular testing is recommended to confirm the phenotypic results and to detect the resistant genes.</li> </ul>
Kabrah et al. (2021)	To identify the antibiotic resistance patterns of prevalent bacterial strains obtained from lower respiratory tract infections (LRTIs), bloodstream infections (BSIs), and urinary tract infections (UTIs) within ICUs	A retrospective study at King Faisal Hospital (KFH), Makkah, KSA	<ul style="list-style-type: none"> <li>- <i>Klebsiella pneumoniae</i> (<i>K. pneumoniae</i>, 59.4%), Coagulase-negative staphylococci (CoNS, 11.5%), <i>Escherichia coli</i> (<i>E. coli</i>, 8.4%), <i>Acinetobacter baumannii</i> (<i>A. baumannii</i>, 7.3%), and <i>Staphylococcus aureus</i> (<i>S. aureus</i>, 6.2%). BSI were frequently caused by CoNS (35.7%) and <i>K. pneumoniae</i> (35.7%), while Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA, 10.7%)</li> <li>- Vancomycin, Synercid, and Teicoplanin are frequently utilized antibiotics that demonstrated complete (100%) sensitivity in <i>Staphylococcus aureus</i>, including methicillin-resistant <i>Staphylococcus aureus</i> (MRSA). While 100% resistance was noted for penicillin and oxacillin in relation to these bacterial strains.</li> <li>- The highest levels of resistance were recorded for aztreonam at 96.4%, followed by ampicillin at 87.3%. Co-amoxiclav exhibited a resistance rate of 83.9%, while cotrimoxazole showed 79.5% resistance, along with the antibiotics belonging to the cephalosporin group.</li> </ul>
Obaid et al. (2023)	To examine the antimicrobial-resistant pathogens responsible for catheter-associated urinary tract infections (CAUTIs) within ICUs.	A multi-center retrospective study in the Western region, KSA	<ul style="list-style-type: none"> <li>- A total of twenty distinct pathogenic microorganisms have been identified as causative agents of CAUTIs. Among these, <i>Candida albicans</i> accounts for 18.4% of cases, followed by <i>Escherichia coli</i> at 13.5%, other yeasts excluding <i>Candida</i> at 10.4%, and <i>Klebsiella pneumoniae</i> at 8.5%.</li> <li>- A total of 19.67% of the pathogens identified as causative agents in CAUTIs were found to be resistant to antibiotics.</li> <li>- The isolates exhibiting the highest resistance from CAUTIs in ICUs included carbapenem-resistant Enterobacteriaceae, specifically <i>Klebsiella pneumoniae</i> (<math>n = 17</math>), as well as extended-spectrum <math>\beta</math>-lactamase-producing strains of <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i>, with counts of 11 and 19, respectively.</li> <li>- The most observed resistance was to ciprofloxacin at 16.5% and to trimethoprim or sulfamethoxazole at 16.1%.</li> </ul>



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