

## Evaluation of the Antibiotic Resistance Pattern at the Medical Services Administration Hospital in Khartoum, Sudan, 2021

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### ABSTRACT

The number of antibiotics available is limited and does not cover the growing antibiotic resistance challenge. Misuse and overuse of antibiotics act as factors that help in improving and increasing the problem of resistance to those currently being prescribed by doctors. The study was carried out at the Medical Services Administration Hospital (MSAH) in Khartoum, Sudan to investigate the antibiotic resistance pattern for the period between Dec. 2020 and Jan. 2022. The results showed that, in a total of different clinical samples that were collected and processed, a total number of 980 organisms were isolated. The result indicated that 345 out of the total isolates (35.20%) were *Klebsiella pneumonia*, 326 (33.27%) *Escherichia coli*, 154 (15.71%) *Pseudomonas aeruginosa*, 130 (13.27%) *Proteus mirabilis*, and 25 (2.55%) *Staphylococcus aureus*. The results showed that *K. pneumonia* was quite resistant to piperacillin, cefuroxime, and azithromycin. The amikacin, imipenem, and meropenem antibiotics showed significant activity against *K. pneumonia*. The isolates of *E. coli* showed significant resistance to azithromycin and were more sensitive to imipenem and meropenem. *P. aeruginosa* was resistant to penicillin, amoxicillin/clavulanic acid, and azithromycin in a big way, but it was very sensitive to cefuroxime, the drug used to treat strep throat infections. *P. mirabilis* was found to be resistant to nalidixic acid, nitrofurantoin, amoxicillin/clavulanic acid, and azithromycin. It showed good sensitivity to amikacin, imipenem, and meropenem. It was clear that *S. aureus* was resistant to cefuroxime, ceftriaxone, nitrofurantoin, and norfloxacin, while tests showed that it was sensitive to imipenem.

**Keywords-** Antibiotics, resistance, MSA hospital, Sudan.

### I. INTRODUCTION

Antibiotics are a crucial line of defense against bacterial infections by suppressing the growth of or killing other microorganisms at very low concentrations. Most bacteria are becoming resistant to various antibiotics, which creates a limitation for treating minor and major infectious diseases (Dugassa and Shukuri 2017).

Antibiotic resistance is occurring due to various causes like widespread use of antibacterial drugs, incorrect use of antibiotics, patient-related factors, prescriber's prescription habits, veterinary prescriptions, commercial promotion, over the counter sale of antibiotics, underuse of microbiological testing, globalization, and incorrect use of antibiotics such as too short a time/improper use like too low dose, at inadequate potency, or wrong diagnosis (Pinder et al. 2015).

The antibiotic resistance consequences lead to prolonged illness and a greater risk of death; longer periods of hospitalization and infections, which increase the number of infections spread in the community (Friedman, Temkin, and Carmeli 2016). Nosocomial infections are becoming more and more common because doctors are doing more invasive procedures on patients and using more antimicrobials to save their lives (Friedrich 2019).

The impact of resistance on public health and the economy leads to a large pool of resistant genes and an increased burden on society regarding morbidity, mortality, and cost (Friedman, Temkin, and Carmeli 2016). The current situation demonstrates that a significant number of second- and third-line medicines are proving to be ineffective in clinical settings due to alterations in bacterial or host genes (Pulingam et al. 2021). The Centers for Disease Control and Prevention

(CDC) estimates that as much as 50% of all antibiotics prescribed for people are either no longer wanted or are inappropriate (Ashraf and Cook 2016). If current trends continue and resistance continues to rise, some studies estimate that by 2050 there will be ten million antimicrobial resistance-related deaths worldwide, costing the world economy up to \$100 trillion (Majumder et al. 2020).

Resistance is most common in health-care settings such as hospitals and nursing homes, where infections can spread quickly among patients who use clinical devices such as ventilators and catheters, which are more susceptible to infection (Kollef et al. 2021). Hospitals often use antibiograms to help with manual antimicrobial treatment and to track the trend of antimicrobial resistance (Joshi 2010).

Hence, this study was carried out to know the pattern of microbes' resistance to antibiotics at the Medical Services Administration Hospital (MSA hospital). The MSA hospital is one of the largest hospital compounds in Sudan and contains several separate hospitals, namely; medicine, orthopedics, surgery, pediatrics, obstetrics and gynecology, ophthalmology, ENT, CCU, ICU, and wards with a central lab and radiology unit serving the different hospital departments. The current work aims to study the frequency and distribution of nosocomial pathogens and their resistance patterns to antibiotics at MSA hospital.

The instructional and academic value of this research is in particular beneficial for microbiologists and infection disorder clinicians. The information collected from the current research is beneficial in improving antimicrobial use in the hospital and could be applied to other hospitals in Khartoum state.

In our setting, the status quo of surveillance programs to monitor the proper volume of resistance on the local, regional, and country-wide tiers is urgently needed. This will make it easier to spot a rising trend in resistance in the near future, which will help doctors make decisions, deal with infections, and figuring out ways to stop antimicrobial resistance.

Data analysis of culture and sensitivity tests aids doctors in the implementation of antibiotic management therapy by choosing the most efficient antimicrobial agent. Choosing the best antimicrobial therapy for an infected person, defining the antimicrobial agent's ability to kill bacteria, and keeping track of developments in bacterial resistance to these agents are also included. Culture and sensitivity analysis is a useful tool for figuring out how resistant bacteria are to certain drugs in a short amount of time.

## II. METHODOLOGY

### 2.1. Study Area.

The Medical Services Administration Hospital (MSA hospital) in Khartoum, Sudan, served as the site of this retrospective investigation. The MSA hospital is one

of the biggest governmental hospitals in Khartoum and serves as a referral center for both public and private hospitals in Khartoum and also for the neighboring states. The hospital serves more than four million people by providing clinical services. The MSA hospital also functions as a teaching facility for medical students.

### 2.2. Study design

This study was a hospital-based retrospective analysis of antimicrobial drug susceptibility data obtained from the microbiology lab for the time period between December 2020 to January 2022. Records and data were gathered from the MSA hospital's central laboratory's microbiology department.

### 2.3. Data collection

The culture and sensitivity data were collected from the microbiology department records in the central laboratory of the MSA hospital for the period between December 2020 and January 2022 after official permission from the hospital administration. The targeted data includes the species of the isolated pathogens and the results of antibiotic culture and sensitivity tests.

The samples of urine, pus, blood, ear discharge, eye swab, genital swab, stool, cerebrospinal fluid (CSF), sputum, and nasal swab samples suspected of any bacterial infection are usually sent from different wards in MSA hospital to the microbiology department at the central lab to perform culture and sensitivity tests. Based on standard operating procedures and the most recent clinical and laboratory Standard Institute guidelines, the lab uses standard techniques and biochemical analytical methods for culturing and identifying microorganisms.

The antibiotic culture and sensitivity tests are carried out using the Kirby-Bauer disc diffusion method according to the Clinical Laboratory Standards Institute (CLSI) guidelines. Descriptive statistics were used for analysis, and the results were expressed as frequency and percentage. Microsoft Excel 2016 software was used to analyze the data.

### 2.4. Ethical consideration

Ethical approval was not obtained as this study is a retrospective study involving the collection of secondary data on the antimicrobial susceptibility of bacterial isolates, which does not require ethical approval in Sudan. No patient information was accessed during this research. For the use of the data, official permission was obtained from the MSA hospital administration to collect the antimicrobial susceptibility data from the microbiology lab registration book. All data obtained during the study was kept confidential and used only for this study.

## III. RESULT AND DISCUSSION

### 3.1. The percentages of isolated and identified microbes in the samples processed at the microbiology department in the central lab.

Based on the antimicrobial culture and sensitivity data from the records of the microbiology

department at the central laboratory of MSA hospital from December 2020 to January 2022, the current research showed that *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Staphylococcus aureus* were the most common pathogens found in the processed samples.

In a total of different clinical samples that were processed during the study period, 980 organisms were isolated. The results showed that out of the 980 isolated bacteria, 345 (35.20%) were *K. pneumoniae*, 326 (33.27%) were *E. coli*, 154 (15.71%) were *P. aeruginosa*, 130 (13.27%) were *P. mirabilis*, and 25 (2.55%) were *S. aureus* (Figure 1).

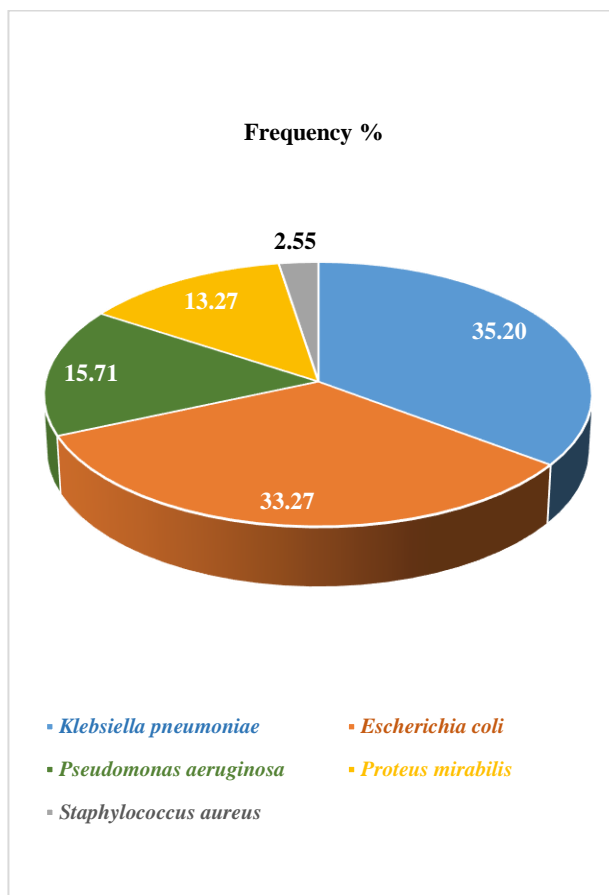


Figure 1: The percentages of isolated and identified microbes in the samples processed at the central lab of MSA hospital.

### 3.2. The antimicrobial resistance pattern of *Klebsiella pneumoniae* at the MSA hospital

The results showed that *K. pneumoniae* was highly resistant to azithromycin (100% of the total cases were resistant), amoxicillin/clavulanic (98.7% of the total cases), piperacillin (98.8%), cefuroxime (98.2%), amoxicillin/clavulanic (96.2%), colistin (93.6%), ceftazidime (91.3%), cefixime (90.1%), and cefepime (86.9%), as shown in figure (2). On the other hand, *K. pneumoniae* was found to be more sensitive to imipenem (78.8% of the total cases were sensitive), meropenem (78.2%), and amikacin (77.6%) as shown in figure (2).

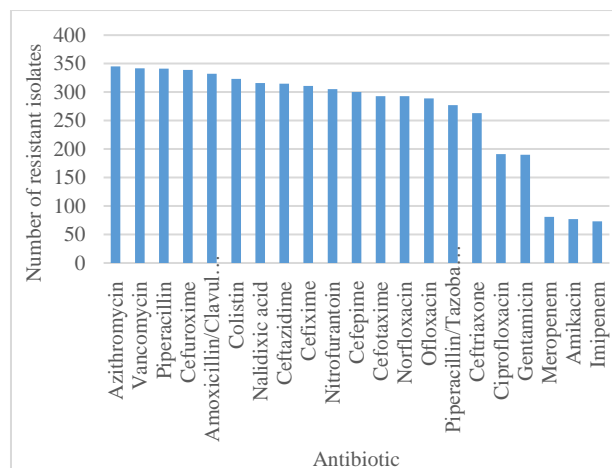


Figure 2: The antimicrobial resistance pattern of *Klebsiella pneumoniae* at the MSA hospital

*Klebsiella pneumoniae* is one of the multi-drug resistant (MDR) organisms and it has been identified as an urgent threat to human health by the World Health Organization, the US Centers for Disease Control and Prevention and the UK Department of Health (Navon-Venezia, Kondratyeva, and Carattoli 2017).

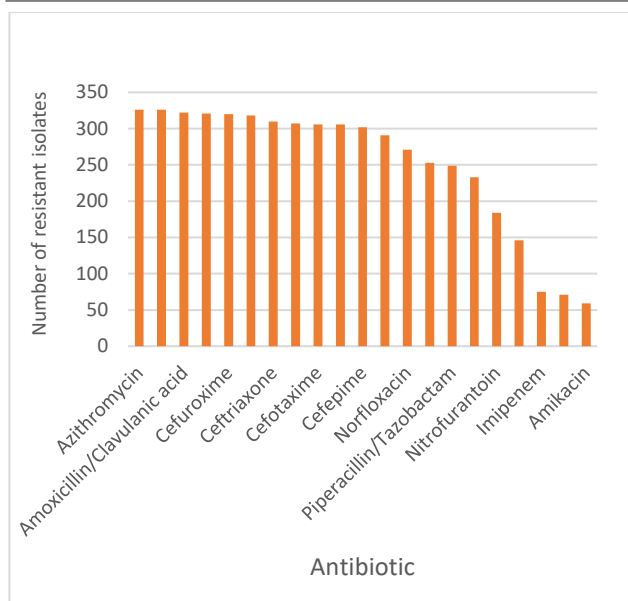
In hospitals, *K. pneumoniae* infections are most common in newborns, the elderly, and people with weak immune systems. This organism is also the cause of a lot of infections that people get from other people, like pneumonia and sepsis (Khan, Ahmad, and Mehboob 2015).

Antibiotic resistance in *K. pneumoniae* is associated with high rates of morbidity and mortality in clinical patients. Acquisition of antibiotic resistance genes and intrinsic resistance to several classes of antibiotics limits treatment options for infections caused by *K. pneumoniae* (Bassetti et al. 2018). Currently, *K. pneumoniae* strains producing Extended Spectrum Beta-Lactamases (ESBLs) and carbapenemases have spread globally (Younas et al. 2018).

The  $\beta$ -lactamases in antibiotic-resistant *K. pneumoniae* are varied, and penicillin-binding proteins (PBPs) expression is variable in the  $\beta$ -lactam system. In addition, PBPs and  $\beta$ -lactamases are two important resistance mechanisms in *K. pneumoniae* caused by the frequent use of antibiotics in patients with pneumonia (Wang et al. 2020).

### 3.3. The antimicrobial resistance pattern of *Escherichia coli* at the MSA hospital

The results as shown in figure (2) indicated that *E. coli* was highly resistant to azithromycin (100% of the total cases were resistant), amoxicillin/clavulanic (98.7% of the total cases), piperacillin (98.8%), cefuroxime (98.1%), colistin (97.4%), ceftazidime (94.1%), cefixime (93.8%), cefotaxime (93.8%), and cefepime (92.6%). Regarding the pattern of sensitivity, it was found that *E. coli* was more sensitive to amikacin (81.9% of all cases were sensitive), meropenem (78.2%), and imipenem (73.9%), as shown in figure (3).



**Figure 3: The number of resistant cases of *E. coli* to the assessed antibiotics.**

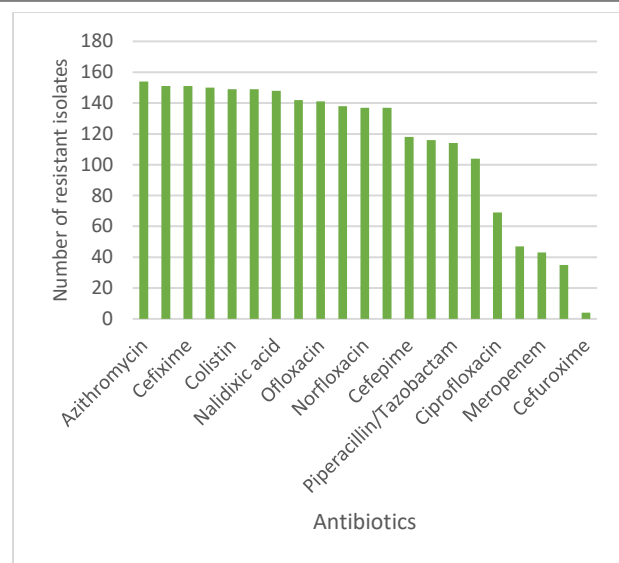
The acquired, or extrinsic, and continuously increasing resistance of *E. coli* to antibiotics is already considered a major public health problem around the world (Galindo-Méndez 2020). In 2018, more than half of the *E. coli* isolates sent to the European Centre for Disease Prevention and Control were resistant to at least one group of antimicrobials that were being watched. Often, they were resistant to more than one group (Peñalva et al. 2019).

The ability of *E. coli* to colonize different environments, including the guts of humans and animals, has provided this organism with the evolutionary advantage of acquiring antibiotic resistance traits from other bacteria within its environment, as well as being easily transmitted via the fecal-oral route (Lee, Lee, and Choe 2018). People can have more than a thousand different antibiotic-resistant genes in their gut microbiota, and these traits are always being passed on from one gut commensal to another (Galindo-Méndez 2020).

The blaCTX-M gene, which codes for class-A extended-spectrum  $\beta$ -lactamases (ESBLs), and the OXA-48-type carbapenem-hydrolyzing class D  $\beta$ -lactamases, which are found in many *Enterobacteriaceae* such as *E. coli*, are good examples of how resistance genes can be passed from bacteria in the environment, such as gut commensals, to human pathogens (Mairi et al. 2018; Son et al. 2021).

### 3.4. The antimicrobial resistance pattern of *Pseudomonas aeruginosa* at the MSA hospital

The results indicated that *Pseudomonas* was found to be highly resistant to Azithromycin (100% of the total cases were resistant), amoxicillin/clavulanic (97% of the total cases), and Cefixime (98% of total cases). Regarding sensitivity pattern, cefuroxime showed good activity against *P. aeruginosa* (96.7% of cases were sensitive), as shown in figure (4).



**Figure 4: The number of resistant cases of *E. coli* to the assessed antibiotics.**

The mechanisms of intrinsic antibiotic resistance possessed by *P. aeruginosa* include restricted outer-membrane permeability, efflux systems that pump antibiotics out of the cells, and the production of antibiotic-inactivating enzymes (Pang et al. 2019).

*P. aeruginosa* possesses a number of specific porins, including the carbohydrate-specific porin OprB, the basic amino acid-specific porin OprD, the phosphate-specific porin OprP, and the pyrophosphate-specific porin OprO. Among these porins, OprD is involved in antibiotic uptake. It contains the binding sites for carbapenems and absence of OprD in *P. aeruginosa* increases the resistance to this class of antibiotic.

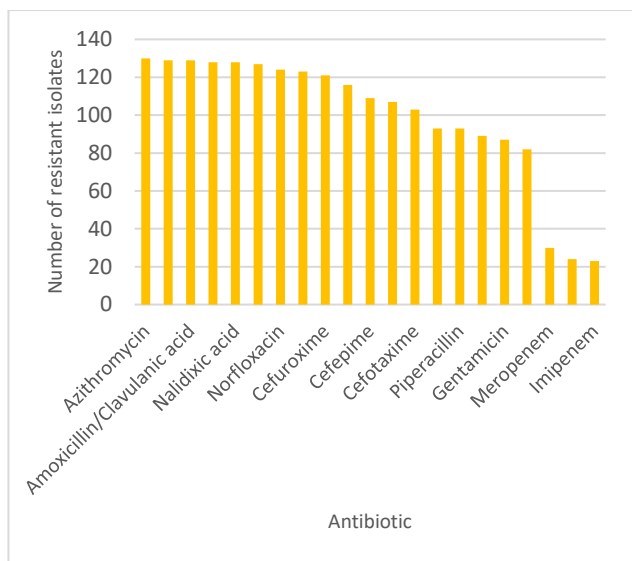
Additionally, OprH is the smallest *P. aeruginosa* porin, and overexpression of OprH as a consequence of Mg<sup>2+</sup> starvation has been found to be associated with increased resistance to polymyxin B and gentamicin through stabilization of the outer membrane by inducing LPS modification (Ben Jeddou 2021; Pang et al. 2019).

Overexpression of multiple efflux pumps has been found in some clinical strains of *P. aeruginosa*, broadening bacterial antibiotic resistance and contributing to the development of multidrug resistance. Therefore, the use of efflux pump inhibitors has emerged as a potential therapeutic strategy for the treatment of *P. aeruginosa* infections (Rahbar et al. 2021).

### 3.5. The antimicrobial resistance pattern of *P. mirabilis* at the MSA hospital

The results showed that *P. mirabilis* was highly resistant to azithromycin (100% of the total cases were resistant), amoxicillin/clavulanic (99.2%), nalidixic acid (98.4%), ofloxacin (98.4%), nitrofurantoin (97.6%), norfloxacin (95.3%), colistin (94.6%), and cefuroxime (93% of total cases were resistant). On the other hand, *P. mirabilis* showed good sensitivity to imipenem (82.3% of the total cases were sensitive) and amikacin (81.5% of the total cases were sensitive) as shown in figure (5).





**Figure 5: The number of resistant cases of *P. mirabilis* to the assessed antibiotics.**

*P. mirabilis* is a commensal member of the *Enterobacteriaceae* in the human digestive tract. At the same time, *P. mirabilis* is commonly involved in urinary tract infections (UTI) (Behzadi et al. 2020). *P. mirabilis* is naturally resistant to several antibiotics, including colistin, and shows reduced susceptibility to imipenem. However, higher levels of resistance to imipenem commonly occur in *P. mirabilis* isolates consecutively to the loss of porins, reduced expression of penicillin binding proteins (PBPs), PBP1a, PBP2, or acquisition of several antibiotic resistance genes, including carbapenemase genes (Hammoudi Halat and Ayoub Moubareck 2020; Girlich et al. 2020).

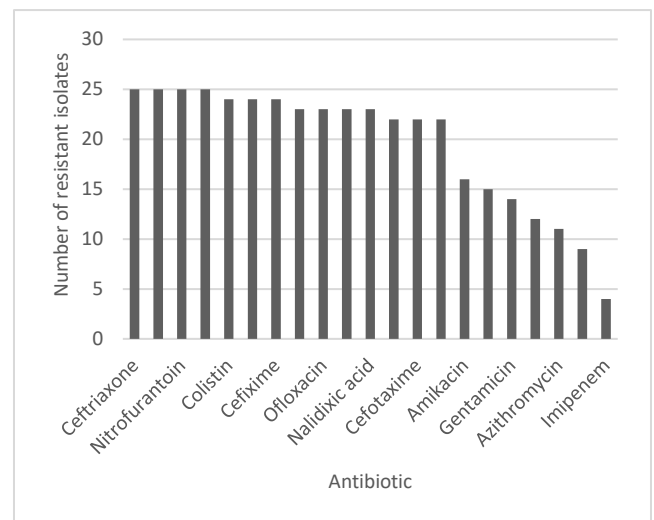
A lot of bacteria are also resistant to drugs that aren't lactamases, like fluoroquinolones and nitrofurans, which are used to treat UTIs. The emergence and spread of multidrug-resistant *P. mirabilis* isolates, such as those producing ESBLs, AmpC cephalosporinases, and carbapenemases, is also becoming more common (Girlich et al. 2020).

Concerning antibiotic resistance determinants, *P. mirabilis* has integrative and conjugative elements (ICEPm) and other ICEs in the SXT/R391 family that can self-replicate and self-transfer to other strains and species, transferring virulence genes and antibiotic resistance as well (Girlich et al. 2020).

### 3.6. The antimicrobial resistance pattern of *Staphylococcus aureus* at the MSA hospital

The results revealed that *S. aureus* was highly resistant to cefuroxime, nitrofurantoin, ceftriaxone and norfloxacin (100% of the tested samples were resistant), cefixime, amoxicillin/clavulanic and colistin (96% of the tested samples were resistant), cefepime, ceftazidime and nalidixic acid (92% of the tested samples were resistant), piperacillin/tazobactam, cefotaxime, and piperacillin (88% of the tested samples were resistant). The study findings indicated that *S. aureus* was most sensitive to

Imipenem (84% of the total cases were sensitive, as shown in figure (6)).



**Figure 6: The number of resistant cases of *S. aureus* to the assessed antibiotics.**

*Staphylococcus aureus* shows the adaptive evolution of bacteria in the antibiotic era better than any other human pathogen. It has a unique ability to quickly adapt to each new antibiotic, from penicillin and methicillin to the most recent ones, linezolid and daptomycin (Guo et al. 2022; Silva et al. 2022).

The mechanisms of *S. aureus* resistance include enzymatic inactivation of the antibiotic (penicillinase and aminoglycoside-modification enzymes); alteration of the target with decreased affinity for the antibiotic (notable examples being penicillin-binding protein 2a of methicillin-resistant *S. aureus* and D-Ala-D-Lac of peptidoglycan precursors of vancomycin-resistant strains), trapping of the antibiotic (for vancomycin and possibly daptomycin) and efflux pumps (fluoroquinolones and tetracycline) (Peterson and Kaur 2018).

Complex genetic arrays (staphylococcal chromosomal cassette mec elements or the vanA operon) have been acquired by *S. aureus* through horizontal gene transfer, while resistance to other antibiotics, including some of the most recent ones (e.g., fluoroquinolones, linezolid, and daptomycin), has developed through spontaneous mutations and positive selection. Detection of the resistance mechanisms and their genetic basis is an important support for antibiotic susceptibility surveillance in *S. aureus* (Partridge et al. 2018; Gheorghe, Popa, and Măruțescu 2018).

## IV. CONCLUSION

Misuse and overuse of antibiotics worldwide has transformed antibiotic-resistant bacteria into a global health crisis. The present retrospective study, which has been carried out at the microbiology department in the

central laboratory of MSA hospital, indicated that all the isolated bacteria had developed significant rates of resistance to most of the antibiotics that are frequently used in the hospital. Our research offers significant information on the bacterial spectrum, with the main isolated pathogens being *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *S. aureus*. Besides the most resistant bacteria, the current study highlighted the antibiotics that showed decreased antimicrobial activities against the isolates, which constitute a major challenge for antibiotics' empirical use. As a result, the current study assists doctors at MSA hospital with empirical treatment by prescribing appropriate antibiotics based on drug susceptibility reports. Moreover, this study helps the hospital at the managerial level to evaluate and continually track the use of antibiotics and to regularly apply hospital antibiograms analysis to ensure sustained efficacy of the routinely used antibiotics as well as to assist manual empiric antimicrobial remedies and track trends in antimicrobial resistance.

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## AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation; or taking part in drafting, revising, or critically reviewing the article. All authors gave final approval of the version to be published agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest for this work

## REFERENCES

- [1] Ashraf, Muhammad Salman, and Paul P Cook. 2016. 'Antibiotic misuse in hospital, outpatient, and long-term care settings', *North Carolina medical journal*, 77: 346-49.
- [2] Bassetti, Matteo, Elda Righi, Alessia Carnelutti, Elena Graziano, and Alessandro Russo. 2018. 'Multidrug-resistant *Klebsiella pneumoniae*: challenges for treatment, prevention and infection control', *Expert review of anti-infective therapy*, 16: 749-61.
- [3] Behzadi, Payam, Edit Urbán, Mária Matuz, Ria Benkő, and Márió Gajdács. 2020. 'The role of gram-negative bacteria in urinary tract infections: current concepts and therapeutic options', *Advances in Microbiology, Infectious Diseases and Public Health*: 35-69.
- [4] Ben Jeddou, Fatma. 2021. 'Responses of *Pseudomonas aeruginosa* and other escape pathogens to antimicrobial peptide dendrimers', University of Geneva.
- [5] Dugassa, Jiregna, and Nesrie Shukuri. 2017. 'Review on antibiotic resistance and its mechanism of development', *Journal of Health, Medicine and Nursing*, 1: 1-17.
- [6] Friedman, N Deborah, Elizabeth Temkin, and Yehuda Carmeli. 2016. 'The negative impact of antibiotic resistance', *Clinical Microbiology and Infection*, 22: 416-22.
- [7] Friedrich, Alex W. 2019. 'Control of hospital acquired infections and antimicrobial resistance in Europe: the way to go', *Wiener Medizinische Wochenschrift*, 169: 25-30.
- [8] Galindo-Méndez, Mario. 2020. 'Antimicrobial resistance in *Escherichia coli*', *E. Coli Infections-Importance of Early Diagnosis and Efficient Treatment*: 1-20.
- [9] Gheorghe, Irina, Marcela Popa, and Luminița Gabriela Măruțescu. 2018. 'Molecular features of virulence and resistance mechanisms in nosocomial and community-acquired *Staphylococcus aureus*.' in, *Staphylococcus Aureus* (IntechOpen London, UK).
- [10] Girlich, Delphine, Rémy A Bonnin, Laurent Dortet, and Thierry Naas. 2020. 'Genetics of acquired antibiotic resistance genes in *Proteus* spp', *Frontiers in microbiology*, 11: 256.
- [11] Guo, Henan, Yucui Tong, Junhao Cheng, Zaheer Abbas, Zhongxuan Li, Junyong Wang, Yichen Zhou, Dayong Si, and Rijun Zhang. 2022. 'Biofilm and Small Colony Variants—An Update on *Staphylococcus aureus* Strategies toward Drug Resistance', *International Journal of Molecular Sciences*, 23: 1241.
- [12] Hammoudi Halat, Dalal, and Carole Ayoub Moubareck. 2020. 'The current burden of carbapenemases: Review of significant properties and dissemination among gram-negative bacteria', *Antibiotics*, 9: 186.
- [13] Joshi, S. 2010. 'Hospital antibiogram: a necessity', *Indian journal of medical microbiology*, 28: 277-80.
- [14] Khan, Hassan Ahmed, Aftab Ahmad, and Riffat Mehboob. 2015. 'Nosocomial infections and their control strategies', *Asian pacific journal of tropical biomedicine*, 5: 509-14.
- [15] Kollef, Marin H, Antoni Torres, Andrew F Shorr, Ignacio Martin-Loeches, and Scott T Micek. 2021. 'Nosocomial infection', *Critical care medicine*, 49: 169-87.
- [16] Lee, Dong Sup, Seung-Ju Lee, and Hyun-Sop Choe. 2018. 'Community-acquired urinary tract infection by *Escherichia coli* in the era of antibiotic resistance', *BioMed research international*, 2018.
- [17] Mairi, Assia, Alix Pantel, Albert Sotto, Jean-Philippe Lavigne, and Aziz Touati. 2018. 'OXA-48-like

carbapenemases producing Enterobacteriaceae in different niches', *European Journal of Clinical Microbiology & Infectious Diseases*, 37: 587-604.

[18] Majumder, Md Anwarul Azim, Sayeeda Rahman, Damian Cohall, Ambadasu Bharatha, Keerti Singh, Mainul Haque, and Marquita Gittens-St Hilaire. 2020. 'Antimicrobial stewardship: Fighting antimicrobial resistance and protecting global public health', *Infection and drug resistance*, 13: 4713.

[19] Navon-Venezia, Shiri, Kira Kondratyeva, and Alessandra Carattoli. 2017. 'Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance', *FEMS microbiology reviews*, 41: 252-75.

[20] Pang, Zheng, Renee Raudonis, Bernard R Glick, Tong-Jun Lin, and Zhenyu Cheng. 2019. 'Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies', *Biotechnology advances*, 37: 177-92.

[21] Partridge, Sally R, Stephen M Kwong, Neville Firth, and Slade O Jensen. 2018. 'Mobile genetic elements associated with antimicrobial resistance', *Clinical microbiology reviews*, 31: e00088-17.

[22] Peñalva, Germán, Liselotte Diaz Högberg, Klaus Weist, Vera Vlahović-Palčevski, Ole Heuer, Dominique L Monnet, ESAC-Net Study Group, and EARS-Net Study Group. 2019. 'Decreasing and stabilising trends of antimicrobial consumption and resistance in Escherichia coli and Klebsiella pneumoniae in segmented regression analysis, European Union/European Economic Area, 2001 to 2018', *Eurosurveillance*, 24: 1900656.

[23] Peterson, Elizabeth, and Parjit Kaur. 2018. 'Antibiotic resistance mechanisms in bacteria: relationships between resistance determinants of antibiotic producers, environmental bacteria, and clinical pathogens', *Frontiers in microbiology*, 9: 2928.

[24] Pinder, RJ, D Berry, A Sallis, and T Chadborn. 2015. 'Antibiotic prescribing and behaviour change in healthcare settings: literature review and behavioural analysis'.

[25] Pulingam, Thiruchelvi, Thaigarajan Parumasivam, Amirah Mohd Gazzali, Azlinah Mohd Sulaiman, Jiun Yee Chee, Manoj Lakshmanan, Chai Fung Chin, and Kumar Sudesh. 2021. 'Antimicrobial resistance: prevalence, economic burden, mechanisms of resistance and strategies to overcome', *European Journal of Pharmaceutical Sciences*: 106103.

[26] Rahbar, Mohammad, Ramin Hamidi-Farahani, Ali Asgari, Aylin Esmailkhani, and Saeed Soleiman-Meigooni. 2021. 'Expression of RND efflux pumps mediated antibiotic resistance in Pseudomonas aeruginosa clinical strains', *Microbial Pathogenesis*, 153: 104789.

[27] Silva, Vanessa, José L Capelo, Gilberto Igrejas, and Patrícia Poeta. 2022. 'Molecular Mechanisms of Antimicrobial Resistance in Staphylococcus aureus Biofilms', *Emerging Modalities in Mitigation of Antimicrobial Resistance*: 291-314.

[28] Son, Trinh Van, Nguyen Dang Manh, Ngo Tat Trung, Dao Thanh Quyen, Christian G Meyer, Nguyen Thi Kim Phuong, Phan Quoc Hoan, Vu Viet Sang, Dennis Nurjadi, and Thirumalaisamy P Velavan. 2021. 'Molecular detection of blaCTX-M gene to predict phenotypic cephalosporin resistance and clinical outcome of Escherichia coli bloodstream infections in Vietnam', *Annals of clinical microbiology and antimicrobials*, 20: 1-9.

[29] Wang, Guoying, Guo Zhao, Xiaoyu Chao, Longxiang Xie, and Hongju Wang. 2020. 'The characteristic of virulence, biofilm and antibiotic resistance of Klebsiella pneumoniae', *International Journal of Environmental Research and Public Health*, 17: 6278.

[30] Younas, Sonia, Hasan Ejaz, Aizza Zafar, Asiya Ejaz, Rabia Saleem, and Humera Javed. 2018. 'AmpC beta-lactamases in Klebsiella pneumoniae: An emerging threat to the paediatric patients', *JPMA*, 68.