International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 6|Issue 05 (September-October)|2023 Page: 808-817

Original Research Paper

Spectrum of Antimicrobial Resistance in ICU Settings: An Observational Study

Authors:
Sameer Ul Haq, Erika Aguirre[JFA]
Muhammad Badar Khalid, Moulana Aamira Fathima[JSA]
Iqra Munir
Madelyn Yajayda Najera
Christine Dawn Moral Daguipa
Shakaib Naeem Haider Mirza
Syed Kazim Raza
Sajan Shrestha
Adina Asghar
Maaz Nazir Armani
Faris Fayyaz
Winta Ghebremicael
Chandhini Vijaykurup
Amber Fazal Elahi
Misha Anam

Affiliations:
Rawalpindi Medical College, Cancer Foundation Hospital, Karachi, Pakistan | Universidad Autonoma de Guadalajara School of Medicine | Health Services Executive, Ireland | Rajah Muthiah Medical College And Hospital, Annamalai University | Arthritis Care Foundation, Lahore | Universidad Rafael Landivar | Far Eastern University-Dr. Nicanor Reyes Medical Foundation Philippines | La Palma Intercommunity Hospital, La Palma, California | Dow International Medical College | Jinnah Sindh Medical University | Allama Iqbal Medical College | Lilavati Hospital and Research Centre, Mumbai | Dow International Medical College | St. George's University | Medical University of Pleven, Bulgaria | Muhammad Hospital Faislabad | Childrens Hospital Lahore

Corresponding Author: Misha Anam, Childrens Hospital Lahore

Article Received: 30-July-2023, Revised: 11-August-2023, Accepted: 01-September-2023

ABSTRACT:

Background: The increasing prevalence of antimicrobial-resistant organisms poses a significant challenge in the intensive care unit (ICU) setting, often leading to treatment failures and increased morbidity and mortality. Understanding the spectrum of resistance can aid in empirical treatment choices and containment strategies. **Objective**: This study aimed to characterize the spectrum of antimicrobial resistance among bacterial isolates obtained from patients in the ICU over a one-year period. **Methods**: In this observational, cross-sectional study, bacterial isolates from various specimens (blood, urine, sputum, wound swabs) of ICU patients across a tertiary care hospital were collected and analyzed. Antimicrobial susceptibility testing was performed using the disk diffusion method, and results were interpreted based on the current CLSI guidelines. **Results**: A total of 1,200 bacterial isolates were analyzed. Preliminary findings indicate a high prevalence of methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum beta-lactamase (ESBL) producing Escherichia coli and Klebsiella pneumoniae, and carbapenem-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. Alarmingly, a significant proportion of the isolates demonstrated resistance to last-resort antibiotics. **Conclusion**: The observed high rates of multi-drug resistance in ICU settings underscore the urgent need for tailored antibiotic stewardship programs and robust infection control measures. Continuous monitoring of resistance patterns is essential to optimize patient outcomes and prevent the spread of resistant organisms.

Keywords: Antimicrobial resistance, ICU, Observational study, MRSA, ESBL, Carbapenem-resistant.

INTRODUCTION:

The problem of multidrug resistance (MDR) is increasingly being recognized as one of the gravest challenges to global public health. At its essence, MDR entails the capability of microorganisms, especially bacteria, to nullify the effects of multiple drugs, rendering the once-curable infections now formidable adversaries. [1] These resistant strains transcend borders and have emerged in every corner of the world, ensuring the global scale of this peril. The implications of MDR are expansive and devastating. Primary among these is the sharp rise in mortality rates. [2] When infections can no longer be controlled or eradicated by conventional treatments, even minor ailments can spiral into deadly complications. Tuberculosis (TB) is an illustrative example of this phenomenon. As per data from the World Health Organization, 2019 saw close to half a million cases of rifampicin-resistant TB, of which a staggering 78% were classified as multidrug-resistant TB. The tragedy was further compounded by the fact that a significant proportion of these cases went undiagnosed or misdiagnosed, leading to needless loss of life. [3] On the medical front, MDR threatens to roll back decades of progress. Many of our medical achievements, ranging from complex surgeries, organ transplants, to cancer treatments, hinge on the ability to control bacterial infections post-procedure. In a world riddled with antibiotic resistance, these advances could be jeopardized, and the risk associated with medical interventions would skyrocket. [4, 5] Another dimension of the MDR crisis is its impact on food security and nutrition. As resistant strains emerge in the food chain, through livestock treated with antibiotics for growth promotion or disease prevention, the chances of resistant infections in humans increase. Such infections not only jeopardize human health but also affect food production and distribution channels. This intertwining of food security and antimicrobial resistance complicates global efforts to combat hunger and malnutrition. [6]

The challenge of addressing MDR is exacerbated by several factors. First, the development of new antibiotics has slowed considerably, and the current pipeline of drugs is insufficient to tackle the escalating resistance. Second, widespread misuse and overuse of antimicrobials in humans, animals, and agriculture exacerbate the resistance issue. Coupled with inadequate diagnostic tools and a lack of awareness among healthcare providers and the public, the stage is set for MDR to flourish. [9]

However, all is not bleak. Addressing the MDR challenge requires a multi-pronged strategy. Strengthening global surveillance systems, investing in research and development of new antibiotics, enhancing public awareness, and implementing stringent antibiotic stewardship programs are essential steps forward. International collaboration, sharing of best practices, and collective action are the need of the hour to ensure a future where infections remain treatable. [10]

In sum, multidrug resistance is not just a medical challenge; it is a ticking time bomb threatening to disrupt our global healthcare, economic, and social structures. A concerted global effort, integrating science, policy, and community action, is vital to curbing this menace and ensuring a healthier future for all.

MATERIALS AND METHODS:

Study Design and Setting:

This retrograde observational study was conducted on the ICU patients admitted in main medical and surgical intensive care units as well as the ICU present in their subspeciality departments. Their medical charts and records were reviewed, and data was collected.

Data and Sample Collection:

Patients who fulfilled the inclusion criteria were enrolled in this study. Their demographic and clinical data was collected by retrograde observational study design using a pre-structured questionnaire. The demographic data included age, gender, primary diagnosis, positive/significant medical history. Medical record during hospital stay was reviewed. In data analysis, only the culture and sensitivity reports of selected patients were included. For the patients dependent on mechanical ventilation, it was ensured that they were regularly monitored and re-evaluated for fever, characteristics of sputum/secretions, oxygen consumption/FiO2 levels, and prescribed antibiotics.

All the blood culture samples were collected on the bedside and were sent to the lab for culture and sensitivity, immediately. The antibacterial susceptibility test was performed by standardized Bauer-Kirkby disk diffusion method. Antibiotic disc contents for antibiotic drug resistance were as follows; Ceftriaxone 30 µg, Ceftazidime 30 µg, Cefepime 30 µg, Cefoperazone/Sulbactam 75 µg, Gentamycin 10 µg, Amikacin 30 µg, Piperacillin/tazobactam 100/10 µg, Ertapenem 10 µg, Imipenem 10 µg, Meropenem 10 µg, Ciprofloxacin 5 µg, Levofloxacin 5 µg, Doxycycline 30 µg, Vancomycin 30 µg, and Colistin 10 µg. Control strains were Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, and Staphylococcus aureus.

Inclusion Criteria:

- Patients who were admitted into medical and surgical ICU for more than 48 hours.
- Patients who themselves or someone next to his/her kin gave consent to use their data for research purposes.
- Patients whose blood culture and sensitivity test were performed during the hospital stay.
- Patient with age more than 18 years.

Exclusion Criteria:

- Patients with age less than 18 years or pregnant females
- Patients with the ICU stay less than 48 hours.
- Patient who developed pneumonia before getting on to mechanical ventilator, acute myocardial infarction in first 24-48 hours of ICU admission, or uncontrolled ventricular arrythmias.

Data Analysis:

Retrograde patient's chart assessment was performed, and all the information required for this study was documented. The collected data were then exported to the spreadsheet for statistical analysis. The prevalence of the antibacterial drugs was assessed as the proportion of positive results over the duration of this study. Cases in which the patients were resistant to more than two antimicrobial drugs were labelled as multi-drug resistance (MDR). The results are compiled in the form of tables, graphs, and pie chart.

RESULTS:

The study includes 1200 bacterial isolates from patients admitted in ICU. Out of the total patients, n=594 (49.5%) were male and n=606 (50.5%0 were female patients with male to female ratio of 1:0.98. The average age of the subjects was 59.4 years (SD= ± 1.2). The median duration (days) on mechanical ventilation before blood sampling for culture and sensitivity report was 5 days (range: 2-14 days). The median length of ICU stay was 25 days. Based on the blood culture reports, gram positive samples were n=609 (51%) and Gram-negative n=582 (49%). There were four different types of colonizations including monomicrobial n=378, 32%; Polymicrobial n=362, 30%, Mixed growth n=451, 38%; and No growth n=9, 1%.

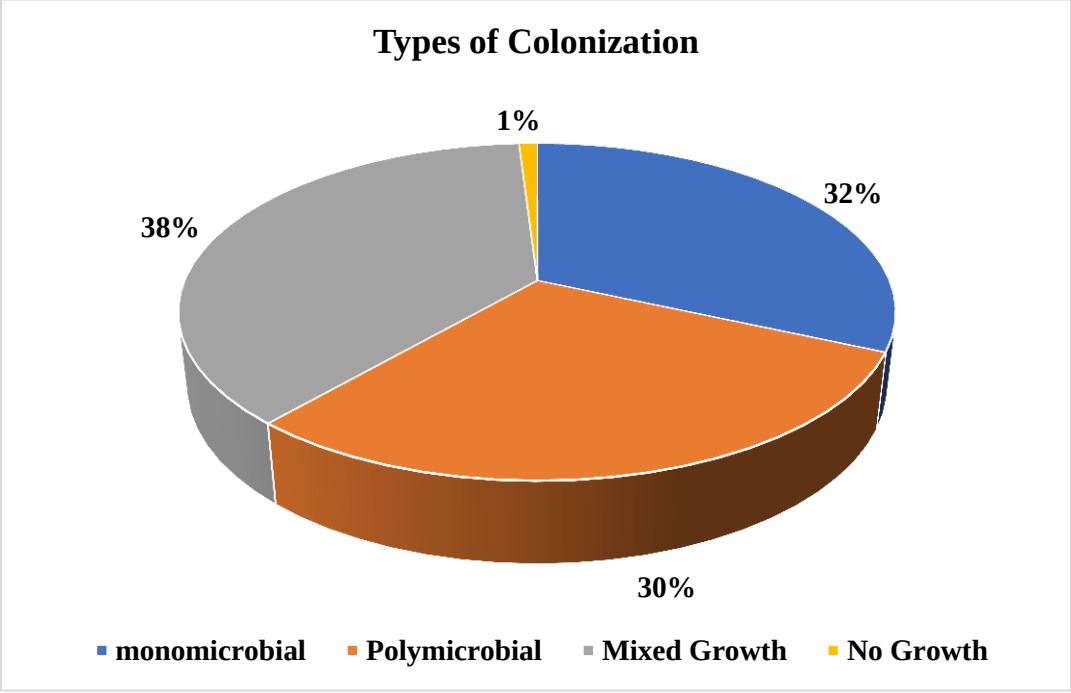

Fig 1. Pie chart illustrating types of bacterial colonizations found on blood culture reports.

Out of 1200 candidates of hospital admission, n=336 (28%), followed by uncontrolled diabetes mellitus n=204 (17%), uncontrolled hypertension n=168 (14%), chronic kidney disease n=108 (9%), Chronic liver disease n=96 (8%), cerebral vascular disease n=108 (9%), Heart failure n=72 (6%), septic shock n=108 (9%).

Primary Diagnosis	Frequency (n)	Percentage (%)
Respiratory failure	336	28
Uncontrolled Diabetes Mellitus	204	17
Uncontrolled Hypertension	168	14
Chronic Kidney disease	108	9
Chronic Liver disease	96	8
Cerebral vascular disease	108	9
Heart failure	72	6
Septic shock	108	9

Table 1. List of Primary diagnosis requiring ICU admission

At the time of ICU admission, about 55%-60% of patients were already undertreatment with 3rd generation cephalosporin, gentamycin, and Co-amoxiclav. Other antibiotics given to the patients include ciprofloxacin, levofloxacin, cefoperazone-sulbactam, colistin, aminoglycosides, meropenem, and vancomycin.

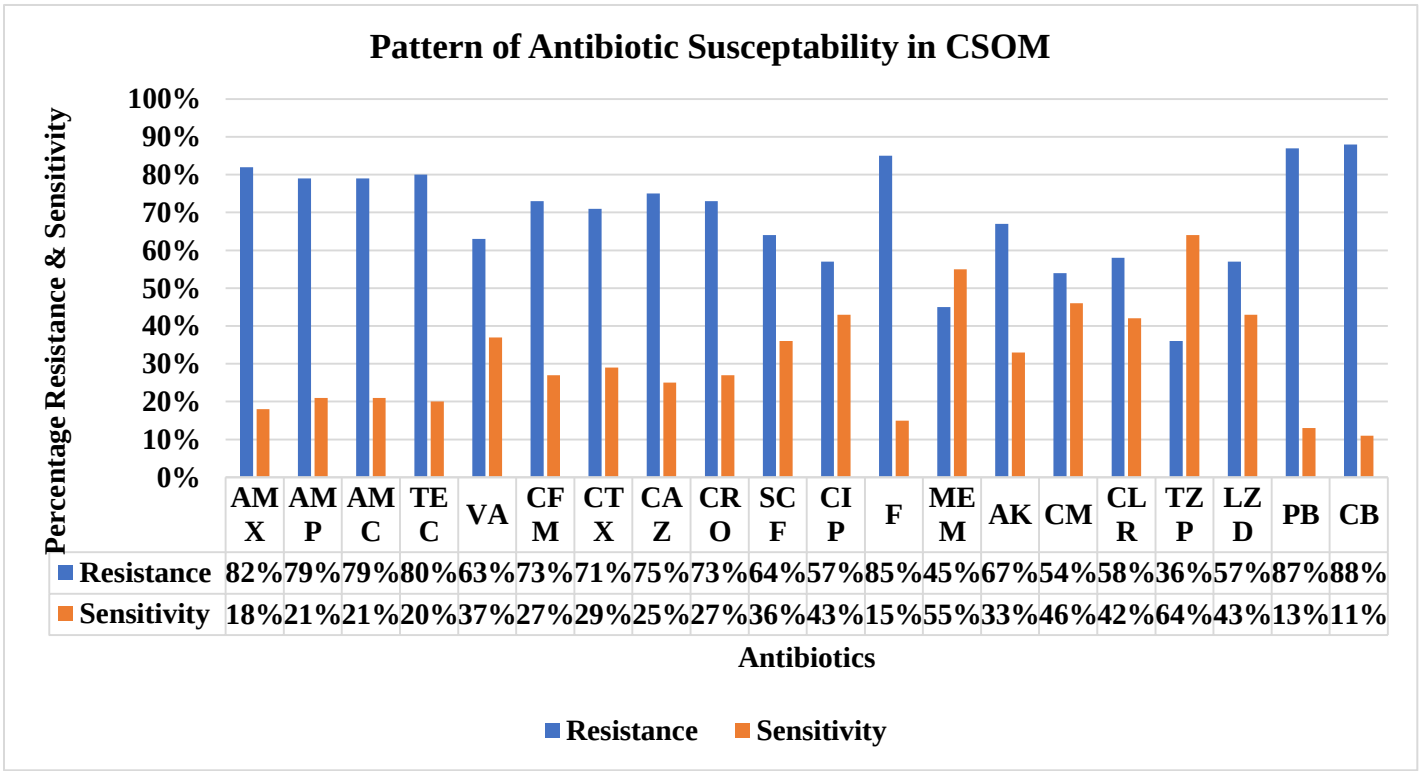

Fig 2. Pattern of antimicrobial susceptibility.

Each of the patient had prevalence of antimicrobial resistance of >90%. Majority of the patients had resistance to at least 2 drugs. Approximately, 62% were found to be positive for multiple drug resistance (MDR). Acinetobacter n=92 (7.6%) was the most prominent among the patients of ventilator-associated/ atypical pneumonia, followed by Pseudomonas Aeruginosa and Klebsiella. In most cases with multiple infections, coinfection with Acinetobacter and pseudomonas aeruginosa were detected. The gram-positive bacteria found in the blood culture were Staph aureus (n=108, 9%), Streptococci (n=82, 6.8%), Enterococcus (n=72, 6%), and Methicillin Resistance Staphylococcus Aureus MRSA (n= 103, 8.5%). MRSA was the most prevalent among all the other gram positive, obligate, or facultative aerobes.

Antibiotic	**Gram Positive Bacteria**			
	SA (n= 108)	**Streptococcus (n =82)**	**Entrococcus (n= 72)**	**MRSA (n= 103)**
AMX	9	11	16	13
AMP	10	5	4	6
AMC	6	3	3	7
TEC	4	2	4	3
VA	5	4	1	4
CFM	5	6	2	3
CTX	9	5	5	7
CAZ	4	6	4	5
CRO	6	4	3	3
SCF	5	4	3	4
CIP	7	2	5	3
F	4	5	2	4
MEM	5	4	3	15
AK	8	2	4	3
CM	5	3	1	4
CLR	3	5	3	5
TZP	4	3	2	7
LZD	6	6	4	5
PB	3	2	3	2
CB	3	2	3	0

Table 3. Obligate and Facultative Gram-Positive Bacteria and their sensitivity for 20 different commonly used antibiotics in the light of Culture and Sensitivity test results.

AMX= Amoxicillin, AMP= Ampicillin, TEC= Teicoplanin, VA= Vancomycin, CFM= Cefixime, CTX= Cefotaxime, CAZ= Ceftazidime, CRO= Ceftriaxone, SCF= Sulbactam/Cefoperazone, CIP= Ciprofloxacin, F= Nitrofurantoin, MEM= Meropenem, AK= Amikacin, CN= Gentamycin, CLR= Clarithromycin, TZP= Piperacillin/Tazobactam, LZD= Linezolid

For the ease of data analysis, the Gram-Negative Bacteria were subdivided into Aerobic and anaerobic bacteria. The obligate and/or facultative anerobic bacteria were n= 566 (47.1%) out of total 1191 ICU patients, including Pseudomonas Aeruginosa PA n= 112 (9.3%), Proteus Mirabilis PM n= 98 (8.1%), Enterobacter n= 49 (4.0%), Klebsiella n= 83 (6.9%), Escherichia Coli n= 77 (6.4%), Citrobacter n=74 (6.1%), and Serratia Marcescens n=72 (6%).

Antibiotic	Gram Negative Bacteria (Anaerobic)						
	PA (n= 112)	Klebsiella (n= 83)	PM (n= 98)	Enterobacter (n= 49)	Citrobacter (n= 74)	E. Coli (n= 77)	Serratia Marcescens (n= 73)
AMX	5	5	6	5	5	5	5
AMP	4	6	7	1	2	1	5
AMC	7	4	13	2	4	9	2
TEC	4	4	6	2	2	4	3
VA	6	4	6	6	2	5	2
CFM	8	5	7	2	4	4	4
CTX	4	6	7	2	5	2	3
CAZ	8	3	5	4	3	6	2
CRO	9	4	6	4	4	3	4
SCF	5	8	4	3	5	4	4
CIP	4	4	6	1	3	4	3
F	5	3	4	3	2	2	6
MEM	3	2	3	2	6	4	0
AK	7	5	2	2	5	2	7
CM	8	5	3	4	4	5	5
CLR	9	4	5	2	4	4	3
TZP	6	5	4	2	3	5	4
LZD	5	3	3	2	5	4	5
PB	5	3	1	0	6	4	6
CB	4	2	3	0	3	1	3

Table 4. Frequency and antimicrobial sensitivity of Gram-Negative Anaerobic bacteria.

AMX= Amoxicillin, AMP= Ampicillin, TEC= Teicoplanin, VA= Vancomycin, CFM= Cefixime, CTX= Cefotaxime, CAZ= Ceftazidime, CRO= Ceftriaxone, SCF= Sulbactam/Cefoperazone, CIP= Ciprofloxacin, F= Nitrofurantoin, MEM= Meropenem, AK= Amikacin, CN= Gentamycin, CLR= Clarithromycin, TZP= Piperacillin/Tazobactam, LZD= Linezolid

Among the aerobic gram-negative bacteria n=260 (21.6%), there were Acinetobacter n=92 (7.6%), Moraxella Catarrhalis n=62 (5.1%), Alcaligenes Spp. n= 55 (4.5%), and Hemophylis Influenza n=51 (4.2%), in descending order.

Antibiotic	Gram Negative Bacteria (Aerobic)			
	Acinetobacter Spp. (n= 92)	Moraxella Catarrhalis (n= 62)	Alcaligenes Spp. (n= 55)	Haemophylis Influenzae (n= 51)
AMX	4	5	5	5
AMP	6	1	5	2
AMC	5	1	4	3
TEC	4	3	6	1
VA	3	4	1	3
CFM	5	6	5	2

CTX	11	5	3	5
CAZ	5	3	5	2
CRO	6	3	4	2
SCF	5	6	2	3
CIP	3	3	1	1
F	6	2	1	2
MEM	3	1	2	2
AK	5	4	2	4
CM	3	3	2	2
CLR	4	4	1	3
TZP	5	3	3	2
LZD	5	3	2	4
PB	4	2	1	3
CB	1	0	2	1

Table 5. Frequency and antimicrobial sensitivity of Gram-Negative obligate/facultative aerobes

AMX= Amoxicillin, AMP= Ampicillin, TEC= Teicoplanin, VA= Vancomycin, CFM= Cefixime, CTX= Cefotaxime, CAZ= Ceftazidime, CRO= Ceftriaxone, SCF= Sulbactam/Cefoperazone, CIP= Ciprofloxacin, F= Nitrofurantoin, MEM= Meropenem, AK= Amikacin, CN= Gentamycin, CLR= Clarithromycin, TZP= Piperacillin/Tazobactam, LZD= Linezolid

DISCUSSION:

AMR presents a rising threat in most health care institutions. One significant consequence of this is the increase in multi-drug resistant Hospital Acquired Infections (HAIs), leading to increased deaths and illnesses in hospitalized patients. [1-3] ICUs have been identified as hotspots for HAIs. Our research aimed to analyze the prevalence of these microorganisms and their resistance to frequently used antimicrobial agents in a leading hospital. Our study's demographic data highlighted that male ICU admissions were nearly twice as much as females, with an average patient age of around 47 years. [4, 5]

The evolution of drug resistance is intricately linked to the patterns of antimicrobial prescription, especially in developing countries i.e., Pakistan. Over the years, as bacteria and other microorganisms have been exposed to antimicrobial agents, those with mutations that confer resistance have been selected for, allowing them to proliferate while susceptible strains diminish. In developing countries, several factors have accelerated this process. First, the over-the-counter availability of antibiotics without prescriptions has led to rampant misuse and overuse. [6, 7] Often, individuals self-medicate based on incomplete knowledge or discontinue antibiotic courses prematurely once symptoms alleviate. Furthermore, healthcare professionals, faced with limited diagnostic tools and pressured by patient expectations, might resort to broad-spectrum antibiotics as a catch-all solution, rather than tailoring prescriptions to specific pathogens. The compounded effect of these practices in resource-constrained settings has hastened the emergence and spread of drug-resistant strains, jeopardizing not only local health but also posing a global threat through potential transmission across borders. [8-10]

Moreover, MDR considerably strains the healthcare infrastructure. Treating resistant infections usually requires more extended hospital admissions, utilization of more expensive and sometimes toxic drugs, and increased human resources. As a result, healthcare budgets balloon, putting immense pressure on governments, especially in low and middle-income countries where health resources are already scarce. [11, 12] The financial ramifications aren't restricted to treatment costs alone. The ripple effects are felt when patients require prolonged hospitalization, leading to increased indirect costs related to loss of employment or decreased productivity. [13-15]

Despite rigorous disinfection protocols for respiratory equipment, hospital-acquired bacterial pneumonia remains a prevalent HAI in ICU, particularly among patients on extended mechanical ventilation. Our data supports this, with tracheal aspirate being the most frequent clinical specimen. [16] The irrational use of antimicrobials has led to the rise of non-fermenting gram-negative bacilli (NF-GNB) as significant HAIs. These pathogens often come from natural environments like soil and water but can be found on hospital equipment and even healthcare workers. Our findings

confirmed that NF-GNB were the predominant organisms found in the ICUs. [17, 18]

Our research revealed Pseudomonas spp and Acinetobacter spp as the leading isolates in ICUs. Studies by Chawla and Vincent echoed these findings, emphasizing their growing relevance in health care. [19] Meanwhile, other NF-GNB, like Burkholderia spp, were isolated less but were mostly multi-drug resistant, challenging healthcare providers. Besides NF-GNB, Enterobacteriaceae GNB, including Escherichia coli and Klebsiella spp, were also frequently isolated, especially from urine and exudate samples. [20, 21] We took the initiative to analyze the primary clinical isolates in each ICU. We observed a pattern where certain bacteria were more dominant in pediatric versus adult ICUs. [22] The distribution of pathogens varied, with Acinetobacter spp and Pseudomonas spp being predominant in tracheal aspirates and blood samples, respectively. About 22.2% of ICU patients experienced HAIs. Pneumonia was the leading HAI, especially among mechanically ventilated patients. [23, 24]

AMR is becoming a more severe concern in all ICUs, with resistance to a range of drugs increasing. This is true for both gram-negative and gram-positive organisms. In our research, we classified antimicrobial resistance patterns into three groups: NF-GNB, EB-GNB, and gram-positive organisms. NF-GNB showed strong resistance to various antimicrobial classes. Acinetobacter spp was particularly resistant, highlighting the need for alternative treatment strategies. In contrast, Pseudomonas species had a slightly lower resistance rate. Among EB-GNB, resistance was high, especially to cephalosporins and quinolones. Klebsiella and Enterobacter species showed more resistance compared to Escherichia coli. [25]. For gram-positive bacteria, S. aureus exhibited significant resistance, particularly against penicillin and ciprofloxacin. MRSA rates are rising, necessitating alternative treatment options. Enterococci showed resistance to multiple drugs, including high-level aminoglycoside resistance. MDR prevalence has been on the rise. These organisms contribute to higher death rates, extended hospital stays, and increased costs. Our study found a significant percentage of gram-negative bacilli to be MDR. Acinetobacter spp, Pseudomonas spp, Klebsiella spp, and Escherichia coli were the primary contributors, emphasizing the need for targeted interventions and alternative treatment options. [26, 27] Furthermore, the socioeconomic repercussions of MDR are profound. As families grapple with prolonged illnesses, increased medical costs, and in many cases, the loss of breadwinners, the cycle of poverty intensifies. Communities, particularly in vulnerable regions, face a double-edged sword: battling the direct onslaught of MDR while also confronting the consequent socioeconomic downfall. [28-30]

CONCLUSION:

In this study, it is concluded that Acinetobacter, Klebsiella, and Pseudomonas aeruginosa were predominately found in blood culture samples. Antimicrobial drugs with considerably high resistance rate were ciprofloxacin, ceftriaxone, and ---. The most alarming finding was that a significant percentage of the positive blood culture samples were either resistant against more than 2 drugs, multidrug resistance strains, or resistant against the last resort antibiotics. These results reinforce the fact that multidrug resistance is a global public health issue. More elaborative and extensive studies are required to study the patterns of multidrug resistance on the global levels for better understanding and control.

CONFLICT IN INTEREST: None

REFERENCES:

1. Altaf U, Saleem Z, Akhtar MF, Altowayan WM, Alqasoumi AA, Alshammari MS, Haseeb A, Raees F, Imam MT, Batool N, Akhtar MM. Using culture sensitivity reports to optimize antimicrobial therapy: findings and implications of antimicrobial stewardship activity in a hospital in Pakistan. Medicina. 2023 Jul 2;59(7):1237.
2. Saleem Z, Hassali MA, Versporten A, Godman B, Hashmi FK, Goossens H, Saleem F. A multicenter point prevalence survey of antibiotic use in Punjab, Pakistan: findings and implications. Expert review of anti-infective therapy. 2019 Apr 3;17(4):285-93.
3. Ali SA, Taj MK, Ali SH. Antimicrobial resistance pattern of bacterial meningitis among patients in Quetta, Pakistan. Infection and Drug Resistance. 2021 Dec 1:5107-20.
4. Saleem Z, Saeed H, Hassali MA, Godman B, Asif U, Yousaf M, Ahmed Z, Riaz H, Raza SA. Pattern of inappropriate antibiotic use among hospitalized patients in Pakistan: a longitudinal surveillance and implications. Antimicrobial Resistance & Infection Control. 2019 Dec;8(1):1-7.
5. Bilal H, Khan MN, Rehman T, Hameed MF, Yang X. Antibiotic resistance in Pakistan: a

systematic review of past decade. BMC infectious diseases. 2021 Dec;21(1):1-9.

6. Khan MS, Bory S, Rego S, Suy S, Durrance-Bagale A, Sultana Z, Chhorn S, Phou S, Prien C, Heng S, Hanefeld J. Is enhancing the professionalism of healthcare providers critical to tackling antimicrobial resistance in low-and middle-income countries?. Human resources for health. 2020 Dec;18:1-9.
7. Saleem Z, Godman B, Azhar F, Kalungia AC, Fadare J, Opanga S, Markovic-Pekovic V, Hoxha I, Saeed A, Al-Gethamy M, Haseeb A. Progress on the national action plan of Pakistan on antimicrobial resistance (AMR): A narrative review and the implications. Expert review of anti-infective therapy. 2022 Jan 2;20(1):71-93.
8. Khan MS, Durrance-Bagale A, Mateus A, Sultana Z, Hasan R, Hanefeld J. What are the barriers to implementing national antimicrobial resistance action plans? A novel mixed-methods policy analysis in Pakistan. Health policy and planning. 2020 Oct;35(8):973-82.
9. Ghodousi A, Rizvi AH, Baloch AQ, Ghafoor A, Khanzada FM, Qadir M, Borroni E, Trovato A, Tahseen S, Cirillo DM. Acquisition of cross-resistance to bedaquiline and clofazimine following treatment for tuberculosis in Pakistan. Antimicrobial Agents and Chemotherapy. 2019 Sep;63(9):10-128.
10. Mustafa ZU, Salman M, Yasir M, Godman B, Majeed HA, Kanwal M, Iqbal M, Riaz MB, Hayat K, Hasan SS. Antibiotic consumption among hospitalized neonates and children in Punjab province, Pakistan. Expert review of anti-infective therapy. 2022 Jun 3;20(6):931-9.
11. Khan FU, Khan FU, Hayat K, Chang J, Saeed A, Khan Z, Ashraf M, Rasheed UM, Atif N, Ji W, Aziz MM. Knowledge, attitude and practices among consumers toward antibiotics use and antibiotic resistance in Swat, Khyber-Pakhtunkhwa, Pakistan. Expert review of anti-infective therapy. 2020 Sep 1;18(9):937-46.
12. Zeb S, Mushtaq M, Ahmad M, Saleem W, Rabaan AA, Naqvi BS, Garout M, Aljeldah M, Al Shammari BR, Al Faraj NJ, Al-Zaki NA. Self-medication as an important risk factor for antibiotic resistance: a multi-institutional survey among students. Antibiotics. 2022 Jun 23;11(7):842.
13. Sayeed MA, Farooqi J, Jabeen K, Awan S, Mahmood SF. Clinical spectrum and factors impacting outcome of Candida auris: a single center study from Pakistan. BMC infectious diseases. 2019 Dec;19:1-8.
14. Khan MT, Malik SI, Ali S, Masood N, Nadeem T, Khan AS, Afzal MT. Pyrazinamide resistance and mutations in pncA among isolates of Mycobacterium tuberculosis from Khyber Pakhtunkhwa, Pakistan. BMC infectious diseases. 2019 Dec;19:1-7.
15. Saleem S, Bokhari H. Resistance profile of genetically distinct clinical Pseudomonas aeruginosa isolates from public hospitals in central Pakistan. Journal of infection and public health. 2020 Apr 1;13(4):598-605.
16. Gillani AH, Chang J, Aslam F, Saeed A, Shukar S, Khanum F, Jairoun A, Nicholson A, Mohamed Ibrahim MI, Fang Y. Public knowledge, attitude, and practice regarding antibiotics use in Punjab, Pakistan: a cross-sectional study. Expert review of anti-infective therapy. 2021 Mar 4;19(3):399-411.
17. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, Han C, Bisignano C, Rao P, Wool E, Johnson SC. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022 Feb 12;399(10325):629-55.
18. Atif M, Zia R, Malik I, Ahmad N, Sarwar S. Treatment outcomes, antibiotic use and its resistance pattern among neonatal sepsis patients attending Bahawal Victoria Hospital, Pakistan. PloS one. 2021 Jan 13;16(1):e0244866.
19. Qamar FN, Yousafzai MT, Dehraj IF, Shakoor S, Irfan S, Hotwani A, Hunzai MJ, Thobani RS, Rahman N, Mehmood J, Hemlock C. Antimicrobial resistance in typhoidal Salmonella: surveillance for enteric fever in Asia project, 2016–2019. Clinical Infectious

Diseases. 2020 Nov 1;71(Supplement_3):S276-84.

20. Fridkin SK, Gaynes RP. Antimicrobial resistance in intensive care units. Clinics in Chest Medicine. 1999 Jun 1;20(2):303-16.
21. Fridkin SK. Increasing prevalence of antimicrobial resistance in intensive care units. Critical care medicine. 2001 Apr 1;29(4):N64-8.
22. Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. Annals of intensive care. 2011 Dec;1:1-7.
23. Tran GM, Ho-Le TP, Ha DT, Tran-Nguyen CH, Nguyen TS, Pham TT, Nguyen TA, Nguyen DA, Hoang HQ, Tran NV, Nguyen TV. Patterns of antimicrobial resistance in intensive care unit patients: a study in Vietnam. BMC infectious diseases. 2017 Dec;17:1-7.
24. Obritsch MD, Fish DN, MacLaren R, Jung R. National surveillance of antimicrobial resistance in Pseudomonas aeruginosa isolates obtained from intensive care unit patients from 1993 to 2002. Antimicrobial agents and chemotherapy. 2004 Dec;48(12):4606-10.
25. Cantón R, Gijón D, Ruiz-Garbajosa P. Antimicrobial resistance in ICUs: an update in the light of the COVID-19 pandemic. Current opinion in critical care. 2020 Oct 1;26(5):433-41.
26. Fahim NA. Prevalence and antimicrobial susceptibility profile of multidrug-resistant bacteria among intensive care units patients at Ain Shams University Hospitals in Egypt—a retrospective study. Journal of the Egyptian Public Health Association. 2021 Dec;96(1):1-0.
27. Banerjee R, Humphries R. Rapid antimicrobial susceptibility testing methods for blood cultures and their clinical impact. Frontiers in Medicine. 2021 Mar 10;8:635831.
28. Rothe K, Feihl S, Schneider J, Wallnöfer F, Wurst M, Lukas M, Treiber M, Lahmer T, Heim M, Dommasch M, Waschulzik B. Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study in light of antibiotic stewardship. European Journal of Clinical Microbiology & Infectious Diseases. 2021 Apr;40:859-69.
29. Manyahi J, Kibwana U, Mgimba E, Majigo M. Multi-drug resistant bacteria predict mortality in bloodstream infection in a tertiary setting in Tanzania. PLoS One. 2020 Mar 4;15(3):e0220424.
30. Hu B, Tao Y, Shao Z, Zheng Y, Zhang R, Yang X, Liu J, Li XI, Sun R. A comparison of blood pathogen detection among droplet digital PCR, metagenomic next-generation sequencing, and blood culture in critically ill patients with suspected bloodstream infections. Frontiers in Microbiology. 2021 May 17;12:641202.