EPIDEMIOLOGY AND CLINICAL OUTCOMES OF BACTERIAL INFECTIONS IN ADULT INTENSIVE CARE UNIT: A PROSPECTIVE OBSERVATIONAL STUDY



THESIS

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All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

This is to certify that the thesis titled "Epidemiology and clinical outcomes of bacterial infections in adult intensive care unit: a prospective observational study" is the bonafide work of Dr. Somya Goel carried out under our guidance and supervision in the Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Jodhpur.

Guide Dr. Manoj Kamal

Additional Professor

Department of Anesthesiology and Critical Care
AIIMS, Jodhpur

Co-Guides

Dr Pradeep Bhatia

Professor

Department of Anesthesiology and Critical Care AIIMS Jodhpur

Dr Bharat Paliwal

Associate Professor,

Department of Anesthesiology and Critical Care

AIIMS Jodhpur

Dr Vibhor Tak

Associate Professor,

Department of Microbiology

AIIMS Jodhpur



All India Institute of Medical Sciences, Jodhpur

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Dr Pradeep Bhatia Professor and Head

Department of Anesthesiology and
Critical Care
AIIMS Jodhpur

DECLARATION

I hereby declare that the thesis titled "Epidemiology and clinical outcomes of bacterial infections in adult intensive care unit: A Prospective Observational study" embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

Dr. Somya Goel

Department of Anesthesiology and Critical Care,

All India Institute of Medical Sciences,

Jodhpur

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"Research is to see what others have seen and to think what no one has thought"

- Albert Szent-Gyorgyi

While practicing Medicine in our day-to-day lives, it is easy to forget that the science that forms our foundation is derived from a behemoth of research carried out through millennia. As Isaac Newton famously said, "We stand upon the shoulders of giants". This has never been truer than the present time when "Evidence-based medicine" is finally basking in its much-deserved limelight, reinforcing among us that every bit of evidence, every effort at excavating the truth counts and has ramifications that have the potential to change our world.

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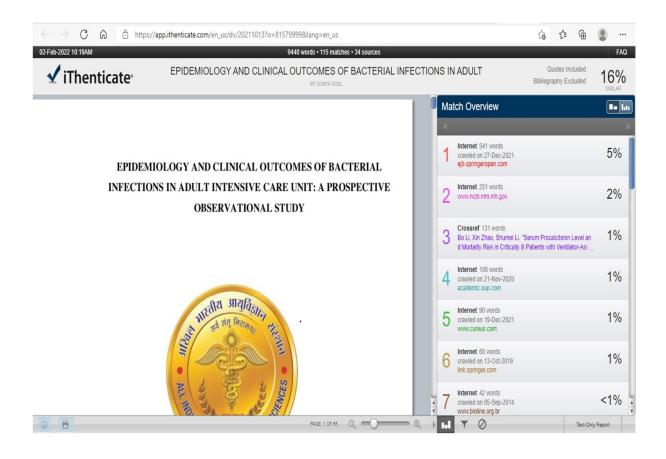
My family have been the voice of my conscience and wisdom during the tempestuous times of my journey and have been instrumental in calming me in every difficulty.

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Last but by far not least, I express my thanks to Mr. Vishal, for always being ready to help in all the office matters and timely information of any notice.



ABBREVIATIONS

BSI: Blood Stream Infections

CLSI: Clinical and Laboratory Standards Institute

CONS: Coagulase-Negative Staphylococci

COPD: Chronic Obstructive Pulmonary Disease

CRE: Carbapenemase Resistance Enterococci

CTX-RO: Ceftriaxone-Resistant Gram Negatives

ESBL: Extended-Spectrum Beta-Lactamases

FDA: Us Food and Drug Administration

GNB: Gram-Negative Bacilli

GPB: Gram Positive Bacteria

GPC: Gram Positive Cocci

HAI: Hospital Acquired Infection

HAMR: Highly Antimicrobial Resistant

ICU: Intensive Care Unit

LAMA: Left Against Medical Advice

MRSA: Methicillin-Resistant Staphylococcus Aureus

NDM: New Delhi Metalloproteinase

NIS: Nosocomial Infections

PCT: Procalcitonin

QSOFA: Quick Sequential Organ Failure Assessment

RTI: Respiratory Tract Infection

SIRS: Systemic Inflammatory Response Syndrome

SOFA: Sequential Organ Failure Assessment

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

TB: Tuberculosis

VAP: Ventilator Associated Pneumonia

VRE: Vancomycin-Resistant Enterococci

WHO: World Health Organization

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SUMMARY

Background

The most common reason for intensive care unit (ICU) admission is sepsis. Patients admitted in ICUs who are previously admitted in wards or transferred from other hospitals may have infection with multidrug-resistant bacteria. During the prolong stay in ICU they may get cross infection from other patients, and can develop ventilator associated pneumonia (VAP) and infections from various indwelling devices like central line, arterial line, and urinary bladder catheterization. Emergence of multiple drug resistance and scarcity of new pharmaceutical agents are leaving physicians with few effective antibiotic alternatives for their patients. The knowledge of epidemiology of pathogen and their antibiotic sensitivity can guide the choice of empirical antibiotic coverage and reduce emergence of drug resistance. Therefore, this study aimed to determine the epidemiology of bacterial infections in patients admitted in adult ICU of tertiary care hospital, their antibiotic sensitivity, total length of stay in ICU and 28 days all-cause mortality, the relationship of serum procalcitonin level and sofa score with mortality risk in critically ill patients with bacterial infections and to compare the mortality between patients who had culture positive and culture negative.

Methods

This is a prospective observational cohort study conducted at adult intensive care unit (AICU) of Department of Anaesthesiology and Critical Care, AIIMS Jodhpur between November 3, 2020 to November 2, 2021. (Due to COVID-19, this study was time bound study and recruitment was done over one year.) All patients admitted in adult intensive care unit (AICU) of either sex, of all age, who were consented for the study and needing the culture and sensitivity test were included in the study. Patient not willing to participate in study and not having suspicion of infection were excluded.

Results and conclusion

A total of 380 patients were included. The most common pathogens isolated in our AICU were Gram negative microorganisms (27.63%). The Gram-positive microorganisms were found in 3.5% of the samples. *Acinetobacter baumannii* isolates were most commonly found (31.3%) in blood specimen, followed by *Klebsiella pneumoniae* (29.8%). In urine specimen the *Enterococcus* species were most common (37.78%) followed by *Klebsiella pneumoniae* (26.67%) and *E coli* (26.67%) while in tracheal specimen *Acinetobacter baumannii* isolates

were predominant (53.85%) followed by *Klebsiella pneumoniae* (21.9%). The median duration of stay of the patients in the ICU was 8 days with IQR of 5-14 days in our study population. Using Mann Whitney U test, the duration of ICU stay was not statistically significant among survivors and non survivors. Among bacterial infections, *Klebsiella pneumoniae* showed highest mortality (70.3%) followed by *Acinetobacter* (69.9%). Among Gram positive infections, *Staphylococcus aureus* (MRSA) showed highest mortality (66.7%). Using multiple logistic regression analysis, the procalcitonin levels were not associated with mortality. (OR=1.001, 95% CI 0.989-1.012, P = 0.906). The median total SOFA score was significantly higher in non-survivors than in survivors [6(IQR=2-6) vs. 3(IQR=5-9)].

Using multiple logistic regression models to evaluate the SOFA associated with mortality and it showed that the odds of death increased with change in SOFA of \geq 2 scores (OR=1.444(95% CI=1.308-1.594), P =0.000 which is statistically significant.



INTRODUCTION

The most common reason for intensive care unit (ICU) admission is sepsis. Patients admitted in ICUs are previously admitted in wards, transferred from other hospitals are more severely diseased and may have infection with multidrug-resistant bacteria. The prolong stay in ICU may have chances to get cross infection from other patients, ventilator associated pneumonia (VAP) and infections from various devices like central line, arterial line, and urinary bladder catheterization. Although, intensive care units (ICUs) handle only around 5% to 10% of all hospitalized patients, and they account for roughly 25% of all nosocomial infections. In ICUs, infection rates are five to ten times greater than in other hospital wards.^[1,2]

Hence patients admitted in ICUs has more chances to get life-threatening infections from multidrug-resistant bacteria.

Majority of times, the patients admitted in ICU are severely ill and need empirical broad spectrum antibiotic administration against common pathogen after sending the blood for culture and sensitivity to improve the outcome. The early use of antibiotics is double edge sword, at one side it improves the outcome while at another end it increases the use of antibiotic (un-necessary use of antibiotic), inappropriate antibiotic usage, which may lead to emergence of antibiotic resistance.^[3]

Many times, the culture report is not positive because of previous antibiotic usage, or inappropriate collection may cause wrong report.

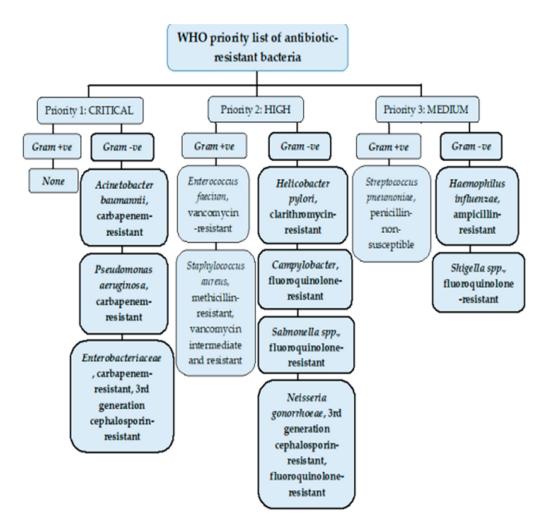
The knowledge of epidemiology of pathogen and their sensitivity is mandatory to decide the empirical broad-spectrum antibiotic. At the same time, new pharmaceutical agents are becoming scarce, leaving physicians with few effective antibiotic alternatives for their patients.^[4,5] Infections with antibiotic-resistant organisms have been linked to longer hospital stays, higher mortality, and higher expenses.^[6]

On the one hand, the critical care unit is the area of greatest antimicrobial use ^[7] and the epicentre of antimicrobial resistance in most hospitals. ^[8] However, the sensitivity of critical care patients and the intricacy of their clinical management may make antibiotic use decreases difficult. ^[9]

Natural products have long been used to cure a number of ailments such as; cinchona tree containing quinine to treat malaria. ^[10] In 1945, less than a year after the discovery of penicillin, the first penicillin-resistant Staphylococcus aureus appeared. ^[11]

The World Health Organization (WHO) enunciated a list of bacteria in need of new antibiotics in 2017, categorising them as critical, high, or medium priority. (Figure 1) [10]

Figure 1: WHO list of priority pathogens grouped under three priority categories according to their antibiotic resistance: Critical, high and medium to encourage research and development of new antibiotics



Gram-positive bacteria are a significant cause of bloodstream and other infections in hospitalised patients in the United States, and the number of nosocomial bloodstream infections caused by antibiotic-resistant gram-positive bacteria is on the rise. Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) are two Gram-positive bacteria that pose a serious threat. MRSA is now responsible for over

60% of staphylococcal infections in intensive care units in the United States, and the rates are continuing to grow. For serious MRSA infections, vancomycin is the therapy of choice. [12] MRSA bloodstream infection rates have decreased, owing to initiatives focused at reducing vascular catheter infections (universal nasal surveillance, contact precautions, hand hygiene, and an institutional culture change programme). [13]

In ICUs, the prevalence of Gram-negative bacterial infections is rising.^[14] This is owing to an increase in the use of invasive devices in ICUs, such as mechanical ventilators, monitoring devices, blood and urine catheters, immunosuppressive agents, and excessive broad-spectrum antibiotic therapy.^[15,16] Gram-negative bacilli are becoming more resistant to antibiotics, owing to extended-spectrum beta-lactamases and carbapenem-resistant Enterobacteriaceae.^[17]

Most occurrences of ventilator-associated pneumonia, catheter-related bloodstream infections, and other ICU-acquired sepsis, such as urinary tract infections, are caused by resistant GNB. Enterobacteriaceae and non-fermenting Gram-negative bacteria are the most common Gram-negative bacteria that pose complications (*Pseudomonas aeruginosa*, *Acinetobacter baumannii and Stenotrophomonas maltophilia*). [10]

A contaminant is a microorganism that is not pathogenic for the patient and is intended to be introduced into the culture during specimen collection or processing. Coagulase-negative staphylococci (CoNS) are the most commonly isolated bacteria, accounting for 75 to 88 % of contaminated BCs, followed by Bacillus spp., viridans group Streptococci, Corynebacterium spp., Propionibacterium spp., Micrococcus spp., and Clostridium perfringens. [18]

The term "colonisation" refers to a situation in which a patient has a sufficiently high concentration of organisms at a location where they may be detected but the organism is not producing any signs or symptoms. This is different from contamination, where the organism was never present in the site where it was detected but was introduced into the specimen from another site, or contamination in the laboratory.^[19]

A surge in multidrug-resistant bacteria is restricting the therapeutic options for infections in the ICU, and empiric therapy decisions are even less likely to provide adequate coverage for prevalent ICU pathogens. [20]

Since 1997, the SENTRY Antimicrobial Surveillance Program has been tracking bloodstream infections (BSI) in patients at medical centres all over the world. Between 1997 and 2002, antibiotic susceptibility was assessed on 81,213 BSI pathogens from North America, Latin America, and Europe. Each year, the three most prevalent BSI pathogens in all three regions were S. aureus, E. coli, and coagulase-negative staphylococci. They also concluded that BSI pathogen resistance was substantially more common in nosocomial infections and in patients in critical care units (ICUs); age disparities were also observed. [21]

The rapid emergence of multidrug-resistant organisms during the last two decades has become a serious concern in terms of infection control. ^[22] The incidence of infections and their antibiotic susceptibility varies hugely amongst institutions. ^[23]

The hospital antibiogram is a description of antibiotic susceptibilities of local bacterial isolates that is continuously updated. Clinicians frequently utilise antibiograms to estimate local susceptibility rates as a tool for choosing empiric antibiotic therapy and tracking resistance trends over time within an institution. Antibiograms can also be used to track resistance trends and compare susceptibility rates among institutions. [24] Antibiogram analysis of subgroups is used to plan an empiric antibiotic policy in a hospital. The American Thoracic Society and the Infectious Diseases Society of America recommend using suitable empiric antibiotic therapy based on local microbiology results and the local antibiogram in the treatment of ventilator-associated pneumonia. [25] The hospital antibiogram cannot be used to determine the optimal empiric therapy for a specific patient since other criteria must be considered, such as the type and severity of the infection, the infectious organism, and the patient's medical history and previous antibiotic use. [24]

Gram-positive bacteria, particularly Gram-positive cocci such as coagulase-negative staphylococcus, streptococcus, and enterococci, are extremely dangerous pathogens in the hospital setting. MRSA (methicillin-resistant Staphylococcus aureus) and VRE (vancomycin-resistant enterococci) are two strains of bacteria that are particularly harmful. [12]

Antimicrobial resistance is rapidly increasing, particularly among Gram-negative bacteria. ^[14] The extended-spectrum -lactamase-producing GNB is the most notable. Newer forms of resistance, such as New Delhi metalloproteinase (NDM) and carbapenemase resistance enterococci (CRE), provide new hurdles. Except for tigecycline and colistin, NDM-resistant E. coli and K. pneumoniae are highly resistant to all antimicrobials. ^[26] As a result, routine

surveillance of various bacterial aetiology cultures (blood, urine, tracheal aspirate) is critical in monitoring the spectrum of bacterial pathogens and their sensitivity pattern in a given area. Such information is not only vital for clinicians to be aware of new pathogen resistant strains that pose a threat to the population, but it also serves as a platform for launching effective empirical therapy. Knowing a hospital's baseline bacterial profile and antibiotic sensitivity helps to prevent unjustified antibiotic use in that hospital, which helps to make progress in the prevention of antibiotic resistance.

In the absence of a gold standard test, diagnosing sepsis can be difficult ^[27,28]. According to a recent international taskforce, "sepsis" should be defined as life-threatening organ failure induced by a dysregulated host response to infection, and the term "severe sepsis" should be abolished. ^[29] The Sequential (sepsis-related) Organ Failure Assessment (SOFA) score ^[29] was stressed by the taskforce, and organ dysfunction can be reflected by an increase in the SOFA score of 2 points or greater. The SOFA score has been shown to be a reliable predictor of ICU mortality. ^[30] Raith et al demonstrated that an increase in SOFA score of 2 or more points showed greater predictive accuracy for in-hospital mortality than SIRS criteria or qSOFA among patients admitted to an ICU with suspected infection. ^[31]

Procalcitonin is a peptide hormone produced mostly by the thyroid's parafollicular cells (C cells) and neuroendocrine cells in the lungs and intestine [32,33]. Healthy people have levels of procalcitonin in their blood that are below the detection limit of clinical testing. [33,34]. In response to proinflammatory stimuli, particularly those of bacterial origin, procalcitonin levels rise. It is mostly formed by the cells of the lungs and intestine in this scenario. Procalcitonin measurement can be used as a marker for severe sepsis produced by bacteria, and it correlates well with the severity of sepsis. [33,34] Procalcitonin tests are currently frequently employed in clinical settings. According to previous research, patients with infections generally have elevated serum procalcitonin levels. [34-36]

The infectious pathogen, the host immune response, underlying diseases, diagnostic processes, and medicinal therapies all interact to cause mortality in bacteremia patients. It can be difficult to separate these elements and their consequences. A comparison of mortality rates between patients who had positive blood cultures and those who had negative blood cultures could reveal the role of bacteremia in mortality. Bacteremia caused by at least two different organisms isolated from the same blood sample is known as polymicrobial bacteremia. [39,40]

Therefore, this study aimed to determine the epidemiology of bacterial infections in patients admitted in adult ICU of tertiary care hospital, their antibiotic sensitivity, total length of stay in ICU and 28 days all-cause mortality, to investigate the relationship of serum procalcitonin level and sofa score with mortality risk in critically ill patients with bacterial infections and to compare the mortality between patients who had culture positive and culture negative.



AIM AND OBJECTIVES

Aim: This study aimed to determine the epidemiology of bacterial infections and their clinical outcomes of patient admitted in adult intensive care unit of our institute.

Objectives: The objectives were as follows:

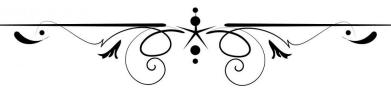
Primary objective: To find out the Incidence of various bacterial infections and their antimicrobial resistance in adult intensive care unit.

Secondary objectives were:

- 1. To find out the association of procalcitonin with all-cause mortality
- 2. To find out the association of SOFA score on the day of sending the cultures with allcause mortality
- 3. To find the total length of stay in ICU.
- 4. To find out the association of culture positive microorganism with 28 days all-cause mortality



REVIEW OF LITERATURE



REVIEW OF LITERATURE

Incidence of various bacterial infections

In a retrospective Study by **Kabrah et al** ^[41] (2021) to resistance profile of common bacteria isolated from blood stream, lower respiratory tract and urinary infections in intensive care unit in Saudi Arabia, compromised 96 patients admitted to the ICU at least for 48 hours and have a central venous catheter (CVC), from a period between November 1, 2020, and January 31, 2021. Their results showed LRTIs were the most common isolates (51 samples), followed by BSIs (28 samples) and UTIs (17 samples). The isolated pathogens in this study were *Klebsiella pneumoniae* (K. pneumoniae) (59.4%), Coagulase-negative *Staphylococci* (CoNS) (11.5%), *Escherichia coli* (E. coli) (8.4%), *Acinetobacter baumannii* (A. baumannii) (7.3%), and *Staphylococcus aureus* (S. aureus) (6.2%). BSI were frequently caused by CoNS (35.7%) and K. pneumoniae (35.7%), while Methicillin-resistant Staphylococcus aureus (MRSA) represented 10.7% of BSI. Vancomycin, Synercid, and Teicoplanin were the commonly used antibiotics and showed 100% sensitivity among S. aureus, including MRSA. They saw maximum resistance with aztreonam (96.4%), ampicillin (87.3%), followed by co-amoxiclav (83.9%), cotrimoxazole (79.5%) and cephalosporin group antibiotics).

A systemic review by **Zeinab et al.** ^[42] (2020) on resistance of Gram-Negative Bacteria to current Antibacterial agents and approaches to resolve it showed resistant Gram-negative bacteria such as Enterobacteriaceae, *Pseudomonas aeruginosa, Acinetobacter baumannii*, *Salmonella spp., Neisseria gonorrhoeae, Haemophilus influenza, Campylobacter, Helicobacter pylori*, and *Shigella* spp. are a real threat and a burden on the health and economy, which is why the WHO has published a priority list for antibiotic-resistant bacteria to discover and develop new treatments urgently.

Negm EM et al. ^[43] (2019) conducted a retrospective record-based cross-sectional study from the first of January to the last of December 2019 with a total of 45,221 diagnostic first-isolate culture/patient obtained from different ICUs in Zagazig University Hospitals in Egypt. Their results showed the positive blood isolate was the most prevalent infection site (32.37%) followed by sputum and urine isolates. Gram-negative microorganisms (74.41%) were the most common pathogens, with *Klebsiella pneumoniae* as the most frequently identified one with an incidence of 33.51% followed by *Escherichia coli* with 19.3% incidence. Antibiotic sensitivity showed that colistin is the most effective antibiotic with 96.2%, 94.7%, and 89.9% sensitivity for Klebsiella, E. coli, and Acinetobacter, respectively, while carbepenems

sensitivity was extremely low, showing 19.5% and 19% imipenem and meropenem sensitivity for Klebsiella, 48% imipenem and 52.7% meropenem sensitivity for E. coli, 20.1% imipenem and 20.3% meropenem sensitivity for Acinetobacter, and 17.3% imipenem and 15.2% meropenem sensitivity for *Pseudomonas aeruginosa*. Fungal infection represented less than 1%. They concluded that their study provides a local baseline epidemiological data which describes the extent of the ICU infections problem in this tertiary care hospital.

Mogasale et al. ^[44] (2019) did a descriptive analysis of antimicrobial resistance patterns of WHO priority pathogens isolated in children from a tertiary care hospital in India. Of 12,256 culture specimens screened, 2335 (19%) showed culture positivity, of which 1556 (66.6%) were organisms from the WHO-PPL. E. coli was the most common organism isolated (37%), followed by Staphylococcus aureus (16%). 72% of E. coli were extended-spectrum beta-lactamases (ESBL) producers, 55% of Enterobacteriaceae were resistant to 3rd generation cephalosporins due to ESBL, and 53% of Staph. Aureus were Methicillin-resistant. This kind of local priority difference needs to be recognized in local policies and practices.

In a cross-sectional, retrospective study by **Savanur SS et al.** ^[45] (2019) for a period of 1 month in October 2017 on a total of 195 patients of ICU of tertiary care hospital, most commonly isolated bacteria were mostly gram-negative bacilli, of which Escherichia coli was (18.6%), Acinetobacter (14.5%), Klebsiella (11.6%), Pseudomonas (9.8%), and Proteus (1.74%). Among the gram-positive organisms, coagulase negative staphylococcus (CoNS) (15.6%) was most commonly isolated followed by Streptococcus (2.32%). Fungal growth was also seen in 26 (15.11%) samples. These findings are concreting the fact that Gramnegative bacterial infections are increasing in ICUs, leading to inappropriate selection of antibiotics.

Garg VK et al. ^[46] (2019) evaluated microbial and Antibiotic Susceptibility Profile among isolates of clinical samples of cancer patients admitted in the Intensive care unit at Regional Tertiary Care Cancer Center. Bacteria isolated were *Escherichia coli*, *Acinetobacter* spp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus and Enterococcus* spp.. In positive bacterial cultures, majority were Gram-negative isolates (84.14 %). Klebsiella was the most common gram-negative isolate (34.78%) and Enterococcus spp. were the most common Gram-positive isolates (61.53%). Majority of the Gram-negative isolates were sensitive to Imipenem, Meropenem, and Colistin sensitivity among Gram-negative isolates was 100%. Linezolid, Teicoplanin and Vancomycin were most sensitive

antimicrobials against the Gram-positive bacteria. They concluded that regular monitoring of the pattern of resistance of bacteriological isolates in cancer patients is critical to develop antibiotic policy to combat these infections and reduce morbidity and mortality.

Gill et al. ^[47] (2016) did a_hospital based retrospective cross-sectional study to evaluate the bacteriological profile and antibiotic resistance pattern in blood stream infection in critical care units of a tertiary care hospital in North India. The data was collected by reviewing the records of 565 patients admitted to various critical care units (ICUs) of the hospital from May 2015 to March 2016. Out of these isolates 74(53%) were Gram positive bacteria (GPB) and 55(39.3%) were Gram negative bacteria (GNB) and 11(7.9%) were non-albicans Candida. The predominant bacterial isolate was Coagulase negative staphylococcus (CoNS) 49 (34.5%) followed by Acinetobacter 22 (15.4%) and Staphylococcus aureus 20 (14%). The antimicrobial resistance profile of both Gram positive and Gram-negative isolates showed a high prevalence of resistance among them.

Qadeer et al. ^[48] (2016) conducted a cross-sectional analysis of 802 patients from a medical intensive care unit (ICU) of Shifa International Hospital, Islamabad. Specimens collected were from blood, urine, endotracheal secretions, catheter tips, tissue, pus swabs, cerebrospinal fluid, ascites, bronchoalveolar lavage (BAL), and pleural fluid. They concluded Gram-negative bacteria were more frequent as compared to gram-positive bacteria. Most common bacterial isolates were *Acinetobacter* (15.3%), *Escherichia coli* (15.3%), *Pseudomonas aeruginosa* (13%), and Klebsiella pneumoniae (10.2%), whereas Enterococcus (7%) and methicillin resistant *staphylococcus aureus* (MRSA) (6.2%) were the two most common gram-positive bacteria.

Moolchandani K et al. ^[49] (2016) studied the occurrence of different types of HAIs in patients admitted to various ICUs of JIPMER and the AMR pattern of the bacterial pathogens isolated during the period from April 2015 to March 2016. Most common culture positive clinical specimen received was tracheal aspirate (29.9%) followed by exudate (22.7%). Acinetobacter spp from tracheal aspirate and Pseudomonas spp from blood specimens were the most common organisms isolated; whereas Escherichia coli was the predominant organism found in urine, exudate and sterile fluid specimens. Antimicrobial susceptibility pattern revealed that most of Gram-Negative Bacilli (GNB) was Multi Drug Resistant (MDR) i.e., resistant to three or more class of antibiotics such as cephalosporins, carbapenems, aminoglycosides, tetracyclines and fluoroquinolones. The prevalence of Methicillin resistant

Staphylococcus aureus (MRSA) and Vancomycin resistant Enterococci (VRE) were found to be 40.6% and 11.9% respectively. The increasing trend AMR among the hospital acquired pathogens such as MDR-GNBs, MRSA and VRE pose a great threat to HCWs as well as to the other critically ill patients of the ICUs. The study on AMR surveillance is the need of the hour as it helps the centers to generate local antibiogram which further helps in formulating the national data.

In a multicentric cohort study of 17 430 adults with culture-positive sepsis admitted to 104 US hospitals by **Rhee C et al.** ^[50], 67.0% received empiric broad-spectrum antibiotics, but resistant gram-positive organisms were isolated in only 13.6% of patients and resistant gram-negative organisms in 13.2%. The most common pathogens were *Escherichia coli* (5873 [33.7%]), S aureus (3706 [21.3%]), and *Streptococcus* species (2361 [13.5%]). Among 15 183 cases, most patients (12 398 [81.6%]) received adequate empiric antibiotics. Empiric therapy targeted resistant organisms in 11 683 of 17 430 cases (67.0%; primarily vancomycin and anti-Pseudomonal β-lactams), but resistant organisms were uncommon (MRSA, 2045 [11.7%]; CTX-RO, 2278 [13.1%]; VRE, 360 [2.1%]; ESBLs, 133 [0.8%]). The patients with community onset sepsis did not have resistant pathogens, yet broad-spectrum antibiotics were frequently administered. They concluded that both inadequate and unnecessarily broad empiric antibiotics were associated with higher mortality.

Khan et al. ^[51] (2012) did a Prospective descriptive study to evaluate the microbiological spectrum and susceptibility pattern of pathogens in intensive care unit (ICU) and intermediate care unit (IMCU) in a single medical center from June 2011 to May 2012. *Acinetobacter spp, Klebsiella species and Pseudomonas* species were the most common Gram-negative isolates, while *Staph. Aureus and Coagulase-negative staphylococci* (CoNS) were the two leading Gram-positive isolates. 81% Acinetobacter spp were found Multidrug- Resistant. They concluded that the high incidence of reduced antibiotic susceptibility among Gram negative bacteria in ICUs suggests that more effective strategies are needed to control the selection and spread of resistant organisms.

Radji M et al. ^[52] (2010) evaluated the sensitivity pattern of bacterial pathogens in 722 patients of intensive care unit (ICU) of a tertiary care of Jakarta Indonesia, during January 2009 to March 2010. They found most predominant isolate was *Pseudomonas aeruginosa* (*P. aeruginosa*) (26.5%) followed by *Klebsiella pneumoniae* (*K. pneumoniae*) (15.3%) and

Staphylococcus epidermidis (14.9%). They concluded Most bacteria isolated from ICU were resistant to the third generation of cephalosporins, and quinolone antibiotics.

Bayram A et al. ^[53] (2006) found in a survey in Turkey that most common isolates microorganisms were: *Pseudomonas aeruginosa* (20.3%), Candida species (15%) and *Staphylococcus aureus* (12.9%). Among the Gram-negative microorganisms *P. aeruginosa* were mostly resistant to third-generation cephalosporins (71.3–98.1%), while *Acinetobacter baumannii* were resistant in all cases to piperacillin, ceftazidime and ceftriaxone. Isolates of S. aureus were mostly resistant to penicillin, ampicillin, and methicillin (82–95%), whereas coagulase-negative staphylococci were 98.6% resistant to methicillin and in all cases resistant to ampicillin and tetracycline. They concluded that in order to reduce the emergence and spread of antimicrobial-resistant pathogens in ICUs, monitoring and optimization of antimicrobial use in hospitals are strictly recommended. Therefore, local resistance surveillance programs are of most value in developing appropriate therapeutic guidelines for specific infections and patient types.

PROCALCITONIN

Bo Li et al. ^[54] (2015) investigated the relationship between serum procalcitonin level and mortality risk in critically ill patients with ventilator-associated pneumonia in 115 critically ill patients with ventilator-associated pneumonia admitted to the ICU. They showed that serum procalcitonin level was not associated with age, gender, or other comorbidities. Univariate Cox regression model showed that high serum procalcitonin level was associated increased risk of morality within 2 months after diagnosis. They concluded that high serum procalcitonin level is an independent prognostic biomarker of mortality risk in critically ill patients with ventilator-associated pneumonia, and it's a promising biomarker of prognosis in critically ill patients.

The PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients (PRORATA) trial, a large multicenter study in 5 academic hospitals in France conducted by **Bouadma L et al.** ^[55] that included 621 adult patients with suspected bacterial infection at admission or during their stay in the ICU. This study was unique in the ICU-based trials in that the algorithm included an initial procalcitonin to help assess whether to start antibiotics in addition to subsequent daily procalcitonin levels to help decide when to stop antibiotics. The cutoff procalcitonin value for discontinuation was <0.5 µg/L or a decrease from peak value by ≥80%. The procalcitonin group had significantly more days at 28 days without antibiotics (14.3 days vs 11.6 days) and an overall 23% relative reduction in days of antibiotic exposure (mean 10.3 vs 13.3 days)

Alvarez MJ et al. ^[56] (2009) showed the diagnostic efficacy and prognostic value of procalcitonin for sepsis in a consecutive series of 103 patients with suspected sepsis in the intensive care unit over a 2-year period. In their study, multivariate Cox regression analysis revealed that procalcitonin was not independently associated with mortality. They concluded Assessment score, age, and gender showed to be helpful to improve the prediction of mortality risk, but not procalcitonin.

SOFA

Lie KC et al. ^[57] conducted a multinational multicenter prospective observational study in Southeast Asia to know the utility of SOFA score, management and outcomes of sepsis. They recruited hospitalized adults within 24 h of admission with community-acquired infection at nine public hospitals in Indonesia (n = 3), Thailand (n = 3), and Vietnam (n = 3). In patients with organ dysfunction (total SOFA score \geq 2), they analyzed sepsis management and outcomes and evaluated mortality prediction of the SOFA scores. Organ failure was defined as the maximum SOFA score \geq 3 for an individual organ system. The results showed total SOFA score on admission of those who subsequently died was significantly higher than that of those who survived (6.7 vs. 4.6, p < 0.001). The number of organ failures showed a significant correlation with 28-day mortality, which ranged from 7% in patients without any organ failure to 47% in those with failure of at least four organs (p < 0.001) inferring that SOFA scores are associated with mortality.

Raith EP et al. ^[58] (2017) did a retrospective cohort analysis of 184 875 patients with an infection-related primary admission diagnosis in 182 Australian and New Zealand intensive care units (ICUs) from 2000-2015 and externally validate and assess the discriminatory capacities of an increase in SOFA score by 2 or more points, 2 or more SIRS criteria, or a qSOFA score of 2 or more points for outcomes among patients who are critically ill with suspected infection. Results showed SOFA score increased by 2 or more points in 90.1% patients. They concluded that among adults with suspected infection admitted to an ICU, an increase in SOFA score of 2 or more had greater prognostic accuracy for in-hospital mortality than SIRS criteria or the qSOFA score.

Mortality between culture positive and culture negative

Lakbar I et al. ^[59] (2021) compared the ICU mortality rates between patients with ICU-acquired pneumonia due to highly antimicrobial-resistant (HAMR) bacteria and those with ICU-acquired pneumonia due to non HAMR bacteria in multicenter, retrospective cohort study. Using the French National Surveillance Network for Healthcare Associated Infection in ICUs ("REA-Raisin") database, gathering data from 200 ICUs from January 2007 to December 2016 and The HAMR group was associated with increased ICU mortality (40.3% vs. 30%, odds ratio (OR) 95%, CI 1.57 [1.45–1.70], P< 0.001). They were concluded that

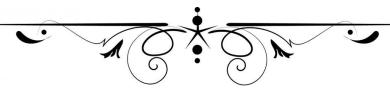
ICU acquired pneumonia due to HAMR bacteria is associated with an increased ICU mortality rate, ICU length of stay, and mechanical ventilation duration.

Søgaard M et al. ^[60] (2011) compared mortality among patients with community acquired bacteremia with mortality among patients with negative blood cultures and determined the effects of bacteremia type and comorbidity level on mortality among patients with positive blood cultures in a cohort of 29273 adults. They observed mortality was higher among patients with Gram-positive (adjusted 0-2-day MRR 1.9, 95% CI: 1.6-2.2) and polymicrobial bacteremia (adjusted 0-2-day MRR 3.5, 95% CI: 2.2-5.5) than among patients with Gram-negative bacteremia (adjusted 0-2-day MRR 1.5, 95% CI 1.2-2.0). They concluded that Community-acquired bacteremia was associated with an increased risk of mortality in the first week of medical ward admission and there was higher mortality among patients with Gram-positive and polymicrobial bacteremia compared with patients with Gram-negative bacteremia and negative cultures emphasizes the prognostic importance of these infections.

Lambert et al. ^[61] (2011) analyzed data collected for surveillance of health-care-associated infections and focused on the most frequent causative microorganisms prospectively. They obtained data for ten European countries (Austria, Belgium, Croatia, France, Italy, Latvia, Portugal, Slovakia, Scotland, and Spain). The final database provided data for 537 intensive-care units that admitted 119 699 patients for more than 2 days to 537 intensive-care units in ten countries between Jan 1, 2005, and Dec 31, 2008. Their results showed antimicrobial resistance did not significantly increase length of stay; the hazard ratio for discharge, dead or alive, for sensitive microorganisms compared with resistant microorganisms (all four combined) was 1·05 (0·97–1·13) for pneumonia and 1·02 (0·98–1·17) for bloodstream infections. P aeruginosa had the highest burden of health-care-acquired infections because of its high prevalence and pathogenicity of both its drug-sensitive and drug-resistant strains. Hence, the conclusion was Health-care-associated bloodstream infections and pneumonia greatly increase mortality and pneumonia increase length of stay in intensive-care units; the additional effect of the most common antimicrobial resistance patterns is comparatively low.



MATERIALS & METHODS



MATERIALS AND METHODS

This study was performed after approval from Institutional Ethical Committee (letter no.

AIIMS/IEC/2019-20/993) and obtained informed consent from the patients or their relatives

and informed that their data would be used unless they disagreed with being included. This

study followed the Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) reporting guideline for cohort studies.

Type of study: Prospective observational cohort study

Period of recruitment: Between November 3, 2020 to November 2, 2021. (Due to COVID-

19, this study was time bound study and recruitment was done over one year.)

Place of study: The study was conducted at adult intensive care unit (AICU) of Department

of Anaesthesiology and Critical Care, AIIMS Jodhpur.

Study participants: All patients admitted in adult intensive care unit (AICU) of either sex,

of all age, who were consented for the study and needing the culture and sensitivity test were

included in the study.

Exclusion criteria's:

• Patient not willing to participate in study

• Patients were not having suspicion of infection

Culture sample Sites:

We included clinical cultures from the blood, respiratory, and urine.

Preparation of patients for sample collection

• For blood culture, two samples each of 10 ml, one from central venous catheter and

another sample taken from any peripheral vessel. In patients who do not have any central

venous catheter present, both the blood samples are taken from periphery but from two

different sites under aseptic precautions.

- Tracheal sample was taken from all the intubated patients and sputum sample from nonintubated patients with all aseptic precautions.
- Urine sample was collected from catheterized patients under all aseptic precautions.

All the samples were properly labelled and sent to microbiology lab. Culture media used: blood agar, Macconkey agar and chocolate agar, Urochrome agar, Brain heart infusion broth, Adult aerobic BACTEC blood culture bottles (B D diagnostics Ltd).

Blood culture bottle were incubated in automated culture system (BACTEC) for 5 days. Whenever machine beeped positive with any blood culture bottle, it was processed further. Direct gram staining was done from blood sample in the culture bottle. On gram staining, the microorganism was identified to be gram positive or gram negative, the blood sample was inoculated on Blood agar, MacConkey's culture media and Chocolate agar. Isolated colonies which grew on these culture media, were further processed according to its biochemical reaction and antibiotic susceptibility testing was performed.

Colonies were subjected to gram staining and gram-negative and gram-positive organisms were isolated. All bacteria were identified by standard microbiological methods, and antibiotic sensitivity/resistance was performed using the disk diffusion technique and sometimes by means of the automation device, *Vitek*®, according to Clinical and Laboratory Standards Institute (CLSI) guidelines 2020.

Urine sample was processed and seen under wet mount. Then it was inoculated and incubated in Urine Chrome media for 24 hours. When the colonies grew on the media, then its gram staining was done. It was further processed according to the biochemical reaction and antibiotic susceptibility testing was done.

Direct gram stain was done for tracheal aspirate sample and sample was further inoculated in Blood agar and MacConkey's agar at $35 \pm 2^{\circ}$ C for 24 to 48 hours. If the media showed growth, then gram staining was done. It was further processed according to the biochemical reaction and antibiotic susceptibility testing was done.

Pathogens of Interest

We focused on pathogens commonly encountered in routine practice. Gram-negative organisms included Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella species, Pseudomonas aeruginosa, and Gram-positive organisms included S aureus,

Streptococcus species, and Enterococcus species. Sensitivity for all isolates was done using maximum possible antibiotics.

Surveillance cultures and cultures positive for other organisms which are skin commensals and oral commensals were excluded, including coagulase-negative Staphylococcus species (because it can be difficult to distinguish contaminants vs true infections) isolated from blood/respiratory samples.

Antibiotic Susceptibilities

We assessed each potential antibiotic-pathogen combination using antibiotic susceptibilities derived from in vitro reports as resistance, Intermediate and susceptible generated by Department of Microbiology, All India Institute of Medical sciences Jodhpur. In some cases, susceptibilities to specific antibiotics administered were not tested but patients were treated. On assumption of knowledge of the spectrum of activity for each antibiotic- pathogen combination.

For blood culture-ampicillin/penicillin, cefoxitin, tetracyclines, co-trimoxazole, erythromycin, clindamycin, ciprofloxacin, ceftriaxone, cefepime, gentamycin, ampicillin/sulbactam, imipenem, meropenem, piperacillin-tazobactam, amikacin, colistin, netilmicin, levofloxacin, vancomycin, teicoplanin, moxifloxacin, minocycline, tigecycline, high level gentamycin and linezolid.

For urine culture- ampicillin, gentamycin, cotrimoxazole, nitrofurantoin, fosfomycin, ceftriaxone, ciprofloxacin, amikacin, piperacillin-tazobactam, ertapenem, imipenem, meropenem, tigecycline, colistin

For tracheal aspirate- cefoperazone/sulbactam, co-trimoxazole, piperacillin/tazobactam, ceftriaxone, gentamicin, ertapenem, minocycline, colistin, tigecycline, amikacin, netilmicin, aztreonam, penicillin, cefoxitin, tobramycin, erythromycin, levofloxacin, cotrimoxazole

Data collection

All the demographic characteristics such as age and gender, clinical data like comorbidity (diabetes mellitus type 1 and type 2, hypertension, chronic kidney disease, acute kidney injury, coronary artery disease, hypothyroidism, alcoholic liver disease, COPD, asthma),

previous antibiotic, procalcitonin and SOFA score (on the day of sample collection), duration of ICU stay, 28 days all-cause mortality were also noted.

The microbiologic assessment data- microorganism isolated from sample and its antibiotic susceptibility was noted.

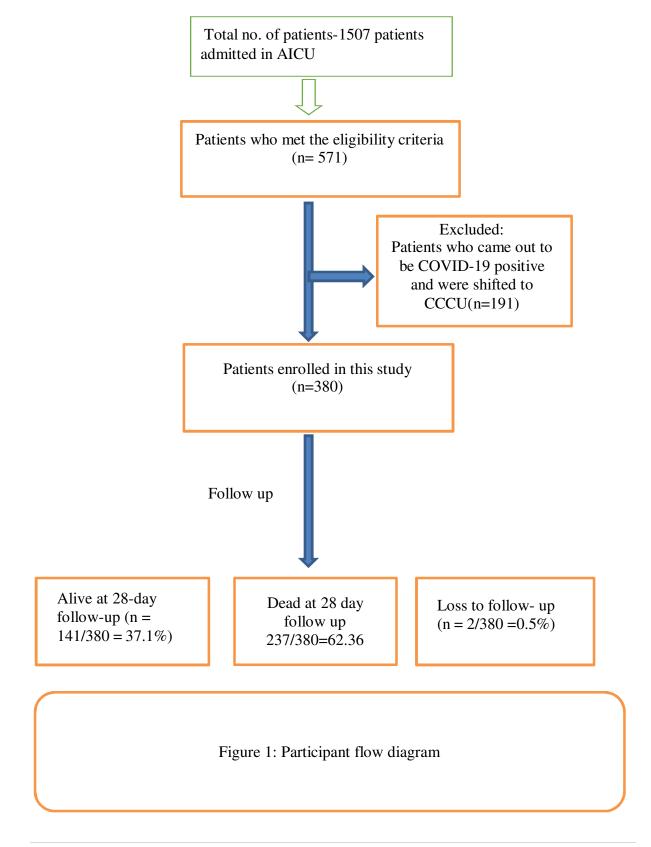


OBSERVATION & RESULTS



OBSERVATIONS AND RESULTS

Figure 2: Study flow diagram



Statistical analysis

The collected data were compiled in a Microsoft Excel spread sheet and analysed statistically using Statistical Package for Social Sciences® version 23 (IBM SPSS® Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp., NY, USA).

The normality of variables was checked using the Kolmogorov-Smirnov test. The normally distributed continuous data was expressed as mean \pm SD and the non-normally distributed continuous and the ordinal data as median and interquartile range, while the categorical variables were expressed as frequencies or percentages. Pearson's Chi-square test was used for comparing categorical variables. The scalar variables were compared using the Mann-Whitney U test for non-parametric data and by t-test for the parametric variable. A multiple logistic regression analysis model was constructed incorporating a statistically significant difference in the two groups, and Odds ratio with the 95% CI calculated for each of the variables. We analysed the patients' survival from the admission to ICU discharge by Kaplan-Meier survival analysis. A two-sided p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 1560 samples were included in the study from 380 patients. Out of which, 240 were male patients and 140 female patients. The 62.37% died, 37.11% discharged and 0.53% took LAMA.

Table 1: Demographic variables and outcome

Demographic Variab	Demographic Variables and outcome		%age
	16-30	58	15.26
	31-40	44	11.58
Age (yrs)	41-50	63	16.58
	51-60	76	20.00
	≥61	139	36.58
	Male	240	63.16
Gender	Female	140	36.84
	Death	237	62.37
Outcome	Discharge	141	37.11
	LAMA	2	0.53

The majority of patients (36.58%) were aged >61 years. Majority of the patients (63.16%) were male. Approximately 62.37% patients died in our study.

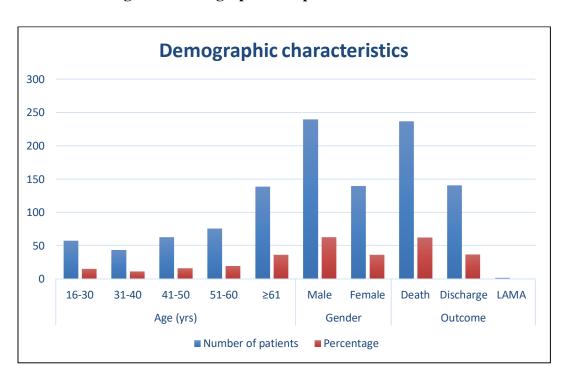


Figure 3: Demographic and patients characteristics

Table 2: Mean age and median ICU stay of survivors and non-survivors

Variables	Non- survivors	Survivors P va	
Age (yrs.) (Mean ± SD)	54.7 ± 16.73	51.52 ± 18.99	0.0006
ICU stays (days) Median (IQR)	8 (5-15)	8 (5-14)	0.6

The overall mean age of the patient was 53.66 years, The mean age was lower in discharged than death patients $(51.52 \pm 18.99 \text{ v/s } 54.7 \pm 16.73)$. This was statistically significant using independent sample t-test (p value=0.0006).

The median duration of stay of the patients in the ICU was 8 days with IQR of 5-14 days in our study population. Using Mann Whitney U test, the duration of ICU stay was not statistically significant among survivors and non survivors. (p value=0.6)

Figure 4: Box whisker plots showing comparison of mean age among survivors and non survivors

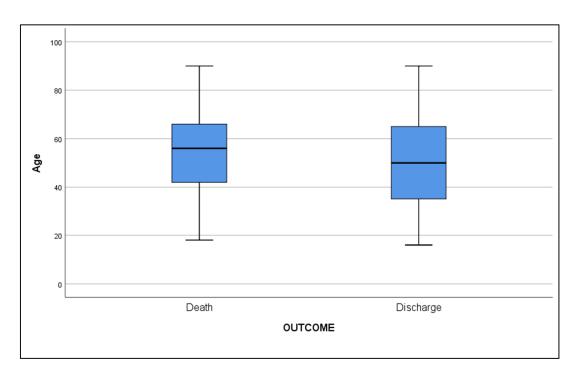


Figure 5: Box-whisker plots showing comparison of length of icu stay of patients among survivors and non survivors

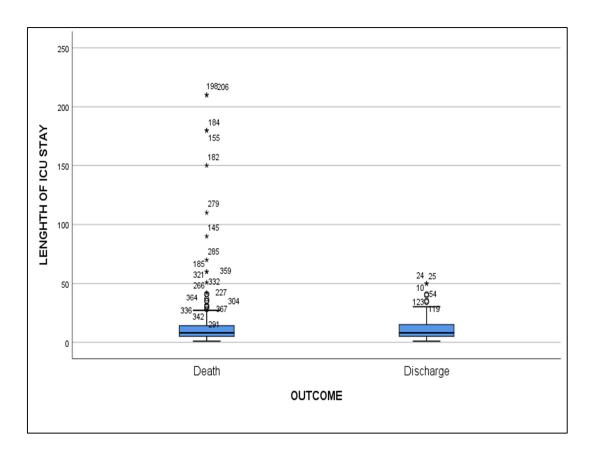


Table 3: Median ICU stay of gram positive and gram-negative infections

	ICU stay		
Variables	Median	IQR	
	Median	(Q1-Q3)	
Gram negative	12	6-19	
Gram positive	15	7-30.5	

The median length of ICU stay among gram-positive bacteraemia patients was slightly longer than gram negative bacteraemia patients (15 vs 12 days). Using Mann Whitney U test, this was not statistically significant. (p value=0.13)

Table 4: Epidemiology of Comorbid illnesses among patients

Comorbidity	%age	Mortality
	(Number of patients)	
No comorbidity	58.4 (222)	57.6%
Diabetes Mellitus	21.5 (82)	73.1%
Hypertension	12.3 (47)	95.7%
Hypothyroidism	1.5 (6)	66.6%
Chronic Kidney Disease	3.9 (15)	66.6%
Acute Kidney Injury	1.3 (5)	60%
Coronary artery disease	2.1 (8)	62.5%
Chronic lung disease	2.1 (8)	75%
Lung illness (COPD, Asthma, TB)	1.8 (7)	71.4%

The 58.4% patients did not have any comorbidity. Diabetes mellitus was the most common comorbidity followed by hypertension.

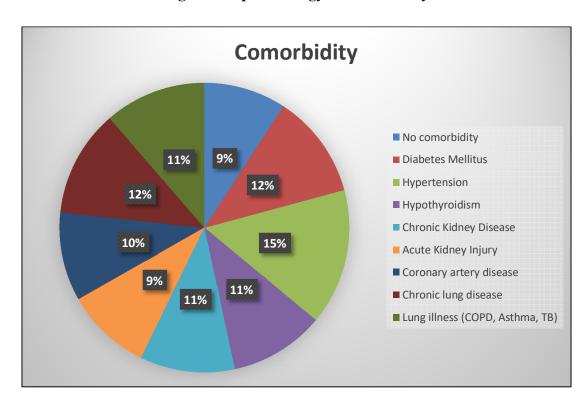


Figure 6: Epidemiology of comorbidity

Table 5: Association of number of comorbidities with mortality

Number of comorbidities	Number of patients	Mortality %(n)	P value
No comorbidity	222	57.6 (128)	0.022
Comorbidity	158	69.6 (109)	

Patients with comorbidity showed high mortality (69.6%) as compared to no comorbidity group (57.6%). Pearson's chi square test was applied to compare mortality between no comorbidity and with comorbidity and it was statistically significant. (p value=0.022)

Table 6: Distribution of clinical specimens

Specimen	Total			
Specifici	n	%		
Urine	334	21.41		
Tracheal	350	22.43		
blood	876	56.17		
Total	1560	100.00		

Total 1560 clinical specimens from 380 adult patients were collected during study period. Out of which, 876 were total blood samples, tracheal samples were 350 and urine samples 334.

Figure 7: Distribution of clinical specimens

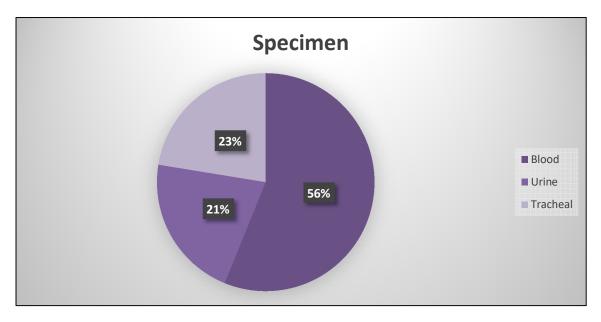


Table 7: Culture positivity among specimens

		Cul				
Specimen	Positive		Positive Negative		T	otal
	n	%	n %		n	%
Blood	279	31.85	597	68.15	876	56.15
Urine	134	40.12	200	59.88	334	21.41
Tracheal	303	86.57	47	13.43	350	22.44
Total	716	45.90	844	54.10	1560	100.00

The 876 blood samples were sent for culture and sensitivity. Out of 876 samples, 279 (31.85%) samples were positive and 597 (68.1%) had negative blood cultures. Total 334 urine samples were sent for culture and sensitivity. Out of 334 samples, 134 (40.12%) samples were positive and 200 (59.88%) were negative. Total 350 tracheal samples were sent for culture and sensitivity. Out of 350 samples, 303 (86.57%) samples were positive and 47 (13.43%) were negative. Among culture positive samples, 42.31% samples were tracheal, 38.96% samples from blood and 18.71% samples of urine.

Table 8: Epidemiology of microorganisms

	Number of samples	%age
Sterile	844	54.1
Gram negative bacteria	431	27.63
Gram positive bacteria	55	3.52
Budding Yeast Cells (Fungus)	13	0.83
Insignificant growth	37	2.37
Mixed growth	21	1.35
Colonizers	29	1.86
Commensals	65	4.17
Contaminants	65	4.17
Total	1560	100

Among various cultures sent 844 (54.1%) samples were sterile. The most common pathogens isolated were Gram negative microorganisms 431 (27.63%). The Gram-positive microorganisms found in 55 (3.5%) samples, insignificant growth in 37 (2.37%), colonisers in 29 (1.86%), mixed growth in 21 (1.35%), budding yeast cells in 13 (0.83%) and commensals and contaminants in 65 (4.17%) samples.

Table 9: Patients with polymicrobial infection

Polymicrobial infection		
Discharge	10	
Death	11	
Total	21	

21 patients had polymicrobial infection, out of which 11 patients died. Mortality was 55% in patients with polymicrobial infection.

Table 10: Distribution of various micro-organisms in adult ICU

0	Т	Total		
Organism	n	%		
Acinetobacter baumannii	163	10.5		
Klebsiella pneumoniae	111	7.12		
E. coli	60	3.85		
Pseudomonas aeruginosa	37	2.18		
Enterococcus	25	1.6		
Candida species	12	0.77		
Enterobacter	11	0.71		
Enterococcus faecium	10	0.64		
Burkelholderia cepacia Complex	9	0.58		
Staphylococcus haemolyticus	8	0.51		
Klebsiella oxytoca	7	0.45		
Serratia marcescens	7	0.45		
Enterobacter cloacae	5	0.32		
Enterococcus faecalis	4	0.26		
Providencia	4	0.26		
Providencia rettgeri	3	0.19		
Providencia stuartii	3	0.19		
Staphylococcus aureus (MRSA)	3	0.19		

Staphylococcus aureus (MSSA)	3	0.19
Citrobacter freundii	2	0.13
Proteus mirabilis	2	0.13
Staphylococcus epidermidis	2	0.13
Stenotrophomonas maltophila	2	0.13
Aerumonas hydrophila/punctata	1	0.06
Candida albicans	1	0.06
Cupriavidus pauculus	1	0.06
Enterobacter aerogenes	1	0.06
Proteus vulgaris	1	0.06

The frequent microorganism isolates were in decreasing order as: Acinetobacter baumannii (10.5%), Klebsiella pneumoniae (7.12%), E. coli (3.85%), Pseudomonas aeruginosa (2.18%), Enterococcus (1.6%), Mixed Growth (1.22%), Candida species (0.77%), Enterobacter (0.71%), Enterococcus faecium (0.64%), Burkelholderia cepacia Complex (0.58%).

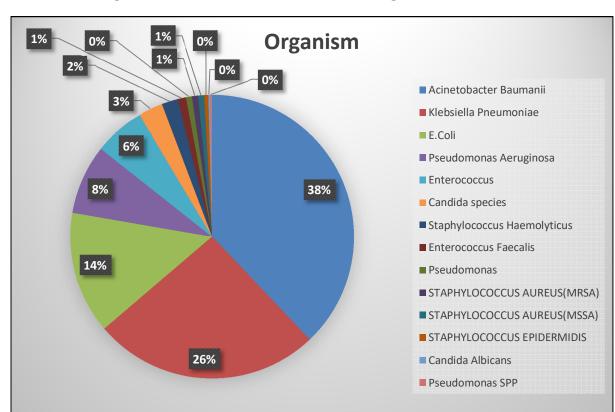


Figure 8: Distribution of bacterial microorganisms in our ICU

Table 11: The frequency of prominent microorganisms isolated from various samples

Organism	В	Blood	Urine		Tracheal		Total	
O'Igumsm	n	%	n	%	n	%	n	%
Acinetobacter baumannii	62	31.31	3	6.67	98	53.85	163	38.35
E. coli	30	15.15	12	26.67	18	9.89	60	14.12
Enterococcus	22	11.11	17	37.78	0	0.00	39	9.18
Klebsiella pneumoniae	59	29.80	12	26.67	40	21.98	111	26.12
Pseudomonas aeruginosa	14	7.07	1	2.22	23	12.64	38	8.94
Staphylococcus aureus (MRSA)	2	1.01	0	0.00	1	0.55	3	0.71
Staphylococcus aureus (MSSA)	1	0.51	0	0.00	2	1.10	3	0.71
Staphylococcus haemolyticus	8	4.04	0	0.00	0	0.00	8	1.88
Total	198	100.00	45	100.00	182	100.00	425	100.00

Acinetobacter baumannii isolates were most commonly found (31.3%), followed by Klebsiella pneumoniae (29.8%) in blood specimen. The Enterococcus species were most common 37.78% followed by 26.67% Klebsiella pneumoniae and E coli 26.67% in urine specimen while Acinetobacter baumannii isolates were 53.85% and Klebsiella pneumoniae (21.9%) in tracheal specimen.

Table 12: Mortality among various micro-organisms

Organism	De	eath	Disc	harge	LA	MA	Total	
Organishi	n	%	n	%	n	%	n	%
Acinetobacter baumannii	114	69.9	49	30.1	0	0	163	10.5
Klebsiella pneumoniae	78	70.3	33	29.7	0	0	111	7.12
E. coli	29	48.3	31	51.7	0	0	60	3.85
Pseudomonas aeruginosa	23	62.1	15	40.5	0	0	37	2.18
Enterococcus	20	80	5	20	0	0	25	1.6
Candida species	12	100	0	0	0	0	12	0.77
Enterobacter	8	72.7	3	27.3	0	0	11	0.71
Enterococcus faecium	6	60	4	40	0	0	10	0.64
Burkholderia cepacia Complex	6	66.7	3	33.3	0	0	9	0.58
Staphylococcus haemolyticus	6	75	2	25	0	0	8	0.51
Klebsiella oxytoca	5	71.4	2	28.6	0	0	7	0.45
Serratia marcescens	6	85.7	1	14.3	0	0	7	0.45
Enterobacter cloacae	3	60	2	40	0	0	5	0.32
Enterococcus faecalis	3	75	1	25	0	0	4	0.26
Providencia	2	50	2	50	0	0	4	0.26
Providencia rettgeri	0	0	3	100	0	0	3	0.19
Providencia stuartii	2	66.7	1	33.3	0	0	3	0.19
Staphylococcus aureus (MRSA)	2	66.7	1	33.3	0	0	3	0.19
Staphylococcus aureus (MSSA)	1	33.3	2	66.7	0	0	3	0.19
Citrobacter freundii	2	100	0	0	0	0	2	0.13
Proteus mirabilis	1	50	1	50	0	0	2	0.13
Staphylococcus epidermidis	2	100	0	0	0	0	2	0.13
Stenotrophomonas maltophila	2	100	0	0	0	0	2	0.13
Aerumonas hydrophila/punctata	0	0	1	100	0	0	1	0.06
Candida albicans	1	100	0	0	0	0	1	0.06
Cupriavidus pauculus	1	100	0	0	0	0	1	0.06
Enterobacter aerogenes	0	0	1	100	0	0	1	0.06
Proteus vulgaris	0	0	1	100	0	0	1	0.06

Among bacterial infections, *Klebsiella pneumoniae* showed highest mortality (70.3%) followed by *Acinetobacter* (69.9%). Among Gram positive infections, *Staphylococcus aureus* (MRSA) showed highest mortality (66.7%).

Table 13: Number of deaths, discharge and LAMA in gram negative, gram positive and fungal isolates

	Death		Disch	narge	Total		
	n	%	n	%	n	%	
Gram positive bacteria	32	68	15	27.27	47	12.3	
Gram negative bacteria	54	63.5	31	34.57	85	22.3	
Fungus	13	100	0	0	13	0.83	

Among bacterial infections, Gram positive bacterial infection showed 68% mortality whereas Gram negative bacteria showed 63.5% mortality. Using Pearson's Chi Square test, it was statistically significant (P value=0.000). Mortality was 100% in fungal infections.

ANTIBIOTIC SUSCEPTIBILITY PATTERNS OF COMMON BACTERIA ISOLATED FROM ICU

GRAM NEGATIVE BACTERIA

Table 14: Antibiotic susceptibility pattern of Acinetobacter baumannii

Antibiotics	Sen	sitive		nediate sitive	Resistance		
	n	%	n	%	n	%	
Ampicillin	1	7.6	3	23	9	69.2	
Amikacin	20	12.26	1	0.61	142	87.11	
Aztreonam	3	11.5	0	0.00	23	88.4	
Cotrimoxazole	14	8.59	3	1.84	121	74.23	
Cefoperazone-sulbactam	31	32.6	9	9.4	55	57.8	
Colistin	129	79.14	34	20.86	0	0.00	
Ciprofloxacin	5	5.7	0	0.00	82	94.2	
Cefepime	9	5.52	0	0.00	154	94.47	
Ceftriaxone	4	2.45	2	1.23	157	96.31	
Ertapenem	0	0.00	0	0.00	20	100	
Fosfomycin	0	0.00	0	0.00	3	100	
Gentamicin	16	9.81	0	0.00	146	89.57	
Imipenem	8	4.9	0	0.00	155	95.09	
Levofloxacin	22	13.49	18	11.04	123	75.46	
Minocycline	138	84.6	20	12.27	5	3.07	
Meropenem	4	2.45	0	0.00	159	97.54	
Netilmicin	8	15.6	0	0.00	43	84.3	
Nitrofurantoin	0	0.00	0	0.00	3	100	
Piperacillin-tazobactam	15	9.20	2	1.23	136	83.44	
Tigecycline	69	89.6	7	9.09	1	1.2	
Ceftazidime	1	3.3	1	3.3	28	93.3	
Tobramycin	1	25	0	0.00	3	75	
Amp-sulbactam	7	21.8	2	6.2	21	65.6	
Polymyxin B	1	100	0	0.00	0	0.00	

Acinetobacter was highly resistant to 3rd generation cephalosporins (96.31% ceftriaxone) and 4th-generation cephalosporins (94.47% cefepime), beta lactam antibiotics (piperacillin tazobactam 83.44%), aminoglycosides (89.5% gentamicin and 87.11% amikacin), and quinolones (75.46% levofloxacin). The most effective drug is Colistin which showed 79.14% sensitivity and 20.8% intermediate sensitivity followed by minocycline which showed 84.6% sensitivity and 12.2% intermediate sensitivity. There was no resistance to colistin and 3.07% resistance to minocycline.

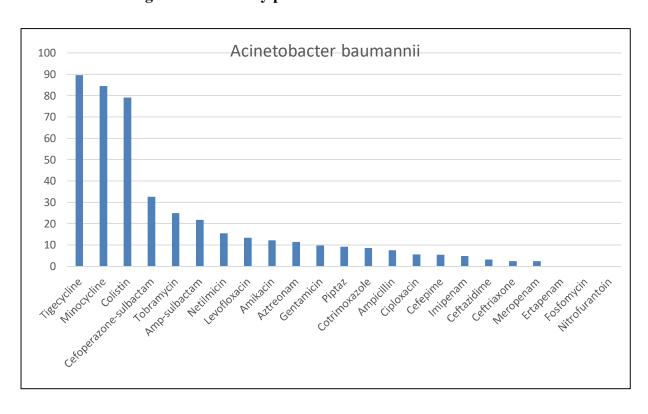


Figure 9: Sensitivity pattern of Acinetobacter baumannii

Table 15: Antibiotic susceptibility pattern of Klebsiella pneumoniae

Antibiotics	Sen	sitive		nediate itive	Resistance		
	n	%	n	%	n	%	
Ampicillin	1	0.90	0	0.00	12	10.81	
Amikacin	19	17.11	4	3.60	88	79.27	
Aztreonam	1	3.22	0	0.00	30	96.7	
Cotrimoxazole	22	19.82	1	0.90	84	75.68	
Cefoperazone-sulbactam	13	14.9	0	0.00	74	85.05	
Colistin	86	77.47	17	15.32	8	7.21	
Ciprofloxacin	3	4.9	1	0.90	57	93.4	
Cefepime	12	10.81	2	1.80	97	87.38	
Ceftriaxone	7	6.3	3	2.70	101	90.99	
Ertapenem	4	7.8	0	0.00	47	92.1	
Fosfomycin	6	100	0	0.00	0	0.00	
Gentamicin	17	15.31	8	7.21	86	77.47	
Imipenem	6	5.41	8	7.21	93	83.78	
Levofloxacin	10	17.2	4	3.60	44	75.8	
Minocycline	76	68.46	14	12.61	21	18.91	
Meropenem	8	7.2	0	0.00	103	92.79	
Netilmicin	0	0.00	0	0.00	19	100	
Nitrofurantoin	1	11.1	0	0.00	8	88.88	
Piperacillin-tazobactam	13	11.71	1	0.90	97	87.38	
Tigecycline	27	64.28	1	2.38	14	33.33	
Ceftazidime	2	1.80	1	0.90	3	2.70	

Klebsiella, the second most common microorganism in our study (26.12%), showed high carbapenem resistance (92.79% meropenem and 83.78% imipenem) and high resistance to beta lactam antibiotics (piperacillin tazobactam 87.38%). There was high pattern of resistance with third-generation cephalosporins (90.99% ceftriaxone) and 87.38% for cefepime (4th generation) and aminoglycosides (77.47% gentamicin, 79.27% amikacin). The most effective drug was colistin, which showed 7.2% resistance in our study.

Note: Latest CLSI guidelines has given MIC breakpoints for Colistin as Intermediate and Resistant:

Intermediate: $\leq 2 \mu g/ml$,

Resistant: $\geq =4 \mu g/ml$

Figure 10: Sensitivity pattern of Klebsiella pneumoniae

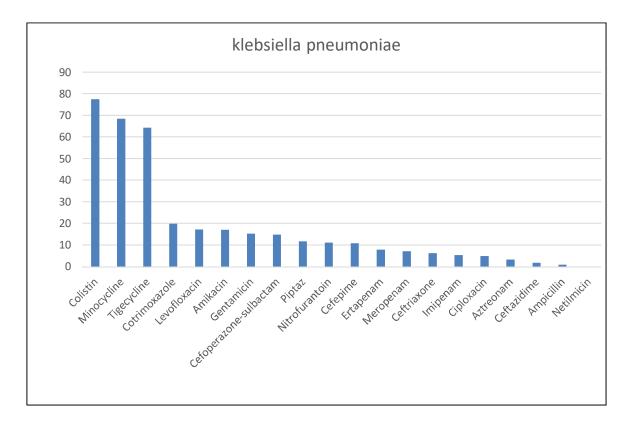


Table 16: Antibiotic susceptibility pattern of E. coli

Antibiotics	Sen	asitive		nediate itive	Resistance		
	n	%	n	%	n	%	
Ampicillin	2	6.6	0	0.00	28	93.3	
Amikacin	43	72.88	1	1.67	15	25.42	
Aztreonam	2	16.6	0	0.00	10	83.3	
Cotrimoxazole	13	23.2	0	0.00	43	76.7	
Cefoperazone-sulbactam	10	24.3	2	4.8	29	70.7	
Colistin	46	77.96	13	21.67	0	0.00	
Ciprofloxacin	2	5.1	0	0.00	37	94.8	
Cefepime	12	20.33	0	0.00	47	79.66	
Ceftriaxone	3	5.00	0	0.00	56	94.91	
Ertapenem	4	16.67	1	4.1	19	79.1	
Fosfomycin	8	80	0	0.00	2	20	
Gentamicin	34	57.62	2	3.33	23	38.98	
Imipenem	9	15.25	4	6.67	46	77.96	
Levofloxacin	2	7.1	0	0.00	26	92.8	
Minocycline	51	86.44	2	3.33	6	10.16	
Meropenem	16	26.67	1	1.67	42	71.18	
Nitrofurantoin	11	100	0	0.00	0	0.00	
Piperacillin-tazobactam	12	20.00	3	5.00	38	63.33	
Tigecycline	53	89.83	0	0.00	6	10.16	
Ceftazidime	0	0.00	0	0.00	3	100	
Penicillin	1	100	0	0.00	0	0.00	
Amp-sulbactam	0	0.00	0	0.00	1	100	
Amoxiclav	0	0.00	0	0.00	13	100	

Our study showed high resistance to third-generation cephalosporins (94.91% ceftriaxone) and 79.66% for cefepime (4th generation) to *E. coli* (third common organism 19.3%). Resistance to beta lactam antibiotics (Piperacillin-tazobactam) is 63.3%. Carbapenem resistance was 77.96% for imipenem and 71.18% for meropenem. Resistance to amikacin and gentamicin were 25.42% and 38.98%, respectively, in our study. Colistin showed no

resistance and 10.17% tigecycline resistance to *E. coli* strains in the present study. The minocycline sensitivity was 89.77% for *E. coli*.

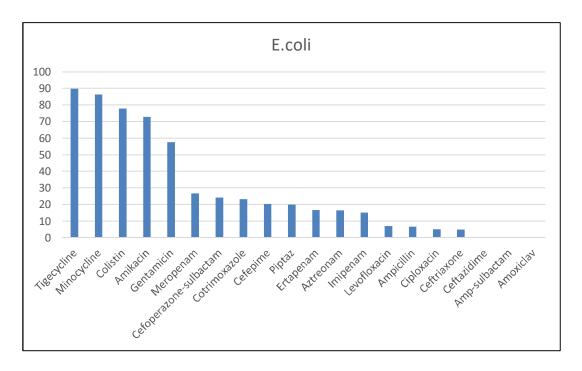
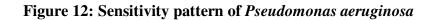


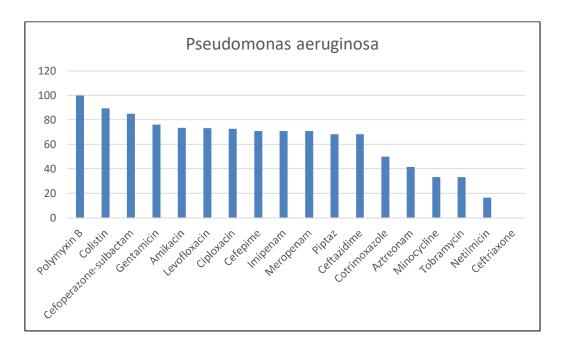
Figure 11: Sensitivity pattern of *E coli*

Table 17: Antibiotic susceptibility pattern of Pseudomonas aeruginosa

Antibiotics	Ser	sitive		nediate sitive	Resistance		
	n	%	n	%	n	%	
Amikacin	28	73.68	0	0.00	10	26.31	
Aztreonam	5	41.6	1	8.3	6	50	
Cotrimoxazole	1	50	0	0.00	1	50	
Cefoperazone-sulbactam	17	85	0	0.00	3	15	
Colistin	34	89.47	4	10.53	0	0.00	
Ciprofloxacin	16	72.7	0	0.00	6	27.2	
Cefepime	27	71.05	0	0.00	11	28.94	
Ceftriaxone	0	0.00	0	0.00	38	100	
Gentamicin	29	76.31	0	0.00	9	23.68	
Imipenem	27	71.05	0	0.00	11	28.94	
Levofloxacin	22	73.3	0	0.00	8	26.6	
Minocycline	1	33.3	1	33.3	1	33.3	
Meropenem	27	71.05	0	0.00	11	28.94	
Netilmicin	1	16.6	0	0.00	5	83.3	
Piperacillin-tazobactam	26	68.42	2	5.26	10	26.31	
Ceftazidime	26	68.42	0	0.00	12	31.05	
Tobramycin	1	33.3	0	0.00	2	66.6	
Polymyxin B	6	100	0	0.00	0	0.00	
Doripenem	1	100	0	0.00	0	0.00	

Pseudomonas aeruginosa (4th prevalent one 2.18%) showed less resistance to beta lactam antibiotics (Piperacillin-tazobactam 26.31%) and carbapenems (28.94% for both imipenem and meropenem. *Pseudomonas* showed high resistance to third generation cephalosporins (100% ceftriaxone) but it is still sensitive to ceftazidime with sensitivity of 68.42% and to cefepime (4th generation), sensitivity is 68.42% while aminoglycosides showed (76.31% gentamicin and 73.6% sensitivity to amikacin). Colistin is most effective antibiotic against *Pseudomonas* with 100% sensitivity.





GRAM POSITIVE BACTERIA

Table 18: Antibiotic susceptibility pattern of Enterococcus

Antibiotics	Ser	nsitive	Intern sens	nediate itive	Resistance		
	n	%	n	%	n	%	
Ampicillin	5	20	0	0.00	20	80	
Clindamycin	0	0.00	0	0.00	1	100	
Cotrimoxazole	0	0.00	0	0.00	1	100	
Ciprofloxacin	3	15	1	4.1	20	83.3	
Erythromycin	3	7.69	0	0.00	19	48.72	
Gentamicin	6	16.6	0	0.00	30	83.3	
Levofloxacin	3	13.04	0	0.00	20	86.9	
Linezolid	39	100	0	0.00	0	0.00	
Tetracycline	8	20.51	7	17.95	16	41.03	
Teicoplanin	27	69.23	1	2.56	11	28.21	
Vancomycin	31	79.48	0	0.00	8	20.51	
Penicillin	5	12.82	0	0.00	24	61.54	
Cefoxitin	2	100	0	0.00	0	0.00	

Among Gram positive bacteria, *Enterococcus* (2.5%) was the most common microorganism to be isolated. It showed highest sensitivity (100%) to linezolid. The vancomycin sensitivity of Gram-positive Enterococcus is 79.48% and 71.7% sensitivity to teicoplanin.

Enterococcus

120

100

80

60

40

20

1 Interdid Cetonicin Feicobachin Ampichin Centranicin Coposcir Penicinin Ampich Lindanicin Copinatalia Coposcir Penicinin Copinatalia Copinatalia

Figure 13: Sensitivity pattern of *Enterococcus*

Table 19: Antibiotic susceptibility pattern of Staphylococcus aureus (MRSA)

Antibiotics	Sei	nsitive		nediate sitive	Resistance		
	n	%	n	%	n	%	
Ampicillin	0	0.00	0	0.00	1	100	
Clindamycin	2	66.67	0	0.00	1	33.33	
Cotrimoxazole	2	66.67	0	0.00	1	33.33	
Ciprofloxacin	1	33.33	0	0.00	2	66.67	
Erythromycin	0	0.00	0	0.00	3	100.00	
Gentamicin	0	0.00	1	33.33	2	66.67	
Linezolid	3	100.00	0	0.00	0	0.00	
Tetracycline	3	100.00	0	0.00	0	0.00	
Teicoplanin	3	100.00	0	0.00	0	0.00	
Vancomycin	3	100.00	0	0.00	0	0.00	
Penicillin	0	0.00	0	0.00	1	100	
Cefoxitin	0	0.00	0	0.00	3	100.00	
Moxifloxacin	1	100	0	0.00	0	0.00	

The vancomycin, teicoplanin, linezolid and tetracycline sensitivity were 100% for MRSA.

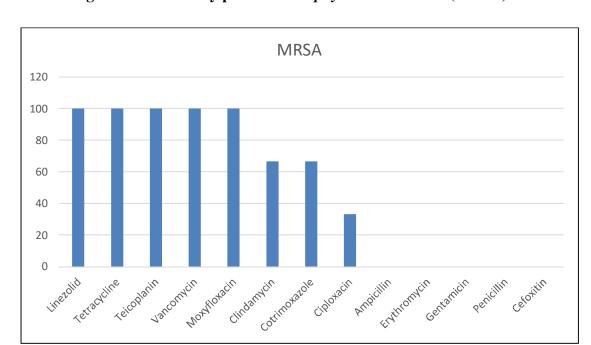


Figure 14: Sensitivity pattern of Staphylococcus aureus (MRSA)

Table 20: Antibiotic susceptibility pattern of Staphylococcus aureus (MSSA)

Antibiotics	Ser	nsitive	Interm		Resistance		
	N	%	N	%	N	%	
Ampicillin	0	0.00	0	0.00	0	0.00	
Clindamycin	1	33.33	0	0.00	2	66.67	
Cotrimoxazole	2	66.67	0	0.00	1	33.33	
Ciprofloxacin	2	66.67	0	0.00	1	33.33	
Erythromycin	0	0.00	0	0.00	2	100	
Gentamicin	3	100.00	0	0.00	0	0.00	
Linezolid	0	0.00	0	0.00	0	0.00	
Tetracycline	0	0.00	0	0.00	0	0.00	
Teicoplanin	0	0.00	0	0.00	0	0.00	
Vancomycin	0	0.00	0	0.00	0	0.00	
Penicillin	0	0	0	0.00	3	100.00	
Cefoxitin	3	100	0	0.00	0	0.00	
Moxifloxacin	0	0.00	0	0.00	0	0.00	
Amoxiclav	0	0.00	0	0.00	0	0.00	

MSSA showed 100% sensitivity to gentamicin. Second line antibiotics were not tested for susceptibility testing.

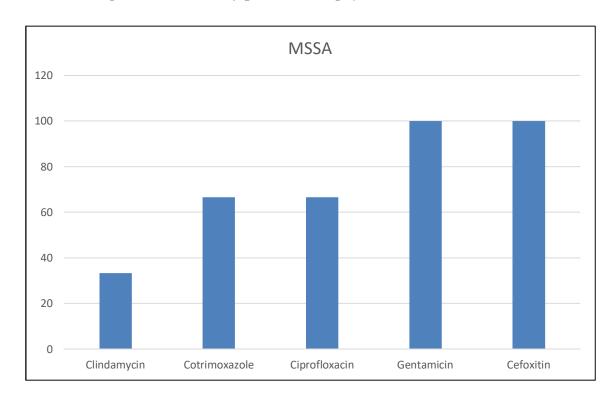


Figure 15: Sensitivity pattern of Staphylococcus aureus (MSSA)

Table 21: Association of Procalcitonin levels at the time of sample collection and mortality

Procalcitonin	Death		Discharge		L	AMA	Total	
(at the time of admission)	n	%	n	%	n	%	n	%
<0.5	24	39.3	38	60.6	0	0.00	62	16.8
≥0.5	213	67.4	103	31.9	2	0.6	318	83.1
Total	237	64.17	141	35.38	2	0.45	380	100.00

When investigating the association between serum procalcitonin level and the clinical outcome of patients with bacterial infections in adult ICU, the serum procalcitonin level were classified into the high procalcitonin level ($\geq 0.5 \, \mu g/L$) and low procalcitonin level ($<0.5 \, \mu g/L$)

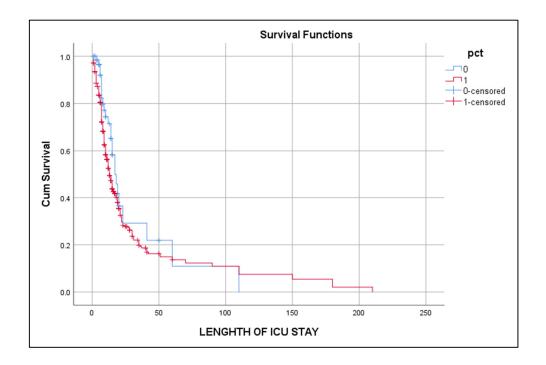
 μ g/L). As per manufacturer's instruction a serum procalcitonin level < 0.5 g/L considered as normal.

Table 22: Association of procalcitonin with mortality in AICU patients

	Med	lian	Odds ratio (95% CI), P
Variable	Non-survivors	Survivors	
	Median (IQR)	Median (IQR)	
Procalcitonin	4 (2-10.1)	4 (1.8-11.2)	1.001 (0.989-1.012) <i>P</i> =0.906

Median procalcitonin for non- survivors was 4 with IQR of 2-10.1 and for survivors was 4 with IQR of 1.8-11.2. Using multiple logistic regression analysis, the procalcitonin levels were not associated with mortality. (OR=1.001, 95% CI 0.989-1.012, P = 0.906)

Figure 16: Kaplan-Meier survival curve of serum procalcitonin level



The above figure shows Kaplan-Meier curve. The blue curve indicates patients who had pct< 0.5 and did not survive while the red curve indicates patients with pct \geq 0.5 and did not survive. The area under both curves is almost similar. It showed that high level of serum procalcitonin level did not have significant effect on mortality. (P Log-Rank=0.110).

Table 23: Association of SOFA scores on the day of sending culture with mortality

SOFA score	Death		Discharge		L	AMA	Total		
SOFA SCORE	n	%	n	%	n	%	n	%	
<2	2	12.5	14	87.5	0	0.00	16	3.78	
≥2	235	64.5	127	34.8	2	0.5	364	96.22	
Total	237	62.3	141	37.1	2	0.5	380	100.00	

Maximum SOFA scores on the day of sending the culture for each of six organ systems were determined. The mortality is 64.5% in patients with organ dysfunction as determined by total SOFA score ≥ 2 compared to 12.5% mortality in patients with sofa score <2. The mortality ranged from 30.2% (13/43) among those who had SOFA score 2 to 70.6% among those who had SOFA score >6.

Table 24: Median survival time and Confidence Interval for sofa scores at time of sample collection using survival analysis

SOFA score	Median	CI Lower limit	CI Upper limit
<2	30.000	19.508	40.492
≥2	13.000	11.354	14.646
	14.000	12.162	15.838

Using survival analysis, the median survival time using SOFA scores was 30 days (95% CI 19.5-40.49, P = 5.35) for patients with SOFA scores <2, while it was 13 days (95% CI 11.354-14.646, P = 0.84) for patients with SOFA ≥ 2 .

Table 25: Association of SOFA scores with mortality in AICU patients

	Median		Odds ratio (95% CI), P
Variable	Non-survivors	Survivors	
	Median (IQR)	Median (IQR)	
SOFA	6 (5-9)	3 (2-6)	1.444(1.308-1.594) <i>P</i> =0.000

The median total SOFA score was significantly higher in non-survivors than in survivors [6(IQR=2-6) vs. 3(IQR=5-9)].

We used multiple logistic regression models to evaluate the SOFA associated with mortality and it showed that the odds of death increased with higher SOFA \geq 2scores. OR=1.444(95% CI=1.308-1.594), P =0.000 which is statistically significant.

Figure 17: Survival function by Kaplan Meier curve

The above figure shows Kaplan-Meier curve. The blue curve indicates patients who had sofa< 2 and did not survive while the red curve indicates patients with sofa scores ≥ 2 and did not survive. Kaplan-Meier curve showed that patients with high SOFA score (≥ 2) had higher risk of mortality (P Log-Rank=6.813), which is statistically significant. (p=0.009).

MORTALITY COMPARISONS

Table 26: Blood culture positivity

		Blood	culture	
		Negative	Positive	
OUTCOME	Discharge	95	18	113
	Death	149	45	194
Total		244	63	307

Patients who had blood culture positivity had high mortality (71.4%) than patients with negative blood cultures (61%). Using Pearson's Chi Square test, it was statistically significant (P value=0.000).

Table 27: Tracheal culture positivity

		Negative	Positive	Total
OUTCOME	Discharge	22	63	85
	Death	38	87	125
Total		60	150	210

Mortality was 58% in patients with tracheal infection whereas it was 63.3% in negative cultures. Using Pearson's Chi Square test, it was statistically not significant (P value=0.06).

Table 28: Urine culture positivity

		Urine culture		
		Negative	positive	Total
OUTCOME	Discharge	12	4	16
	Death	14	6	20
Total		26	10	36

The mortality was 60% in urine infection and in negative urine cultures, it was 53.8%. Using Pearson's Chi Square test, it was statistically significant (P=0.031).

Table 29: Mortality comparison among gram positive and gram-negative isolates

		Organism		
		Gram negative	Gram positive	Total
OUTCOME	Discharge	31	15	46
	Death	54	32	86
Total		85	47	132

Mortality was 68% in Gram positive bacteraemia whereas 63.5% in Gram negative bacteraemia and it was statistically significant using Pearson's Chi Square test (P=0.000).



DISCUSSION

Our study dealt with the analysis of culture-sensitivity reports of patients admitted in adult ICU of the institute. Culture of every patient was sent on the day of admission and repeated if patient had any sign of community or hospital-acquired infection. The site of sample collection was decided by the consultant in-charge of ICU. Patients admitted were from all speciality and included post-operative patients (from neurosurgery, cardiothoracic and from emergency department) and those transferred from ward. On patient's admission, empirical antibiotic piperacillin + tazobactam was started after appropriate sample collection.

The blood specimens were the most frequent (56.15%) specimen, second most common specimen was tracheal (22.44%) while urine (21.41%) was the third most common specimen collected. Although, blood was most common specimen but maximum positivity was found in tracheal samples (86.6%), while 40.12% of urine samples and 31.85% of blood samples were positive. Results of our study showed that respiratory tract infections (community acquired pneumonia, ventilator associated pneumonia VAP) was the most prevalent infection in our ICU.

The primary objective of the study was to find out the incidence of various bacterial infections in adult intensive care unit. Our results reported that respiratory tract infections (community acquired pneumonia, ventilator associated pneumonia VAP) was the most prevalent infection (86.6%) in our hospital ICU similar to Shao et al.'s study where respiratory tract infection (RTI) accounted for 64.75% of total nosocomial infections (Nis) [62]. *Acinetobacter baumannii*, *Klebsiella spp.*, *E. coli*, *Pseudomonas and Enterococcus* were the predominant isolates in our study. In contrast to our findings, Shebl et al. [63] discovered that out of 554 bacterial isolates, urine specimens had the highest frequency (41.5 %, n = 230), followed by blood (23.1 %, n = 128), and sputum specimens had the lowest frequency (17 %, n = 94).

Infections caused by Gram-negative bacteria have lately been found to be on the rise around the world. Our findings revealed that Gram-negative bacteria were the most commonly isolated pathogens (27.63 %), which could be attributed to their widespread presence in the hospital setting. Their frequent antibiotic resistance may also play a role in their persistence and dissemination. Acinetobacter baumannii and Klebsiella pneumoniae were the Gramnegative bacteria that were most commonly identified. This is consistent with recent statistics

from the US National Healthcare Safety Network, which shows that Gram-negative bacteria are responsible for more than 30% of hospital-acquired infections [64]. Qadeer et al. reported Acinetobacter and E. coli as the most common isolates in their investigation, which was similar to ours. [48].

Acinetobacter baumannii was the most prevalent isolate from the respiratory tract, while Enterococcus was the most common isolate from urine, according to our study. Acinetobacter predominance was also seen in respiratory tract samples, which is consistent with Pradhan et al.'s findings that Acinetobacter species were the most prevalent microbes in the respiratory tract [65] and Kanj et al.'s findings that Acinetobacter species were the most common in VAP [66].

Gram negative bacteraemia was the most common infection in our study, and Acinetobacter baumannii was the most common bacteria. Similar findings were observed in the Republic of South Africa's adult surgical intensive care unit, which revealed high rates of HAI, particularly for lower respiratory tract infection (LRTI) (81.8/1000 IP-Days), surgical site infection (SSI) (31.7/1000 IP-Days), and blood stream infection (BSI) (26.4/1000 IP-Days). *Acinetobacter baumannii* was also discovered to be the most frequent organism, accounting for 31% of all infections. [67]

Antibiotics are one of the most important cornerstones of modern medicine, serving as both for prophylaxis and as treatment for infections. The identification of bacterial pathogens and the selection of an antibiotic effective against that organism are essential for the treatment of patients with bacterial infections. [68]. The most significant contributor to the growing issue of antimicrobial resistance, particularly in low-income countries [69], is the inappropriate use of antimicrobials. It's worth noting that, rather than following universal guidelines, antimicrobial therapy should take into consideration data on the local incidence of causative organisms and their antibiotic resistance profile. [43] Hence one of the secondary objectives of our study was to find antibiotic sensitivity pattern of the organisms found in cultures

1. Sensitivity pattern

Our findings revealed a very high rate of carbapenem resistance among Acinetobacter (the most common organism, accounting for 10.44 % of the total), with 95.09 % for imipenem, and 97.54 % for meropenem. Carbapenem resistance was found to be particularly common among Acinetobacter baumannii in Negm et al.'s study (79.9 % for imipenem and 79.7 % for meropenem) [43]. Carbapenem resistance was shown to be 100 % in a study by Qadeer et al. [48]. Khan et al. reported 79 % imipenem resistance in another study [51], while Rajan et al. found 52 % carbapenem resistance in Acinetobacter [70]. This indicates that Acinetobacter had a wide range of carbapenem resistance, ranging from 80 to 100 %.

In our study, *Acinetobacter* was highly resistant to 3rd generation cephalosporins (96.31% ceftriaxone) and 4th-generation cephalosporins (94.47% cefepime), beta lactam antibiotics (piperacillin tazobactam 83.44%), aminoglycosides (89.5% gentamicin and 87.11% amikacin), and quinolones (75.46% levofloxacin. Acinetobacter was found to be highly resistant to third-generation cephalosporins (97 % ceftriaxone), aminoglycosides (82.2 % gentamicin and 67.9% amikacin), and quinolones in Negm et al.'s study (91.6 % ciprofloxacin and 79.9 levofloxacin) [43]. Acinetobacter was resistant to third-generation cephalosporins (100 % ceftazidime), aminoglycosides (97 % gentamicin and 95 % amikacin), and fluoroquinolones (100% ciprofloxacin and moxifloxacin) in Qadeer et al.'s study as well. [48].

The most effective drug is Colistin which showed 79.14% sensitivity and 20.8% intermediate sensitivity followed by minocycline which showed 84.6% sensitivity and 12.2% intermediate sensitivity. In our study, there was no resistance to colistin and 3.07 % resistance to minocycline whereas the most efficacious antibiotic in Negm et al.'s study was colistin, which showed 10.1 % resistance, followed by tigecycline (29.4 %) [43]. The most effective medicine in Qadeer et al.'s study was colistin, which had a 3% resistance rate [48]. Rajan et al. [70] found similar results for colistin efficiency against Acinetobacter, while Hasan et al. [71] reported that tigecycline was the most efficient antibiotic against Acinetobacter. In Almohammadi-Mehr et al.'s study Acinetobacter, the second most prevalent Gram-negative isolate, exhibited just 25% levofloxacin sensitivity and 100% polymyxin sensitivity. [72]

Klebsiella, the second most common microorganism in our study (26.12%), showed high carbapenem resistance (92.79% meropenem and 83.78% imipenem) and high resistance to

beta lactam antibiotics (piperacillin tazobactam 87.38%), while in Negm et al.'s study, resistance to carbapenems (81% meropenem and 80.5% imipenem) was slightly less than ours^[43]. Even less resistance was detected in Qadeer et al.'s study, 56 % meropenem and 55 % imipenem [48], but Sheth et al. reported 100 % carbapenem sensitivity [73] and Rajan et al. reported 28.13 % carbapenem resistance [70]. We found a high pattern of resistance to third-generation cephalosporins (90.99 % ceftriaxone) and cefepime (4th generation) and aminoglycosides in the current study (77.47 % gentamicin, 79.27 % amikacin). In the study by Negm et al., resistance to third-generation cephalosporins (95.4 % ceftriaxone) and cefepime (4th generation) and aminoglycosides was even higher (96.3 % ceftriaxone) (72.9 % gentamicin, 67.9 % amikacin) [43]. In addition, third-generation cephalosporins (94 % ceftazidime, 82 % ceftriaxone, and 70 % cefoperazone/sulbactam) and aminoglycosides (61 % gentamicin, 48 % amikacin) showed a high pattern of resistance in Qadeer et al.'s study [48]. In Gunjal et al.'s study, amikacin resistance was 60% and gentamicin resistance was 80% [74]. The most effective antibiotic was colistin, which had a resistance rate of 7.2 % in our study. Tigecycline resistance was found in only 42 isolates out of 111, with a resistance rate of 33.33 %, similar to Negm et al.'s study, where colistin showed 3.8 % resistance, followed by tigecycline with 32 % resistance [43], despite tigecycline being found to be the most effective antibiotic against multidrug-resistant Klebsiella in Qadeer et al.'s study. [48].

Our study showed high resistance to third-generation cephalosporins (94.91% ceftriaxone) and 79.66% for cefepime (4th generation) to *E.coli* (third common organism 19.3%). High resistance to third-generation cephalosporins (94.1% ceftriaxone) and 91.3% cefepime (4th generation) was seen in Negm et al.'s study^[43]. Qadeer et al. observed substantial resistance to third-generation cephalosporins (93% ceftazidime and 90% ceftriaxone) [48], while Al mohammady et al. found that more than 90% of E. coli were resistant to third-generation cephalosporins [72]. 63.3% of bacteria are resistant to beta lactam antibiotics (Piperacillintazobactam). Imipenem resistance was 77.96% and meropenem resistance was 71.18% for carbapenems. In a study by Negm et al., carbapenem resistance was 52% for imipenem and 47.3% for meropenem [43], and as low as 10% in a study by Qadeer et al. [48]. Resistance to amikacin and gentamicin was reported to be 34% and 53.2%, respectively, by Negm et al. [43], whereas resistance to amikacin and gentamicin was 25.42% and 38.98% in our study. In this study, Colistin showed no resistance to *E. coli* strains, however in Negm et al.'s study, colistin demonstrated modest resistance to *E. coli* strains of 5.3% [43]. In our study, 10.17% of E. coli had tigecycline resistance, whereas Qadeer et al. found 33% of *E. coli* had

tigecycline resistance [48]. In the study by Negm et al., *E. coli* demonstrated 13.1 % tigecycline resistance. [43]

In our study, *Pseudomonas aeruginosa* (4th prevalent one 2.18%) showed less resistance to beta lactam antibiotics (Piperacillin-tazobactam 26.31%) and carbapenems (28.94% for both imipenem and meropenem similar to a study by Rakhee et al. [75], in which Pseudomonas exhibited 20.8 % imipenem resistance and a study by Rajan et al. [72], in which Pseudomonas showed 12.9 % carbapenem resistance. In contrast to Negm et al., where Pseudomonas showed significant resistance to carbapenems (82.7% imipenem/ 84.7% meropenem)^[43]. In our study although, *Pseudomonas* showed high resistance to third generation cephalosporins (100% ceftriaxone) but it is still sensitive to ceftazidime with sensitivity of 68.42% and if we look at cefepime (4th generation), sensitivity is 68.42% while aminoglycosides showed (76.31% gentamicin and 73.6% sensitivity to amikacin). Pseudomonas demonstrated substantial resistance to third generation cephalosporins (100 % ceftriaxone) and 86.2 % to cefepime (4th generation) in study by Negm et al. [43], but aminoglycosides showed no resistance (80.4 % gentamicin and 78.2% amikacin). Pseudomonas aeruginosa resistance to third-generation cephalosporins was (53% cefoperazone/sulbactam and 39% ceftazidime) and to aminoglycosides (48 % gentamicin and 41 % amikacin) in Qadeer et al.'s study [48]. According to Radji et al., ceftriaxone resistance was 60.9 %, and amikacin was the most effective antibiotic against *Pseudomonas*, with 15.6 % resistance [52]. We conclude that 3rd generation cephalosporin like ceftazidime and aminoglycosides are still effective against *Pseudomonas*. Colistin is most effective antibiotic against Pseudomonas with 100% sensitivity whereas in Negm et al.'s study found colistin showed 20.6% resistance. [43]

Enterococcus (2.5 %) was the most prevalent Gram positive bacteria identified, followed by Staphylococcus haemolyticus, which was similar to the findings of Chidambaram et al. in which the most prevalent Gram-positive isolate was Enterococcus (4.79 %), followed by Staphylococcus aureus.^[76] Our study showed highest sensitivity (100%) to linezolid followed by vancomycin (79.4%) followed by teicoplanin (71.7%).

Staphylococcus aureus constituted 0.38% of all isolates out of which 0.19% was MRSA. MRSA was found to be 100% sensitive to linezolid and vancomycin. In contrast, MRSA's susceptibility to vancomycin and linezolid was 76.8% and 100%, respectively, in a study by Negm et al. [43] Thus, we can conclude that vancomycin and linezolid are effective antibiotics

against MRSA. So, in our study, we saw high resistance to broad spectrum antibiotics which are commonly used like beta lactam antibiotics (piperacillin-tazobactam) and carbapenems (meropenem, ertapenem). Even sensitivity to colistin is also showing reducing trend because some isolates showed intermediate sensitivity to colistin which is very alarming. However, vancomycin and linezolid did not show resistance against gram positive microorganisms. So, antibiotic stewardship is of utmost importance and careful administration of antibiotics is mandatory in current scenario.

2. To find out the association of procalcitonin with all-cause mortality

Procalcitonin is a calcitonin precursor hormone that is undetectable in healthy individuals but is upregulated by cytokines released in response to bacterial infections [77, 78]. Interferongamma, a cytokine secreted in response to viral infections, inhibits procalcitonin synthesis [79]. Procalcitonin has been used in Europe for many years and was approved by the US Food and Drug Administration (FDA) in 2005 as a sepsis diagnostic tool in the United States. In 2016, the FDA approved it for serial use to assess sepsis progression and 28-day mortality risk. The level of procalcitonin in the blood of healthy people is below the detection limit of clinical assays, whereas it rises in those with illnesses. [80,81] Procalcitonin levels can represent the severity of infection, and individuals with greater levels of procalcitonin typically have more severe disease and a worse prognosis. [54].

Procalcitonin has a short half-life (25–30 hours), and its levels drop quickly when inflammation subsides [77,82]. Because of these characteristics, it may be beneficial in determining whether or not to start antibiotics and when to cease them in a clinically improving patient. The kinetics also explain the predictive efficacy of both the first and subsequent procalcitonin levels [83]. Procalcitonin levels differ by infection site in critically ill patients with microbiologically proven infection, with the greatest levels in those with positive blood cultures and the lowest in those with positive respiratory cultures. [84]

Our findings imply that procalcitonin levels in critically ill patients are not linked with mortality (OR = 1.001, 95 % CI 0.989-1.012, P = 0.906). Similar to a study by M. Jet al., who found that the prognostic usefulness of plasma PCT for predicting survival in adults with suspected sepsis is still debatable. PCT was not linked to death (HR 14 0.57, 95 % CI: 0.14-0.25), according to their findings. [56]

3. To find out the association of SOFA score at admission with all-cause mortality

According to the literature, a change in SOFA score of 2 or more had prognostic accuracy or was a predictor of in-hospital death. ^[31] In our study we also found an association between change in SOFA score of ≥2 and risk of mortality. The results also indicate more chances of survival in patients' with low SOFA score compared to patients with high SOFA score. The SOFA score proved to be very powerful predictor of mortality in our study too. Similar results were demonstrated by Raith et al in their study. ^[31] M. J.et al also showed that patients with low SOFA scores were associated with increased survival time 1.54 (HR-4.68, P value= 0.03, 95% CI= 1.14-19.30). ^[56]

In our study, the overall 28-day mortality was 64.5% (235/364). The 28-day mortality rate ranged from 30.2% (13/43) in individuals with a SOFA score of 2 to 70.6% in those with a SOFA score of 6 or more. According to Lie et al's research, the overall 28-day death rate was 22% (99/454 people). The 28-day mortality rate varied from 7% (8/111) for those with a SOFA score of 2 to 39% for those with a SOFA score of > 6. [57]

4. To find the total length of stay in ICU.

The median duration of stay of the patients in the ICU was 8 days with IQR of 5-15 days in our study population. There was insignificant difference (p value=0.6) in the median duration of stay between survivors(8 days, IQR=5-14) and non survivors(8 days, IQR=5-15) in our study whereas in Lakbar et al study there was a significant difference [p value<0.001] between the two (mean duration of icu stay 34.5±25.9 in survivors and 31.7±27.3 in non survivors). [59]

So, we conclude that prolonged ICU stays are not associated with mortality.

Contrary to our findings, critical patients in ICU are typically associated with longer lengths of stay and may have a higher hospital death rate than other patients, according to Lily et al.'s study. [85]

5. To find out the association of culture positive microorganism with 28 days all-cause mortality

In our study we found overall higher mortality in blood culture positive patients compared to blood culture negative patients. Although, gram positive bacterial infections were less prevalent in our ICU, but the mortality was higher in gram positive infections compared to gram negative infections (68% vs 63.5%). The mortality was 100% in patients positive for fungal culture.

According to Søgaard et al patients with community-acquired bacteremia had a two-fold greater mortality rate within the first two days after admission, as compared to patients with negative blood cultures. Following that, patients with bacteremia had a slightly higher mortality rate than those with negative cultures. Patients with Gram-positive and polymicrobial bacteremia had the highest death within the first week following admission, although patients with polymicrobial bacteremia had an elevated mortality for at least 180 days. [60]

The total estimates in the Lambert et al. study imply that pneumonia doubles the risk of death and bloodstream infections triples the risk, with an extra effect of antibiotic resistance of roughly 20%, however this was only significant for pneumonia.^[61]



LIMITATIONS

- Due to shortage of some antibiotics sometimes, sensitivity of microorganism with every antibiotic was not being reported by microbiology lab.
- One disadvantage of the current study is that it was conducted at a single procalcitonin level during ICU hospitalisation.



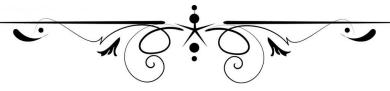
CONCLUSION

The following conclusion were extracted from the study

- 1. Gram negative infections are on the surge while incidence of gram positive infections is reduced.
- 2. Resistance to 3rd generation cephalosporins (ceftriaxone) and 4th-generation cephalosporins (cefepime), beta lactam antibiotics (piperacillin tazobactam), aminoglycosides (gentamicin and amikacin), and quinolones (levofloxacin) is very high among gram negative bacteria. Colistin, tigecycline seems to be effective against GNB.
- 3. Vancomycin and linezolid are effective antibiotics against gram positive microorganisms.
- 4. Single procalcitonin level does not predict mortality in critically ill patients.
- 5. SOFA score \geq 2 proved to be a strong predictor of mortality in critically ill patients.
- 6. Increased length of ICU stays are not associated with increased risk of mortality.



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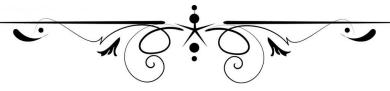
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ANNEXURES



ANNEXURE 1

IEC CERTIFICATE



अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर All India Institute of Medical Sciences, Jodhpur संस्थागत नैतिकता समिति Institutional Ethics Committee

No. AIIMS/IEC/2020/3349

Date: 03/11/2020

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: AIIMS/IEC/2019-20/993

Project title: "Epidemiology and clinical outcomes of bacterial infections in adult intensive care unit: A prospective observational study"

Nature of Project:

Research Project

Submitted as:

M.D. Dissertation Dr.Somva Goel

Student Name: Guide:

Dr. Manoj Kamal

Co-Guide:

Dr. Pradeep Kumar Bhatia, Dr. Vibhor Tak & Dr. Bharat Paliwal

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- · Any unethical principle or practices are revealed or suspected
- · Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveer Sharma

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ANNEXURE 2

INFORMED CONSENT FORM

EPIDEMIOLOGY AND CLINICAL OUTCOMES OF BACTERIAL Title: **INFECTIONS** IN ADULT INTENSIVE CARE UNIT: A **PROSPECTIVE OBSERVATIONAL STUDY** Name of PG Student: Dr. SOMYA GOEL Telephone no: 8958817306 Patient/Volunteer Identification No. : F/o or M/o _____ R/o give my full, free, voluntary consent to be a part of the study "EPIDEMIOLOGY AND CLINICAL OUTCOMES OF BACTERIAL INFECTIONS IN ADULT INTENSIVE CARE UNIT: A PROSPECTIVE OBSERVATIONAL STUDY" the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions. I understand that my participation is voluntary, and I am aware of my right to opt out of the study at any time without giving any reason. I understand that the information collected about me & medical records may be looked at by responsible individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records. Date: _____ Signature/Left thumb impression Place: _____ This to certify that the above consent has been obtained in my presence. Signature of PG Student Place : _____ Witness 1 Witness 2 Signature Signature Name: _____ Name: _____ Address: ____ Address : _____

ANNEXURE 3

ऑल इंडिया इंस्टिट्यूट ऑफ मैडिकल साईंसिस जोधपुर, राजस्थान

सूचित सहमति प्रपत्र

थीसिस / निबंधकाशीर्षकः" वयस्क गहन चिकित्सा इकाई मे बैक्टीरियल संक्रमण का जानपदिक रोग-विज्ञान और रोगविषयक परिणामः एक प्रत्याशित निरीक्षण अध्ययन "

पीजी छात्र का नाम: डॉ . सौम्या गोयल	Tel No. 8958817306
रोगी / स्वयंसेवक पहचान संख्याः	
में,	पुत्र / पुत्री
पता	
अध्ययन " वयस्क गहन चिकित्सा इकाई मे बैक्त रोगविषयक परिणामः एक प्रत्याशित निरीक्षण अ स्वतंत्र, स्वैच्छिक सहमति दें, जिसकी प्रक्रिया और भाषा में समझाई गई है। मैं पुष्टि करता हूं कि मुझे प्र मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और अध्ययन से बाहर निकलने के मेरे अधिकार की जान मैं समझता हूं कि मेरे और मेरे मेडिकल रिक जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन अनुमित देता हूं।	ाध्ययन" का एक भाग बनने के लिए मेरी पूर्ण, र प्रकृति मुझे अपनी पूरी संतुष्टि के लिए अपनी ११न पूछने का अवसर मिला है। मुझे किसी भी कारण दिए बिना किसी भी समय कारी है। ॉर्ड के बारे में एकत्रित की गई जानकारी को (कंपनी नाम) या विनियामक प्राधिकरणों से
तारीख: जगह:	हस्ताक्षर / बाएं अंगूठे का छाप
यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उप तारीख:	ग्रोक्त सहमति प्राप्त की गई है I
जगह:	पीजी छात्र के हस्ताक्षर
गवाह 1	गवाह 2
 हस्ताक्षर	 हस्ताक्षर
नाम	नाम

APPENDIX 4

Participant information sheet

All India Institute of Medical Sciences Jodhpur, Rajasthan
All India Institute of Medical Sciences
Jodhpur, Rajasthan

Patient name:

Patient id:

Title of study: EPIDEMIOLOGY AND CLINICAL OUTCOMES OF BACTERIAL INFECTIONS IN ADULT INTENSIVE CARE UNIT: A PROSPECTIVE OBSERVATIONAL STUDY

Purpose of study: to determine the epidemiology and clinical outcomes of bacterial infections from patient admitted in adult intensive care unit of our institute

Study design: prospective observational study

I have been explained in my own understanding language by the Principal Investigator that they will be taking samples from my body and and explained risk and benefits associated with it.

I have been informed that I can withdraw from the study at any time.

The data obtained from study will be used for the purpose of the study only. All my records will be kept confidential.

Details of the candidate with phone number: Dr. SOMYA GOEL

Mob no: 8958817306

PG Anaesthesiology Critical Care

AIIMS Jodhpur

APPENDIX 5

रोगी सूचना पत्रक

ऑल इंडिया इंस्टिट्यूट ऑफ मैडिकल साईंसिस जोधपुर, राजस्थान

रोगी का नाम:

रोगी आईडी:

अध्ययन का शीर्षक: "वयस्क गहन चिकित्सा इकाई मे बैक्टीरियल संक्रमण का जानपदिक रोग-

विज्ञान और रोगविषयक परिणाम: एक प्रत्याशित निरीक्षण अध्ययन"

अध्ययन डिजाइनः प्रत्याशित निरीक्षण अध्ययन

प्रिंसिपल अन्वेषक द्वारा मुझे अपनी समझ भाषा में समझाया गया है कि वे ये अध्ययन कर रहे हैं और इसके साथ जुड़े जोखिमों और लाभों को भी समझाया गया है। मुझे सूचित किया गया है कि मैं किसी भी समय अध्ययन से मेरे को हटा सकता हूं। मेरे द्वारा प्राप्त आंकड़ों का उपयोग केवल अध्ययन के उद्देश्य के लिए किया जाएगा मेरे सभी रिकॉर्ड गोपनीय रखा जाएगा।

पीजी :डॉ . सौम्या गोयल ,

फोन नंबर वाले उम्मीदवार का विवरण: 8958817306

अनैथीसिओलॉजी और क्रिटिकल केयर

एम्स जोधपुर

APPENDIX 6



All India Institute of Medical Sciences (AIIMS), Jodhpur

Thesis Title: EPIDEMIOLOGY AND CLINICAL OUTCOMES OF BACTERIAL INFECTIONS IN ADULT INTENSIVE CARE UNIT: A PROSPECTIVE OBSERVATIONAL STUDY Department of Anaesthesiology&

Critical Care

	Critical Care		
	PROFORMA		
PATIENT ID			
Name	Age		
Gender			
Parameters to be observed			
Comorbidities			
Previous antibiotic used			
Procalcitonin(at time of culture sample collection):			
SOFA score (at time of culture sample collection):			
Culture sent date:	Report received date:		
Growth of microorganism in blood culture and their sensitivity			
Growth of microorganism in trache	eal culture and their sensitivity		
Growth of microorganism in urine culture and their sensitivity			
Length of stay in ICU			
Outcome (28 days all-cause mortality):			

