Microbiological Profile and resistance patterns in adult medical ICU patients: a multicenter study in Addis Ababa

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Declaration

I, Elias Tekleselassie, do hereby declare that this manuscript is a result of the works of my own making except where due is made in a review of previous literature in the content, and by my knowledge, has never been submitted for any prior academic award or qualification in this institution.

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Approval of thesis submission

I hereby certify that I have read this thesis prepared under my direction and recommend that it can be accepted as fulfilling the thesis requirement.

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Abbreviations

AMR – Antimicrobial resistance

AmpC BL- AmpC Beta-lactamase

BSI – blood stream infection

CAUTI – Catheter associated urinary tract infection

CLABSI – Central line associated blood-stream infection

CoNs – Coagulase negative Staphylococcus aureus

CRE- Carbapenem resistant Enterobacteriaceae

ESBL – Extended spectrum Beta-lactamase

ESKAPE- Enterococcus spp, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp

HAI – Hospital acquired infection

HCAI- Healthcare associated infection

HIC – High income countries

ICU – Intensive care unit

IPC – Infection prevention and control

LMIC – Low-Middle income

LIC – Low-income countries

MDR – Multidrug resistant

MRSA – Methicillin-resistant Staphylococcus Aureus

OR – Operation room

RTI - Respiratory tract infection

SPHMMC – St. Paul hospital millennium medical college

SSI- Surgical site infection

TASH – Tikur Anbessa specialized hospital

UTI – Urinary tract infection

VAP – Ventilator associated pneumonia

VRE – Vancomycin resistant Enterococci

WHO – World Health Organization

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Abstract

Background Antimicrobial resistance (AMR) is one of the most significant threats to humanity, with its impact being highest in low and middle-income countries (LMICs). Although intensive care units (ICUs) house a small proportion of hospital patients, they account for a significant share of multidrug-resistant (MDR) organisms, leading to increased morbidity and mortality.

Objectives To assess microbiologic profile and resistance patterns among adult medical ICU patients

Methods A multicenter retrospective cross-sectional study was conducted in 5 government owned hospital medical ICUs (TASH, St. Paul, Zewditu, Yekatit and ALERT), data was collected via online questionnaire from microbiology logs and patient charts of those with positive cultures excluding contaminant growth from March 2023 up to March 2025. Collected data was analyzed via SPSS version 30 and association with dependent and independent variables was assessed via Chi-square tests, bivariate analysis and logistic regression.

Results A total of 281 cultures analyzed, gram-negatives accounted for 87.9% led by Acinetobacter at 27.4% followed by K.pneumoniae at 23.3% accounting nearly 1/2. Other gram negatives included Pseudomonas 13.5%, E.coli 8.5%, other Klebsiella spp 5.6%, small percentages of Enterobacter, Proteus and Citrobacter. Gram-positives accounted for 8.9% with S.aureus (5.0%) and Enterococcus spp (3.9%) and fungal isolates in 2.1%. CRAB was identified in 20.6%, CRE 21.7%, ESBL 11%, MDR Pseudomonas 7.1%, MRSA 2.8% and VRE 2.1%. Factors associated with AMR included increased total hospital stay prior to cultures and prior use of Meropenem. Overall mortality was 42.7% with half occurring in the first 8 days and strongest predictors being shock, increasing age, longer ICU stay prior to cultures and bloodstream infection.

Conclusion AMR is a significant problem in ICUs in Addis Ababa with very high prevalence of gram-negatives exhibiting resistance to most antibiotics including Carbapenems limiting available options amplifying the need for effective antibiotic stewardship and IPC programs. The strongest predictors of mortality included presence of shock and source of infection (bloodstream, CNS) urging early critical care interventions and improved resource allocation to reduce mortality.

Keywords: AMR, ICU, microbiologic profile, bacterial resistance, mortality

Introduction

Background

WHO considers AMR is one of the top 10 global public health threats facing humanity. (1) An estimated 4·95 million deaths occurred associated with AMR in 2019, highest in western sub-Saharan Africa, at 27.3 deaths per 100 000. The six leading pathogens for deaths associated with resistance were *E.coli* followed by *S.aureus, K.pneumoniae, S.pneumoniae, A.baumannii,* and P.*aeruginosa* which were responsible for 929,000 deaths. MRSA was responsible for more than 100 000 deaths. (2)

Although ICUs account for <10% of total beds in most hospitals, >20% of all nosocomial infections which are usually caused by MDR organisms are acquired in ICUs. (3) The WHO estimates that among hospital-treated sepsis cases worldwide, 23.6% are healthcare-associated, and 48.7% of ICU sepsis cases are hospital-acquired. (4,5)

ESKAPE pathogens have also garnered attention due to their ability to develop high level resistance to multiple drugs limiting therapeutic options and increasing morbidity and mortality. The threat is higher in developing countries due to sub-optimal hygiene conditions, poor infection prevention and control (IPC) measures, lack of surveillance and insufficient antimicrobial stewardship programs. (6,7) Worldwide hand hygiene recommendations remain suboptimal with an average of 59.6% compliance levels in ICUs up to 2018, and extreme differences between High income countries (HICs) and low-income countries (64.5% vs 9.1%). (8)

Statement of the problem

Up to 30% of ICU patients may be affected by healthcare-associated infections (HCAIs), with an incidence 2 to 20 times higher in LMICs compared to HICs. (9,10) Overall mortality among patients affected by health care-associated sepsis is 24.4%, with an increase to 52.3% among patients treated in ICUs. (4,5) and even higher in patients infected by resistant microorganisms, 2-3 times higher than those infected by sensitive microorganisms (9, 11-16). MRSA and carbapenem resistant bacteria pose a serious threat, CRAB, CRE and ESBL are considered critical pathogens by the WHO. These bacteria pose an even higher threat in LMICs, where there may be a limited availability of effective antibiotics against these pathogens. (12-18) There are also limitations in surveillance programs and laboratory capacity. (19)

In 2019 alone, there were 85,300 deaths associated with AMR in Ethiopia, leading to the 35th highest age-standardized mortality rate per 100,000, higher than deaths from maternal and neonatal disorders, cardiovascular diseases, respiratory infections and tuberculosis, enteric infections, and neoplasms. (20)

AMR also has significant economic costs. The World Bank estimates it could result in 1 trillion US$ additional healthcare costs by 2050, and 1 - 3.4 trillion $ GDP losses per year by 2030. (21)

HAIs in general remain a significant burden to Ethiopia's healthcare system with an overall prevalence of 16.9% with resulting prolonged hospital stay (6.3 more days) and increased in hospital mortality (AOR-2.23). (17,22) Lack of an effective ICP program and poor compliance in Ethiopia also likely plays a role (23,24) as a study done in TASH from inanimate object swabs in the ICU showed high prevalence of resistant microorganisms, with 85% of S. Aureus isolates being Methicillin resistant and gram negatives showing high levels of resistance as well. (25)

Significance of the study

A gap exists in current data regarding microbiologic patterns in adult medical ICU patients, making it challenging to establish effective empiric treatments for ICU infections and the main aim of this study is to tackle this problem shedding light on the patterns of microbes and their resistance to commonly employed antibiotics.

Formulation of antibiograms from the results of this study will help guide effective empiric antimicrobial use, knowledge of the resistance patterns will also provide vital information for IPC programs, improve adherence to these programs and antibiotic stewardship. It will also help identify which patients are at risk of dying from AMR.

It can help influence policy makers on import of essential antibiotics used in the treatment of resistant bacteria.

Literature review

Gram-negatives are a significant problem in ICUs internationally accounting 67% (Klebsiella 18%, E.coli 17%, Pseudomonas 16%, Acinetobacter 11%, Enterobacter 7%) of infections while gram-positives account 37% (S.aureus 10%, CoNs 8%, Enterococci 6.8% and S.pneumoniae 2.7%) with 4.6% being MRSA, 1.5% VRE and 8% CRAB. (26) In LMIC A. baumannii is the more prevalent gram-negative accounting 24% of isolates causing 42% of VAP, P. aeruginosa accounts 16% of isolates and 25% of VAP followed by K. pneumoniae which accounts 15% of isolates but is the dominant species for CLABSI (24%). VRE was>50% in Vietnam and MRSA was >50% of in most LMICs. MDR K. pneumoniae, A. baumannii, and P. aeruginosa were found among>50% of the isolates in India, Pakistan, Egypt, Vietnam and Nigeria. (27) A meta-analysis of African studies also found 20% of E.coli and 34% of K.pneumoniae were ESBL, 32% of Acinetobacter were CRAB and 8.9% of S.aureus were MRSA. (28)

In a study conducted in India, 91% of ICU infections were attributed to gram-negative bacteria. Acinetobacter spp. caused most cases of VAP. Among the gram-negative isolates, 34% were ESBL producers, including 41% of Klebsiella spp., 26% of E. coli, and 23% of Pseudomonas spp. (29) Whereas in a systematic review of AMR among HCAI in Africa; Klebsiella, S.aureus, E.coli and Pseudomonas were the common pathogens with 3.9 – 56.8% of infections being caused by MRSA and 1.9 – 53% of infections caused by ESBL organisms. (30)

A meta-analysis of AMR studies in Ethiopia found 35-47% of S.aureus were MRSA, 20% were resistant to vancomycin and 8% of Enterococci were VRE. Among Enterobacteriaceae 38% of E.coli and 56% of K.pneumoniae were ESBL. 14% of K. pneumoniae, 39% of P. aeruginosa and 35% of Acinetobacter species isolates were carbapenem resistant but most of the samples in this study were urine, otic and nasal. (31) A large multicenter study with 1416 cultures from TASH, Yekatit 12, Hawassa and Dessie also found a high number of gram negatives (K.pneumoniae (26.1%), K.variicola (18.1%), E. coli (12.4%) and 0.2% S.maltophilia). 78% of Enterobacteriaceae are ESBL and carbapenem resistance was seen in 17.1% of K. pneumoniae, 27.7% of E. cloacae and 58.8% of Acinetobacter baumannii. (32)

Nosocomial infection based studies have predictably found higher resistances as shown in a study from Dessie among nosocomial infections 93% of Acinetobacter isolates *were resistant to* most beta lactams but relatively sensitive to amikacin (87.5%) and ciprofloxacin (82%). P.aeruginosa isolates were resistant to ceftazidime (83.3%) but were sensitive to Amikacin (88.9%) and Meropenem (83.3%). (33) Similar

findings were reported in Bahir-Dar with A. baumannii having resistance to most beta-lactams and meropenem (33.3%) and P.aeruginosa having resistance to ciprofloxacin (36.4%) and meropenem (45.5%). (34)

An even higher level of resistance was seen in a study from TASH with 52.8% of gram negatives to producing ESBL, 25% carbapenemase, 14.3% AmpC-BL and 5.6% MBL. Most K.pneumoniae (77.3%) and K.oxytoca (77.8%) were ESBL producers and most Acinetobacter spp (53.2%) were CRAB. (35) A Jimma study found a lower level of ESBL compared to TASH with 36% ESBL among gram negatives, 7% AmpC BL but similar carbapenem resistance of 25% overall (21% of Enterobacteriaceae, 44% P. aeruginosa and all isolates of A.buamannii). In this study MRSA rate was 53%. (36) Overall MDR rates among gram negatives in hospitals are high as shown in a TASH study focused on K.pneumoniae with 98% of 132 isolates being MDR, 97% ESBL and Two (1.5%) isolates showed resistance to all tested antimicrobials. (37)

Central laboratory-based studies have also found high gram-negative resistance with 38-67% of isolates being ESBL, 2.4% producing AmpC-BL and 2% carbapenemase. The isolation of resistant gram negative was higher in the ICU ≥70% compared to ≤25 % in the wards (38,39)

Local ICU studies have tried to explore resistance patterns including a study from SPHMMC ICU that included 106 cultures which identified gram negatives in 68% (Acinetobacter-28%, Klebsiella pneumoniae and E.coli -13%) Gram positives in 19% (50%-CONS, 20%-Enterococci and S.aureus each, 10%-Streptococcus Pneumoniae) and fungi in 11% of patients. Acinetobacter isolates retained sensitivity to Meropenem and Aminoglycosides, E.coli were sensitive to meropenem, Piperacillin-Tazobactam, Ciprofloxacin and Aminoglycosides. Pseudomonas isolates were sensitive to Ciprofloxacin, cefepime, Piperacillin-Tazobactam and Meropenem. (40) The relatively lower levels of resistance in this study might be because the ICUs included were trauma and emergency ICUs. As shown in an Arba-Minch study from 22 positive cultures with most (59%) growing Gram-positives (38% S. aureus, 18% Enterococci and 9% CoNS) and from Gram-negatives 18% Klebsiella, 9% E.coli and Pseudomonas, 4.5% Enterobacter 4.5% with 68% of total isolates being MDR. MRSA isolates accounted for 57%, VRE 25%, on the other hand gram negatives showed susceptibility to Cefepime and Ciprofloxacin. The main limitation of this study was its small sample size (41)

A study from Lancet Hospital (private hospital in Addis Ababa) that included adult ICU patients found gram negatives in 77% (commonest being E.coli and K.pneumoniae). ESBL producing Enterobacteriaceae

in 37.5% and Carbapenem resistance in 27% with 70% of A.baumannii isolates being CRAB. In hospital mortality was 14.8% in patients with MDR isolates. (42) A study from Gondar that included pediatric and adult ICU patients showed K.pneumoniae 18%, K.ozanae 10%, K.rhinose 8% and E.coli, Citrobacter, S.aureus each accounted for 7%. Gram negative isolates were found to be resistant to ceftriaxone 77% but Amikacin (95%), Ciprofloxacin (83%) and Meropenem (87%) were relatively effective drugs. MRSA accounted for 57% and ESBL rate was 78%. (43)

Objectives

General Objectives

- To determine the microbiological profile of infections and resistance patterns among adult medical ICU patients in Addis Ababa from March 2023 to March 2025

Specific Objectives

- To determine the microbiological profile of infections among adult medical ICU patients in Addis Ababa from March 2023 to March 2025
- To identify antimicrobial resistance to commonly prescribed antibiotics in adult medical ICU patients among ICUs in Addis Ababa from March 2023 to March 2025
- To assess 30-day mortality caused by AMR among ICU infections
- To assess factors associated with 30-day outcomes associated with ICU infections
- To assess risk factors for development of AMR infections
- To assess appropriateness of empirically employed antimicrobials compared to culture results in the study period
- To recommend antibiograms for the studied ICUs

Methodology

Study area and period

Adult medical ICU patients at the selected government owned hospitals including TASH, SPMMC, Yekatit 12 hospital medical college, Zewditu general hospital and ALERT general hospital. Culture results from March 2023 to March 2025 were collected.

Study design

Retrospective cross sectional multicenter study

Population

Source population- Adult medical ICU patients among government hospitals in Addis Ababa

Study population- Adult medical ICU patients in the selected hospitals in Addis Ababa during the study period

Sample size and sampling design

All positive culture results excluding contaminants in the study period among the selected adult ICUs were included.

Data collection

The data was collected by the primary investigator and a trained collector via a structured online questionnaire from microbiology laboratory logs and patient charts

Data analysis

All information was checked after each data collection for its completeness. Data were analyzed using SPSS Version 30.0. Categorical variables were summarized using frequencies and percentages, and comparisons between groups were assessed using Chi-square (χ^2) tests or Fisher's exact tests where appropriate (expected cell count <5). Statistical significance was considered at $p < 0.05$.

Binary logistic regression was employed to determine independent predictors of adverse clinical outcomes. Variables with p-values <0.2 in bivariate analysis were included in the multivariable model using the Enter method. Model fitness was evaluated with the Hosmer-Lemeshow goodness-of-fit test, and results were presented as adjusted odds ratios (AOR) with 95% confidence intervals (CI).

Inclusion and exclusion criteria

Inclusion criteria- adult medical ICU patients aged ≥18 with suspected infection and confirmed culture growth

Exclusion criteria- patients with contaminant growth on culture (CoNs from blood culture, Yeast from urine)

Operational definitions

- Microbiological profile- proportion of distribution of microorganisms
- Resistance pattern- non susceptibility to one or more class of antibiotics including MDR, MRSA, CRAB, CRE and ESBL (IDSA 2024 definitions)
- MDR Pseudomonas- pseudomonas aeruginosa isolate that is non susceptible to at least 1 antimicrobial in 3 classes of antibiotics that are expected to be effective against pseudomonas (penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems)
- MRSA- a variant of S.aureus that is resistant to methicillin
- ESBL- bacteria with an enzyme that deactivates the Beta lactam ring conferring resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and Aztreonam defined by phenotypic detection of resistance to Ceftriaxone on disc diffusion
- CRAB- Acinetobacter baumannii isolates with resistance to carbapenems on disc diffusion test
- CRE- Enterobacteriaceae group with carbapenem resistance

Variables

Independent variables

- Patient characteristics: Age, gender, comorbidities, length of ICU stay, immune status
- Clinical factors: Type of infection, predisposing interventions (mechanical ventilation, central lines, surgery), prior antibiotic exposure.

Dependent variables

- Microbiologic Profile: The specific microorganisms isolated from patients
- Antimicrobial Resistance Patterns: MDR strains, ESBL, AmpC-BL, CRAB, CRE
- Clinical outcome: Patient mortality rate, factors associated with increased mortality

Ethical Approval

- Ethical approval was obtained from Department of Internal Medicine, College of Health Science Addis Ababa University and Addis Ababa health bureau
- Consent form can be waivered as the study poses minimal risk to participants since data is going to be collected from existing medical records and laboratory logs. And taking consent from already discharged or deceased patients is going to be difficult.
- Patient personal identifiers are not going to be collected and data will be collected while maintaining confidentiality.

Results

Sociodemographic characteristics

A total of 281 adult ICU patients were included in the study, median age of participants was 45 years with mean age of 44.99 ± 18.26. 174 patients (61.9%) were male, and 107 patients (38.1%) were female. With regard to distribution of patients among the involved hospitals; SPMMC contributed 82 patients (29.2%) to the study population, Zewditu Memorial Hospital 75 patients (26.7%), TASH 66 patients (23.5%), Yekatit 12 Hospital 37 patients (13.2%) while ALERT accounted for 21 patients (7.5%).

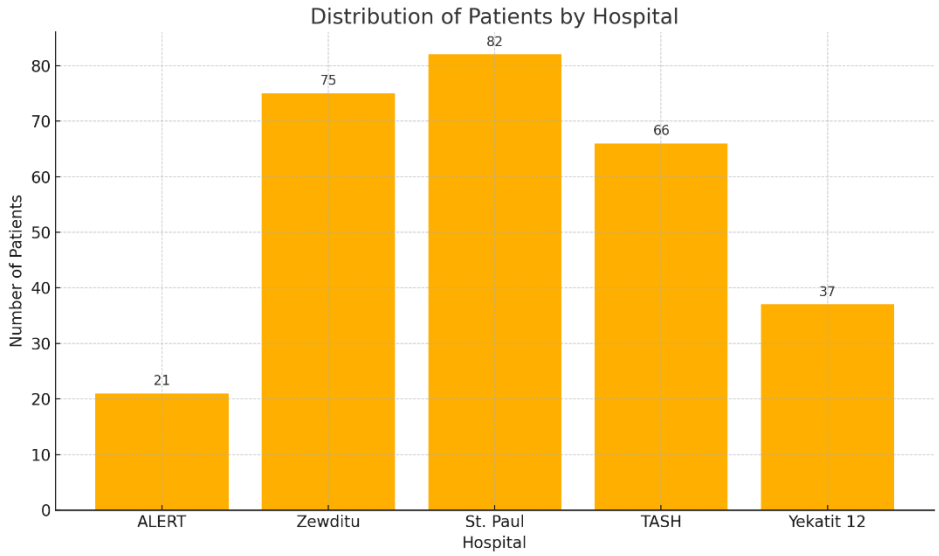

Figure 1: Distribution of patients among the hospitals

Cultured body fluid/sample

Cultures samples taken include tracheal aspirate in 104 isolates (37.0%), 82 blood cultures (29.5%), 55 urine (19.6%), 17 wound/abscess cultures (6.0%), 8 sputum (2.8%), 8 pleural fluid (2.8%), 7 CSF (2.5%), 5 samples from pus, 1 sample each from central catheter tip and joint fluid

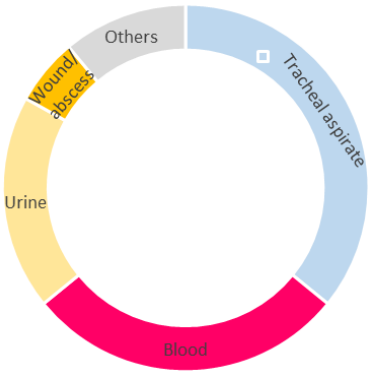

Figure 2: Cultures based on sample site

Primary source of infection

Ventilator-Associated Pneumonia (VAP) accounted for 123 cases, non-VAP (Community/hospital acquired pneumonia) accounted for 73 cases, there were 63 patients having UTIs either alone or in combination with other infection sites. Bloodstream Infections were reported in 54 patients, including those with overlapping diagnoses involving urinary, intra-abdominal, or soft tissue infections. Intra-abdominal infections were observed in 21 patients, while Skin/Soft Tissue Infections were seen in 20. CNS infections, including meningitis, were identified in 18 patients, and 15 patients had sources at other primary sites including aspiration pneumonia, brain abscess, CAUTI, empyema/parapneumonic effusion, postsurgical ventriculitis, pyogenic liver abscess, scrotal abscess, septic arthritis, shunt infection, and superinfected bedsore and 1 instance of CRBSI.

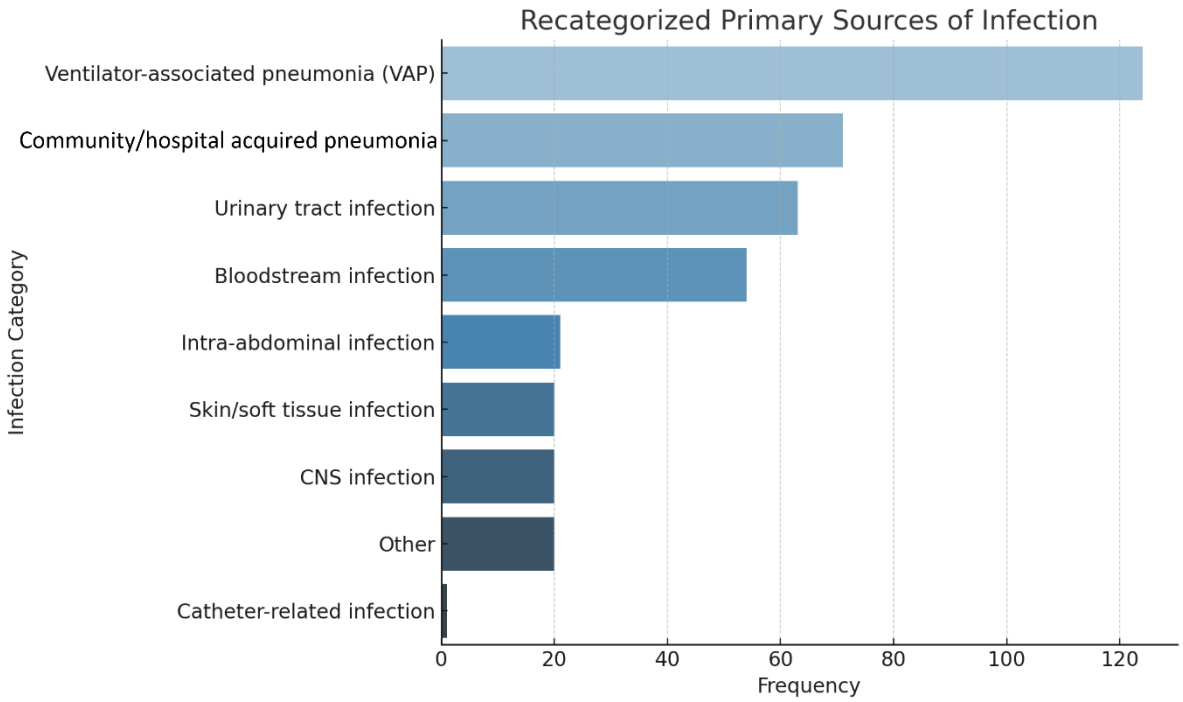

Figure 3**:** Primary sources of infection

Length of hospital stay prior to cultures

The median length of ICU stay prior to sending cultures was 9 days and the median length of total hospital admission duration was 23 days.

Previously used empiric antibiotics

The most common empirically used antibiotic was Vancomycin in 205 patients (73%), Cefepime 129 (45.9%), Ceftriaxone 120 (42.7%), Meropenem in 68 (24.2%), Ceftazidime in 51 patients (18.1%), Metronidazole in 105 (37.4%), and other antibiotics 118 (41.9%). 26 patients (9.25%) hadn't received any prior antibiotics. Commonest pre-culture combination regimen was Cefepime with Vancomycin, accounting for 15.7% of all regimens followed by Meropenem with Vancomycin (7.8%), Ceftazidime with Vancomycin (6.4%) and ceftriaxone with vancomycin (5.3%). 8 patients were on Anti-TB (2.85%) and 1 patient was on Fluconazole.

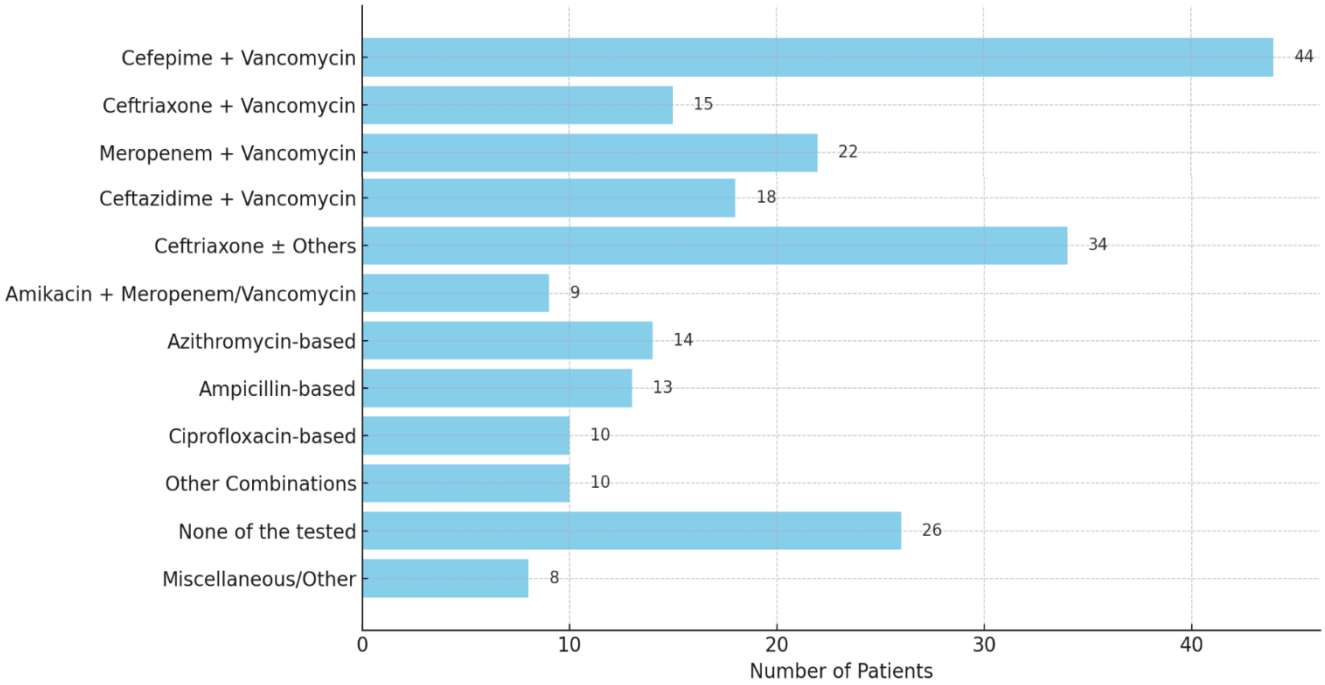

Figure 4: Previously used empiric antibiotic combination regimens

Comorbidities

AKI was the most commonly reported comorbidity, either alone or in combination, affecting 33.8% of the population; heart failure was present in 12.1%, with overlaps including COPD, AKI, and malignancy in some cases. Hypertension in 30 (10.7%).

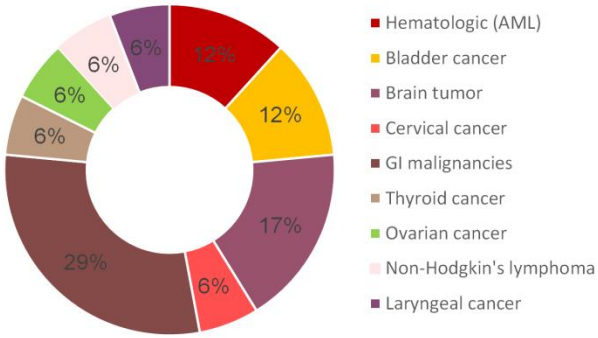

Figure 5: Distribution of malignancies

Comorbidity	Frequency (n)	Percent (%)
AKI	95	33.8
Heart Failure	34	12.1
Hypertension	30	10.7
Diabetes	24	8.5
HIV	18	6.4
Malignancy	17	6%
Stroke (Ischemic/hemorrhagic)	14	4.9
Tuberculosis	12	4.2
CKD	10	3.6
COPD	6	2.1
Liver failure	4	1.4
Asthma	5	1.8
Others	5	1.8
None	11	3.9

Table 1: Comorbidities

Predisposing factors

Among the assessed predisposing factors mechanical ventilation was present in 88 patients (31.3%), urinary catheterization in 31 patients (11.0%) and recent surgery (prior 30 days) in 27 patients (9.6%). Several patients had combinations of risk factors with invasive mechanical ventilation combined with urinary catheterization in 36 patients (12.8%), and mechanical ventilation with recent surgery in the past 30 days was present in 25 patients (8.9%). 58 patients (20.6%) had no predisposing condition identified.

Identified pathogens

Gram-negative bacteria were dominant, comprising approximately 87.9% of all isolates. Acinetobacter baumanii, accounting for 27.4% (n = 77) of cases, followed by Klebsiella pneumoniae at 23.13% (n = 65). Together, these two pathogens constituted nearly half of all first isolates.

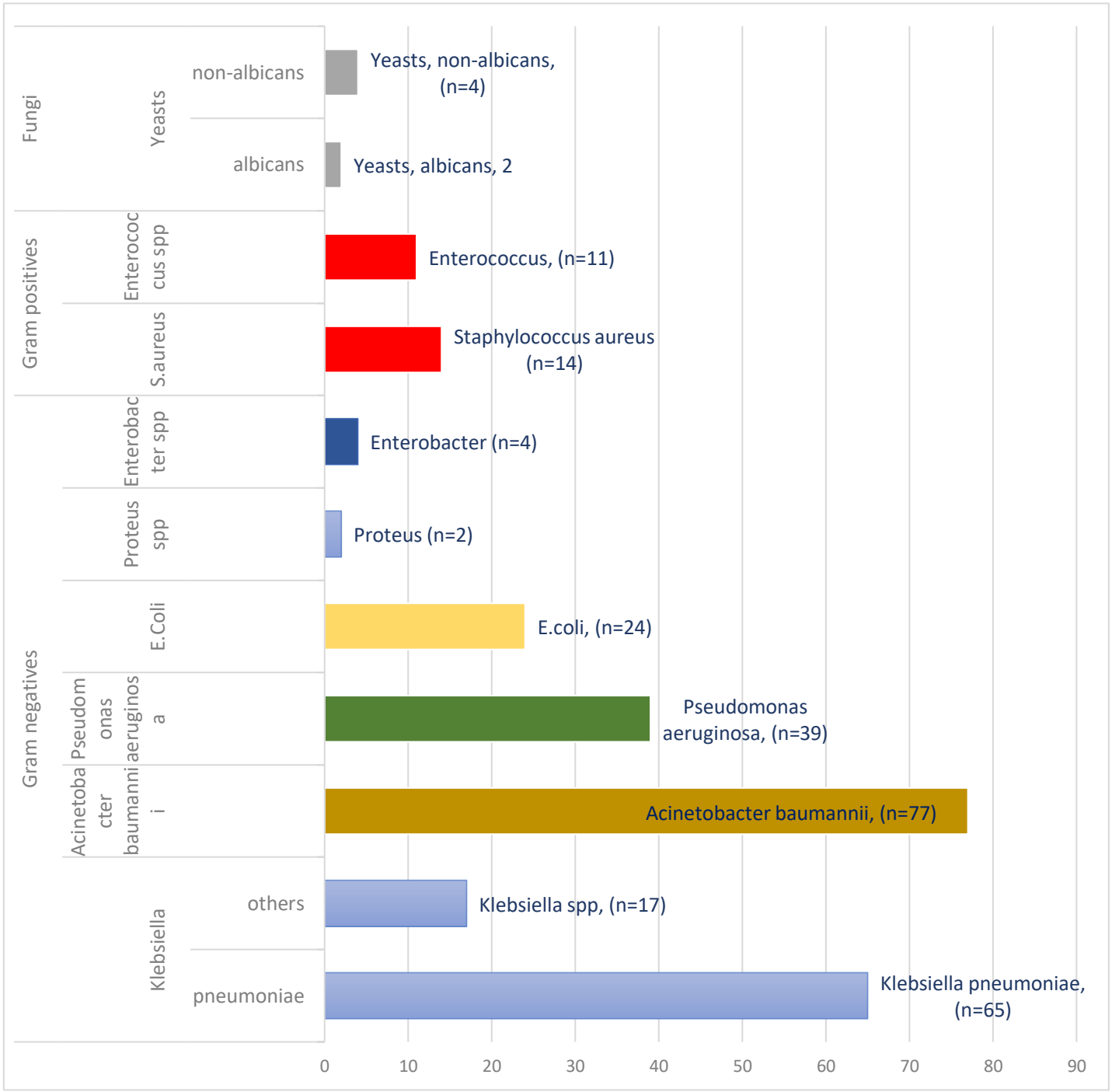

Figure 6: Microbial profile of isolated organisms

Other gram negatives included E. coli (8.5%, n = 24), Pseudomonas aeruginosa (13.9%, n = 39), Klebsiella oxytoca (2.5%, n=7), Klebsiella ozaenae (2.1%, n=6), Klebsiella rhinoscleromatis (1%, n=3) Enterobacter spp (1.4%, n=4) and smaller numbers of Citrobacter (n=2) and 1 isolate of (K.aerogenes, P.mirabilis, P.vulgaris, N.meningitides).

Gram-positive bacteria accounted for 8.9% (n = 25) of isolates, with Staphylococcus aureus (5.0%) and Enterococcus spp. (3.9%). Fungal isolates with Yeast growth (including Candida and non-candidia species) were detected in 6 patients (2.1%) with non-Candida albicans yeast detected in 4 patients (1.4%).

Identified pathogens organized by hospital

Acinetobacter was the overall dominant species in most hospitals including TASH (n=24), SPMMC (n=24) and Zewditu (n=18) followed by Klebsiella pneumoniae

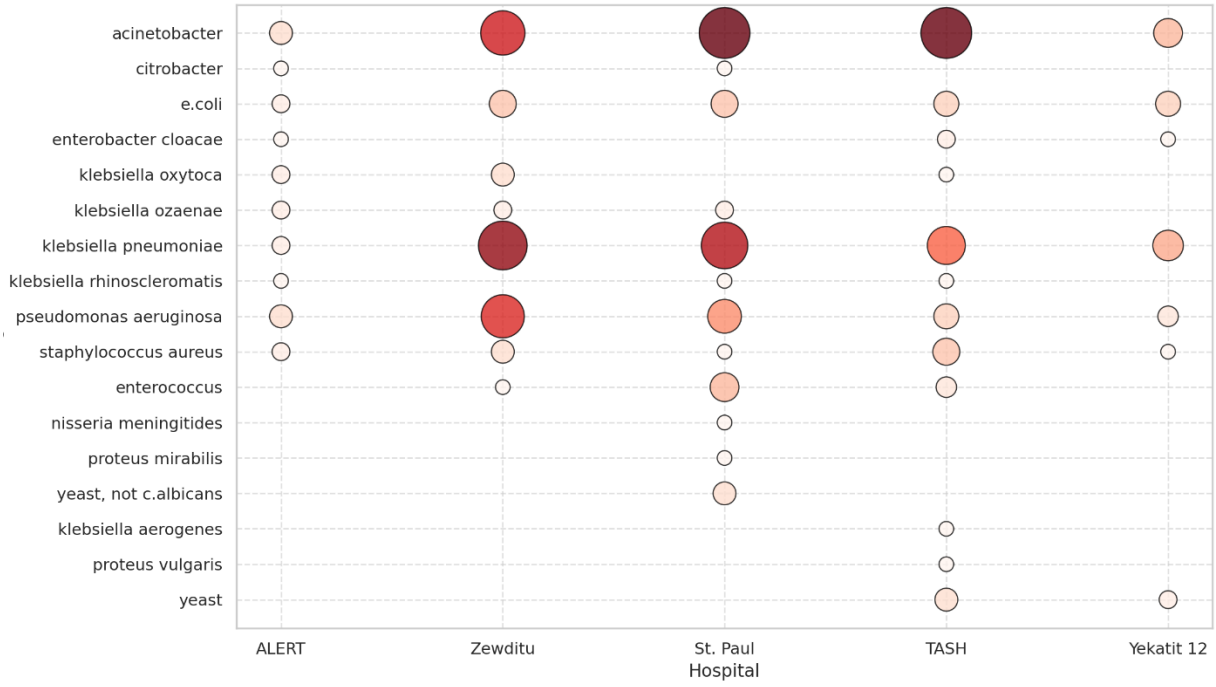

Figure 7: Pathogens specified by hospital

Resistance patterns

A total of 184 pathogens from the 281 had one of the prespecified AMR pattern with 58 isolates of CRAB (20.6%), 61 isolates of CRE (21.7%), 31 isolates of ESBL (11%), 20 isolates of MDR Pseudomonas (7.1%), 8 isolates of MRSA (2.8%) and 6 isolates of VRE (2.1%). 97 isolates (34.5%) didn't fit into one of these AMR categories.

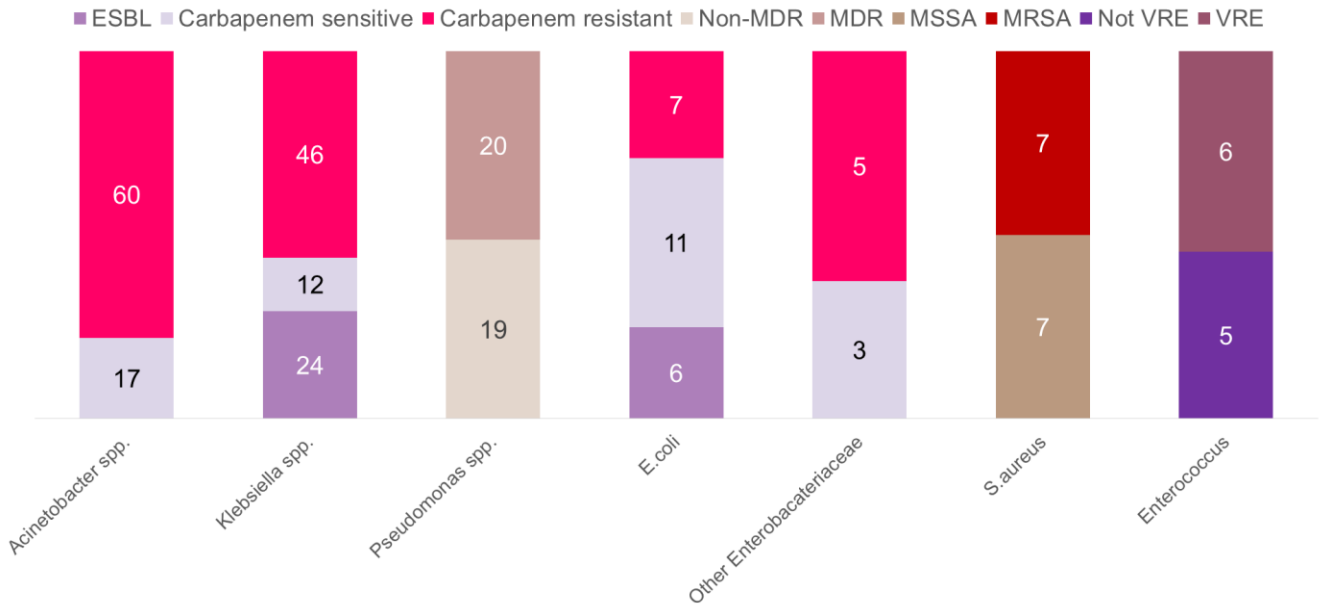

Figure 8: Resistance patterns

Among individual organisms 75.3% of all Acinetobacter baumannii isolates were Carbapenem resistant, 27% of Enterobacteriaceae are ESLB producing and 53% are carbapenem resistant. 50% of S.aureus are MRSA and 54.5% of Enterococci are VRE.

Overall Amikacin was the most commonly effective antibiotic (sensitivity in 107 (38%)) followed by Gentamicin in 66 (23.4%) and Meropenem in 67 cases (23.5%), Ciprofloxacin (35 cases, 12.4%) and Piperacillin-Tazobactam in 24 cases (8.5%). Sensitivity to cephalosporins was comparatively lower overall with; Cefepime (19 cases, 6.4%), Ceftriaxone (17 cases, 6.0%), and Ceftazidime (18 cases, 6.4%).

Carbapenem resistance among Gram negatives overall is 48.7% (n=137) including pseudomonas. Among resistant isolates Amikacin is by far the most effective of the available tested antibiotics 7% of CRAB, 26% of CRE and 45% of MDR pseudomonas. Meropenem retains its activity in 35% of MDR Pseudomonas Gentamicin in 25%.

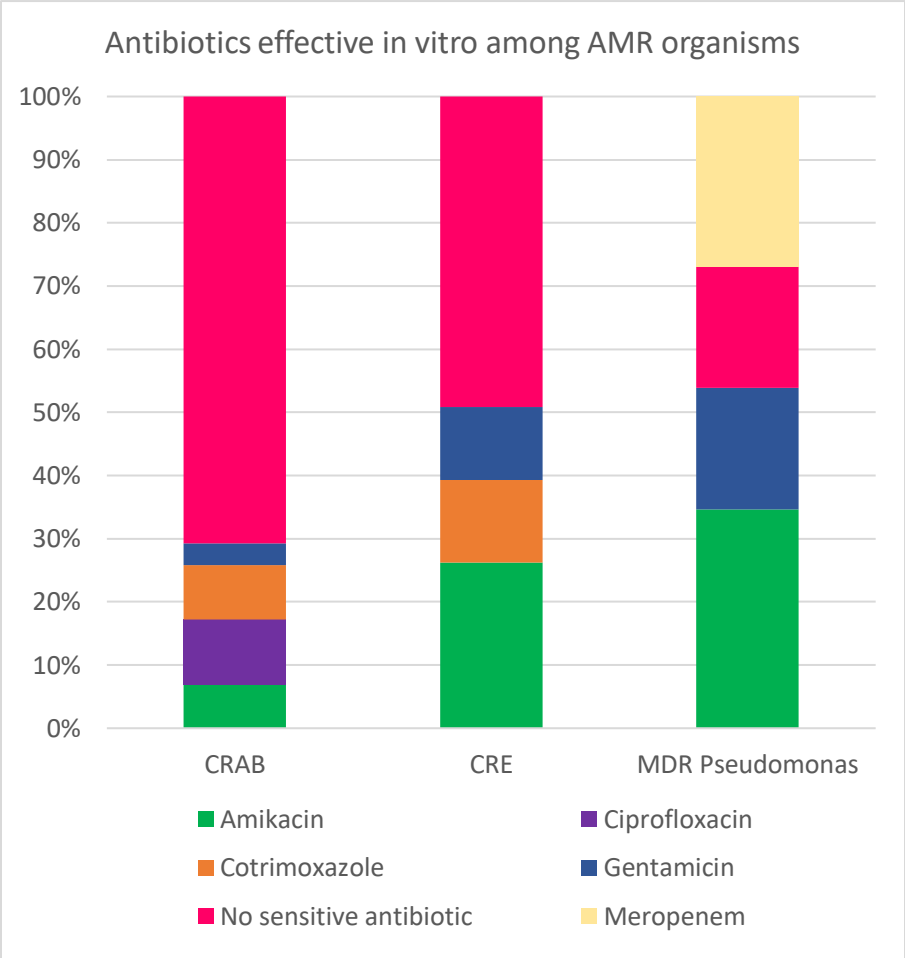

Figure 9: Antibiotics remaining effective in vitro among AMR organisms

Resistance patterns by hospital

CRAB remains the predominant resistance pattern in most hospitals with 34% of all TASH isolates, 18% of SPMMC, 20% of Zewditu, 21% of Yekatit 12, 19% of ALERT and 14.6% of Zewditu isolates followed by CRE which accounted 19% of isolates at TASH and SPMMC, 26% of Zewditu, 42% of Yekatit 12 and 9.5% of ALERT isolates. ESBL and MDR Pseudomonas were the next most prevalent resistance patterns

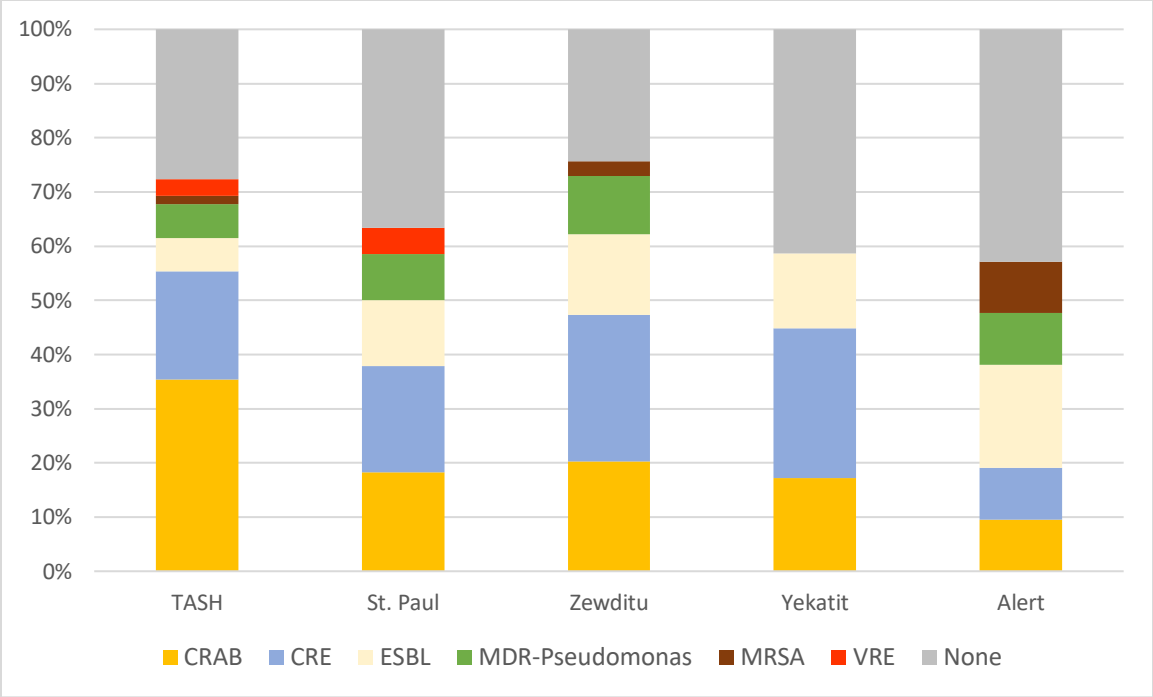

Figure 10: Resistance patterns by hospital

Resistance patterns based on cultured site

CRAB was most frequently isolated from respiratory samples and blood, with 12 isolates in blood (14.5% of blood cultures), CRE appeared prominently across blood and urinary tract isolates, with 18 isolates in blood (21.7%) and also detected in catheter and urine samples, ESBL were found in urine and wound cultures, with 9 isolates in blood (10.8%). MRSA showed highest frequency in wound/abscess cultures, with 5 isolates in blood (6.0%). MDR Pseudomonas was distributed across respiratory, urinary, and wound sites, with 3 isolates in blood (3.6%).

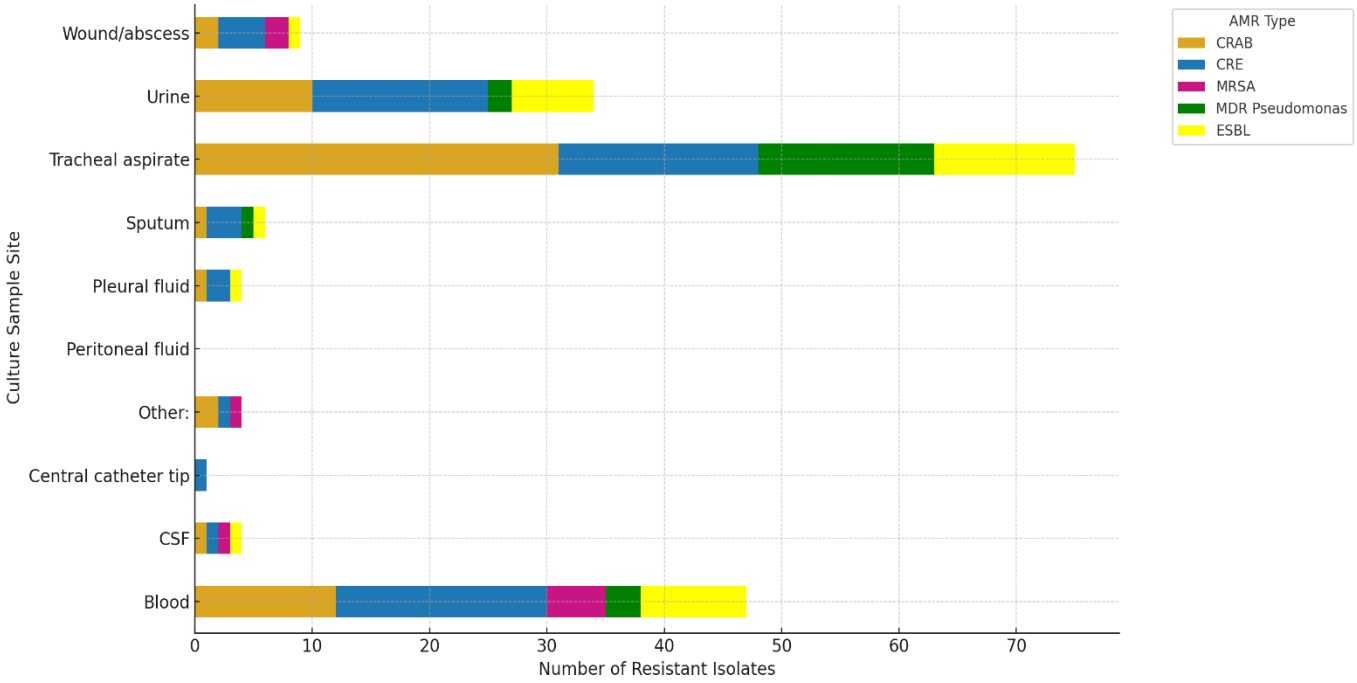

Figure 11: Resistance patterns by culture sample site

30-day outcomes

Out of the total patients in the study 120 (42.7%) died within the ICU, 82 patients (29.2%) were discharged from the ICU and 79 patients (28.1%) were still in the ICU at 30 days of the suspected infection. Half of deaths were observed in the first 8 days of ICU admission.

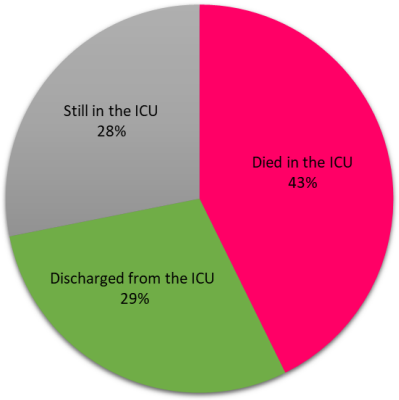

Figure 12: Outcome at 30 days

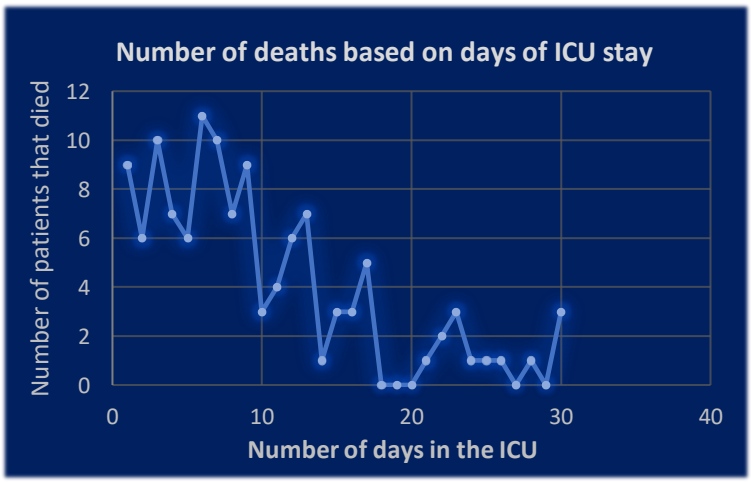

Figure 13: Deaths based on days of ICU stay

Factors associated with development of AMR

Chi-square and logistic regression models for associations between ICU length of stay, mechanical ventilation, age and presence of shock. There was an increased risk of developing AMR in mechanically ventilated patients but it didn't reach statistical significance.

On the other hand, total hospital length of stay prior to sending cultures was associated with increased risk of AMR development (p=0.041)

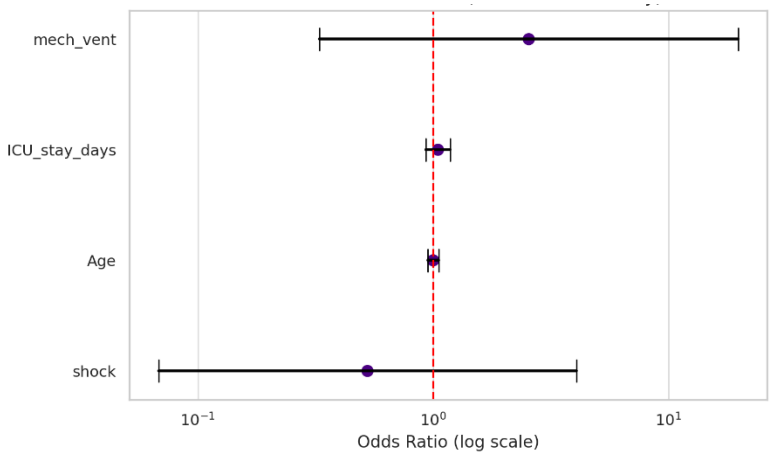

Figure 14: Forest plot of associations with AMR development

Antibiotics

Among prior use of commonly used antibiotics, use of Meropenem was associated with resistance significantly

Antibiotic	N	Chi-Square	p-value	Significant
Cefepime	129	9. 55	0.145	No
Ceftazidime	51	3.95	0.684	No
Ceftriaxone	120	11.55	0.073	No
Meropenem	68	25.53	0.001	Yes
Vancomycin	205	9.14	0.166	No

Table 2: Relation of prior antibiotic use AMR development

Factors affecting 30-day outcomes

Age and comorbidities

Increasing age is correlated with worse outcomes compared with age <40, OR- 1.87 [1.06-3.31] p=0.03 and OR- 2.55 [1.4-4.64] p=0.02 with age >60). The presence of multiple (3 or more) comorbidities was associated with increased mortality (p = 0.027) but on individual analysis of each comorbidity a statistically significant difference wasn't noted.

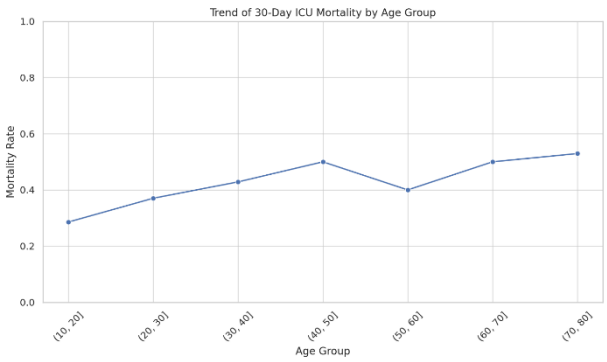

Figure 15:

30-day mortality based on age

Out of the 120 patients who died within the ICU, 75 (62.5%) had experienced shock in contrast to only 10 (12.2%) of patients who were discharged (OR-10.69, 95% CI: [5.96, 19.17] p<0.001). Additionally, among the 79 patients still in the ICU at day 30, 66 (83.5%) had experienced shock.

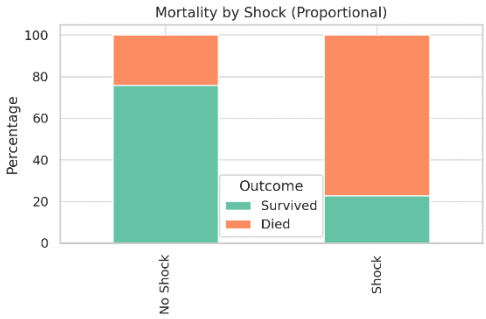

Figure 16: 30-day mortality based on presence of shock

Length of stay and AMR pattern

Increased length of stay in the ICU prior to cultures was associated with increased mortality (p<0.001). Even though there were numerically higher number of deaths in VRE (66.7%), MDR-Pseudomonas (55%) and CRE (47.5%) than CRAB (37.9%), ESBL (38.7%) and MRSA (50%) although lower sample sizes were seen in MRSA and VRE, the association between AMR pattern and mortality was insignificant on Chi-square analysis (p=0.572).

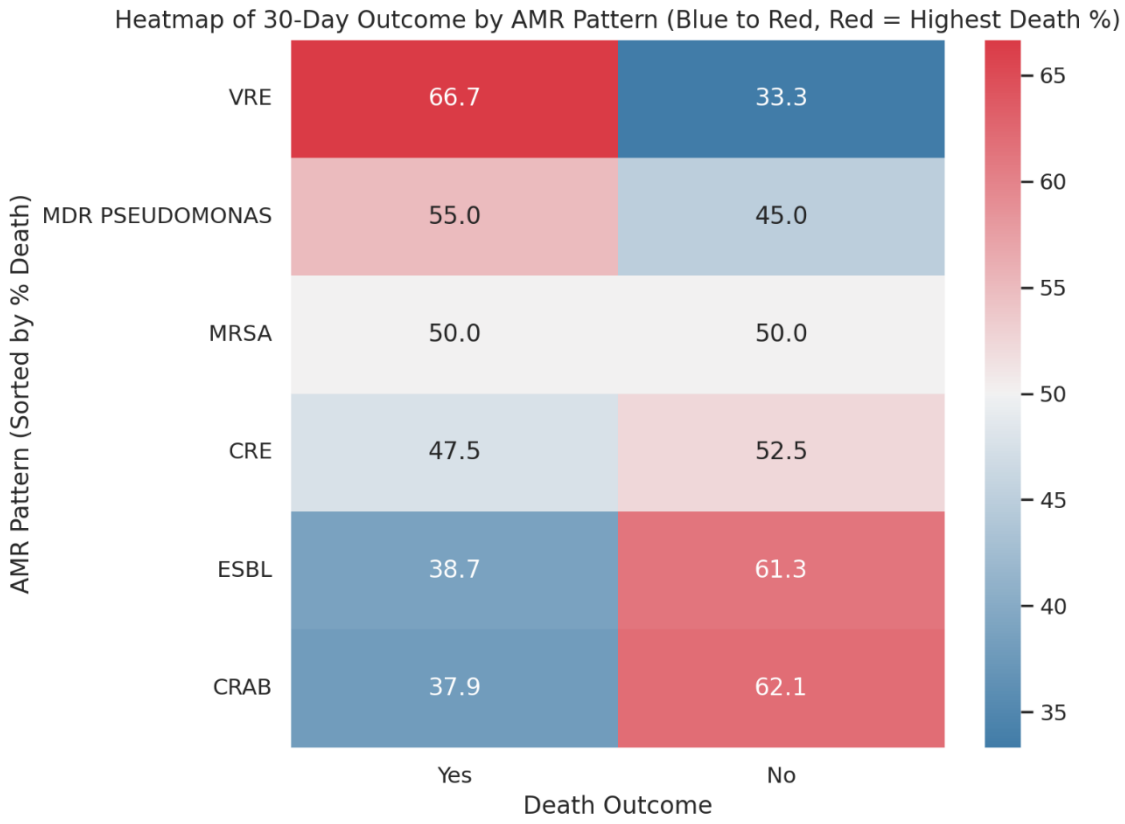

Figure 17: Mortality based on AMR pattern

Source of infection

Bloodstream infections have the highest mortality (63%), followed by CNS infections (50%) and Intra-abdominal infections at 47.6%, respectively. Urinary tract infections are associated with the lowest mortality at 22.6%. (p<0.001)

Infection Source	Survived	Died	Mortality Rate (%)
Bloodstream infection	20	34	63.0
CNS infection	10	10	50.0
Intra-abdominal infection	11	10	47.6
Community/Hospital acquired pneumonia	43	38	46.9
Skin/Soft tissue	12	8	40.0
Ventilator associated pneumonia	80	44	35.5
Urinary tract	24	7	22.6

Table 3: Morality based on infection source

Source of infection with regard to presence of shock

Out of the 82 patients with a positive blood culture, 37 (45.1%) experienced shock, compared to 60 (30.2%) of the 199 patients with a negative blood culture result. (p=0.041)

Hospital of admission

ALERT and TASH had the highest mortalities among the hospitals at 66.7% and 62.1% respectively with lowest mortality observed at St.paul hospital (26.8%) with p-value=0.001

Hospital	Survived	Died	Total	Mortality Rate (%)
ALERT	7	14	21	66.7%
TASH	25	41	66	62.1%
Zewditu	45	30	75	40.0%
Yekatit 12	24	13	37	35.1%
St. Paul	60	22	82	26.8%

Table 4: Mortality by hospital of admission

Hospital of admission and source of infection/presence of shock

Differences in mortality among hospitals weren't significant with regard to AMR patterns (OR- 1.21 95% CI[0.73, 2.01], p=0.461) but were significant for presence of shock (p=0.013)

Hospital	CAP/ HAP	VAP	CNS	BSI	UTI	Intra-abdominal	Skin/ Soft Tissue	Other source	Shock	Mortality in shock patients
ALERT	5	7	3	6	4	3	2	1	14 (66.7%)	92%
Other	14	44	8	9	9	5	6	7	20 (26.7%)	86%
St. Paul	16	37	3	13	27	11	4	3	23 (28.4%)	65%
TASH	28	22	3	21	7	1	6	10	38 (58.5%)	60%
Yekatit 12	13	14	3	4	16	1	2	0	2 (5.4%)	50%

Table 5: Hospital based distributions of infections, shock and shock-related mortality

Effectiveness of pre-culture empiric regimens

58 (20.6%) patients received effective empiric therapy — meaning the pathogen was sensitive to at least one antibiotic given before culture and 223 (79.4%) received ineffective empiric therapy from which 43% and 41.3% died respectively, although numerically higher mortality was seen with ineffective antibiotics impact didn't reach statistical significance (p=0.934)

Discussion

Demographic representation is consistent with other studies done in ICUs locally (40,42) with male predominance at 61.9% for unclear reasons. The overall ICU microbial profile pattern was found to be predominantly gram-negative isolates accounting 87.9% with predominance of Acinetobacter spp accounting 27.4% and Klebsiella spp accounting 23.3% which account around half of all isolates followed by Pseudomonas spp and E.coli which is similar to worldwide data and LMIC patterns. (26,27,29) This was seen in 3 of the hospitals included but not in Yekatit 12 and ALERT hospital for which the data may have been skewed by small sample sizes from those centers. On the contrary the prevalence of gram-positives including S.aureus and Enterococci spp was much lower at 8.9% and with a small number of fungal isolates at 2.1% compared to other local and global studies.

This is also reflected in the resistance patterns where a large number of CRAB (20.6%), CRE (21.7%), ESBL (11%), MDR Pseudomonas (7.1%) were isolated reflecting a high number of Carbapenem resistant gram-negative isolates which is higher than what was found in a meta-analysis of African studies and prior study based in TASH (28,35) Interestingly there was a much lower incidence of MRSA and VRE at 2.8% and 2.1% compared to most other studies including a local studies done at AABET/SPMMC and Arba-minch. (40,41) The much lower incidence of MRSA in this study might be explained by the high usage of empiric vancomycin (72.9%)

Compared with studies from Gondar and Lancet hospital resistance of gram-negatives to carbapenems and Aminoglycosides was much higher (42,43) which might have been driven by the high usage of empiric beta-lactams including Cefepime and Meropenem which was found to be associated with development of resistance in this study as well. Among the remaining antibiotics Amikacin was the only drug with retained efficacy against resistant isolates with 7% of CRAB, 26% of CRE and 45% of MDR pseudomonas being sensitive.

Factors associated with increased development of AMR include total length of hospital stay prior to sending cultures but not length of ICU stay prior to cultures. Prior use of Meropenem was also associated with increased risk but this wasn't seen with other antibiotics. Age, mechanical ventilation and presence of shock were not significantly associated with development of AMR.

Mortality in this is study was much higher (42.7%) compared to other local and international studies (27,40,42) with variation between hospitals; highest in ALERT (66.7%) and TASH (62.1%) with lower

mortality in Zewditu (40%), Yekatit 12 (35.1%) and SPMMC (26%). There was a higher proportion of patients presenting with shock to TASH (66.7%) and ALERT (58.5%) compared to other hospitals among which more percentage of patients died at TASH (92%) compared with other hospitals which might indicate a need for better management of shock. This variation might be due to severity of illness at presentation or resource availability.

Other factors significantly associated with 30-day mortality are presence of shock (OR-10.69, 95% CI: [5.96, 19.17] p<0.001), increasing age (compared with age <40, OR- 1.87 [1.06-3.31] p=0.03 and OR- 2.55 [1.4-4.64] p=0.02 with age >60), ICU length of stay prior to development of the infection and source of infection (highest in bloodstream infections at 63% followed by CNS infections at 50% and intra-abdominal infections at 47.6%). Individual comorbidities were not significant for increasing mortality although the presence of multiple (≥3) comorbidities increased mortality. Morality was not significantly associated with the pattern of AMR although numerically higher differences were seen they were statistically insignificant which is contrary to other studies (27).

Mortality was highest in the first 8 days where ½ of deaths occur pushing the need for early and rapid treatment of shock, use of effective antimicrobials and appropriate intensive care. Even though numerically higher number of patients died while on ineffective empiric pre-culture antibiotics (43% Vs 41.3%) the results didn't reach statistical significance (p=0.934)

The strengths of this study include being a multicenter study enabling assessment of outcomes across different hospital and capturing 30 day mortality and factors associated with it while the limitations are its retrospective and observational nature, certain hospitals were relatively under-represented

Strengths and limitations of the study

The strengths of this study include its multicenter design and inclusion of large sample size. The limitations include lack of strong microbiologic data (sensitivities for critical antibiotics were not done, lack of analysis of resistance mechanism, speciation of bacteria were limited and there were some incomplete data), private hospitals weren't included limiting generalized conclusions and the retrospective nature makes it difficult to incriminate risk factors for mortality with higher certainty.

Conclusion

AMR is a significant problem in ICUs in Addis Ababa with very high prevalence of gram-negatives exhibiting resistance to most antibiotics including Carbapenems limiting available options amplifying the need for effective antibiotic stewardship and IPC programs. The strongest predictors of mortality included presence of shock and source of infection (bloodstream, CNS) urging early critical care interventions and improved resource allocation to reduce mortality.

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Questionnaire

Identification

1. Age in years _____
2. Sex (M/F) _____
3. ID No. _____
4. Hospital _____
5. ICU length of stay prior to culture (days) _____
6. Total length of stay in the hospital (days) _____

Patient data

7. Culture isolated from

☐ Blood ☐ Tracheal aspirate ☐ Skin/wound ☐ Urine

☐ CSF ☐ Pleural/peritoneal ☐ Central catheter tip

☐ Sputum ☐ Another site _____

8. Suspected source of primary infection

☐ Ventilator associated Pneumonia

☐ Hospital acquired pneumonia

☐ Blood stream infection

☐ CNS source (meningitis…)

☐ Urinary tract

☐ Central line related infection

☐ Intra-abdominal infection

☐ Skin/soft tissue

☐ Infective endocarditis

9.

Isolated bacteria	
Previously used antibiotics	
Antibiotics resistant to	
Sensitive antibiotics	
Intermediate antibiotics	

10. Classification of resistance pattern

☐ ESBL ☐ AmpC ☐ CRE ☐ CRAB

☐ MDR Pseudomonas ☐ DTR Pseudomonas

11. Predisposing factor

☐ Mechanical ventilation ☐ Central line ☐ Urinary catheter ☐ Recent surgery (30 days)

12. Comorbidities

☐ Heart failure ☐ AKI ☐ CKD ☐ On hemodialysis

☐ Hypertension ☐ Malignancy (specify if present) _____

☐ Diabetes ☐ COPD/Asthma ☐ HIV ☐ Liver failure

13. Hemodynamic collapse at any time (shock)

☐ Yes ☐ No

Patient outcome (after 30 days)

☐ Discharged from the ICU alive ☐ Died within the ICU ☐ Alive in the ICU