

# Emergence of Extended-Spectrum Beta-Lactamase and Carbapenemase Producing Gram Negative Non-Fermenters at Selected Hospitals of Northeast Ethiopia: A Prospective Cross-Sectional Study

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**Background:** The emergence and spread of extended-spectrum  $\beta$ -lactamases (ESBLs) and carbapenemase (CP) producing gram negative non-fermenters are becoming a serious public health threat globally. Infections caused by these pathogens limit treatment options and contribute to the significant morbidity and mortality. Thus, to reduce their spread, early detection of these superbugs is very crucial. This study therefore aimed to assess the prevalence of ESBLs and CP producing gram negative non-fermenters at selected hospitals of North East Ethiopia.

**Methods:** A cross-sectional study was conducted from January to June 2021. *Acinetobacter baumannii* (*A. baumannii*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) were identified using standard bacteriological techniques. ESBL and CP production were detected by combined disk diffusion and modified carbapenem inhibitory methods, respectively. Data were collected via face-to-face interview and patient card review. Chi-squared and Fisher's exact tests were calculated and p-value < 0.05 was considered statistically significant.

**Results:** A total of 384 patients participated in this study. Overall, 30 (7.8%) patients had positive culture for *A. baumannii* and *P. aeruginosa*. The prevalence of *A. baumannii* was 20 (5.2%) and that of *P. aeruginosa* was 10 (2.6%). From the overall isolates, 16 (53.3%) were ESBL and the proportion of carbapenemase production was 4 (13.3%). ESBL production was 8 (40%) in *A. baumannii* and 8 (80%) in *P. aeruginosa* isolates. ESBL production infections were significantly associated with hospitalization (p=0.004). Intravenous catheterization, hospitalization, and surgery had significant association with ESBL production (p<0.005). All isolates of *A. baumannii* and *P. aeruginosa* were MDR.

**Conclusion:** ESBL and carbapenemase production among *A. baumannii* and *P. aeruginosa* were high in the selected hospitals. The treatment of such resistant infectious agents should be guided by antimicrobial susceptibility test in a study setting. Thus, restricted and wise use of antibiotics is highly recommended to contain the spread of these superbugs. Hospitals should develop infection prevention guidelines to prevent the spread of resistant pathogens in hospitalized patients.

**Keywords:** ESBL, CP, MDR, *A. baumannii*, *P. aeruginosa*, Ethiopia

## Background

*Acinetobacter baumannii* (*A. baumannii*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) are gram negative non-fermenter (GNNF) superbugs responsible for multi-drug resistant infections at different clinical sites.<sup>1–3</sup> They are the main etiologic agents of blood stream infection (BSI), urinary tract infection (UTI), wound infection, and lower respiratory tract infection (LRTI).<sup>1</sup> Infection with these multi-drug resistant (MDR) strains seriously compromise treatment options.<sup>4</sup>

*A. baumannii* and *P. aeruginosa* are ubiquitous in nature, easily survive in moist environments and have innate resistance to many antibiotics.<sup>5,6</sup> They frequently contaminate healthcare facility surfaces and shared medical equipment, and challenge the treatment of hospitalized patients.<sup>7</sup> *Acinetobacter baumannii* is mainly associated with BSI, pneumonia, and wound infections.<sup>5,8</sup> Besides its potential for substantial antimicrobial resistance,<sup>7</sup> carbapenem-resistant *A. baumannii* is one of the

critical-priority pathogens on the WHO priority list of antibiotic-resistant bacteria for effective drug development.<sup>8</sup> Similarly, *Pseudomonas aeruginosa* is involved in serious BSI, UTI, and LRTI and wound infections predominantly affecting hospitalized and immunocompromised individuals, and is highly resistant to many of the available antimicrobial agents including carbapenem.<sup>9–11</sup>

Different virulence factors have been isolated for *A. baumannii*, including hemolytic factors, iron acquisition systems, efflux pumps, lipopolysaccharides and OmpA, which can induce host immune system responses or bacterial adherence to epithelial cells.<sup>12</sup> The production of phospholipases and elastases also facilitates the infection by degrading phospholipids, elastin and destruction of host cell tissue.<sup>13,14</sup> Multiple intrinsic and acquired virulence factors are exploited by *P. aeruginosa*, including modification of drug targets, inactivation of antibiotics, expression of efflux systems, attenuation of membrane permeability, formation of biofilms and quorum-sensing, which, collectively, contribute to its distinctly low antibiotic susceptibility.<sup>15,16</sup>

Besides *A. baumannii*'s and *P. aeruginosa*'s intrinsic resistance to many antibiotics, the bacteria constantly develop new paths of resistance.<sup>17</sup> Hence, the resistance to carbapenem drugs among these bacteria is a current challenge worldwide. They acquire genes encoding for beta-lactamases which are their foremost mechanisms of MDR.<sup>18</sup> Extended spectrum  $\beta$ -lactamases (ES $\beta$ L) and carbapenemases (CP) are now spreading among GNNFs causing serious infections with poor clinical outcomes and high mortality rates, mainly in hospitalized and immunocompromised patients.<sup>19,20</sup> Carbapenems such as doripenem, ertapenem, imipenem and meropenem are the last resort antibiotics against both *A. baumannii* and *P. aeruginosa* infections.<sup>21</sup> However, their efficacy is influenced by the production of carbapenemases. Carbapenemases are enzymes capable of hydrolyzing one or more carbapenem antibiotic in addition to penicillins, cephalosporins, and monobactams.<sup>22</sup> Resistance of *A. baumannii* and *P. aeruginosa* to one of the carbapenem drugs is considered carbapenem resistance according to the Clinical and Laboratory Standards Institute (CLSI) guideline.<sup>23</sup> Thus, infections caused by carbapenem resistant *A. baumannii* and *P. aeruginosa* are of particular concern because treatment options are extremely limited and they are often difficult to treat with available antibiotics.<sup>24</sup>

A few studies in the world documented 14.5–100% and 31–60.3% rates of carbapenem resistance among clinical isolates of *A. baumannii* and *P. aeruginosa*, respectively.<sup>25–28</sup> A surveillance study done in Switzerland indicated there was 10.8% carbapenem resistance among *A. baumannii* species.<sup>29</sup> A systematic review done in Africa also revealed the pooled prevalence of CP *P. aeruginosa* and CP *A. baumannii* among the clinical specimens was 21.36% and 56.97%, respectively.<sup>30</sup> Because the increased incidence of infections with these resistant pathogens is associated with over-use of antimicrobials, prescription without susceptibility test, self-medication, and prolonged hospitalization, and the high immunocompromisation in resource-limited settings,<sup>31,32</sup> the burden could be higher, and containment of these superbugs remains a challenge throughout the world. These highly MDR pathogens; *A. baumannii* and *P. aeruginosa*, are the WHO critical-priorities for effective drug development. Despite this concern, epidemiological data presenting the magnitude are limited in low-income countries including Ethiopia. Therefore, this study planned to estimate the burden of ES $\beta$ L and CP producing GNNFs (*A. baumannii* and *P. aeruginosa*) in the selected hospitals in Northeast Ethiopia.

## Methods

### Study Design, Period and Setting

A hospital-based cross-sectional study was conducted between January and June 2021 among 384 patients presumed to have urinary tract, blood stream, lower respiratory or wound infections at selected hospitals in Northeast Ethiopia. Woldia Comprehensive Specialized Hospital, Lalibela General Hospital, and Kobo primary hospitals were selected among North Wollo Zone. These hospitals provide services to more than 3 million people around the area, but basic antimicrobial susceptibility tests were not performed in the hospitals. The laboratory testing for this study was done at Woldia University microbiology laboratory which is found in Woldia Town.

### Eligibility Criteria

All patients attending those hospitals and clinically presumed to have UTI, BSI, LRTI and wound infections during the study period were included. However, study participants whose data were incomplete and gave inappropriate specimens

(saliva and/or contaminated sputum, insufficient amount of all specimens, and delayed specimen during transportation) in the study period were excluded.

## Data Collection

Information on demographic variables was collected from each participant with face-to-face interview using a structured questionnaire. Clinical data related to chronic disease, history of hospitalization, intravenous catheterization, surgery and use of antibiotics were collected through reviewing patients' medical records in consultation with the respective physicians. With the study team, patients admitted to the different wards and ICU of selected hospitals of Northeast Ethiopia were carefully diagnosed with bacterial infections by different specialists.

## Specimen Collection and Processing

Clinical specimens (blood, urine, sputum and wound swab/pus aspirate) were collected by the study team as soon as infection was reported following standard bacteriological procedures.<sup>23–25</sup>

## Isolation and Identification of Bacteria

All isolates of *A. baumannii* and *P. aeruginosa* were identified by manual standard microbiological methods.<sup>33</sup> All *A. baumannii* and *P. aeruginosa* suspected isolates were also further confirmed by an automated Vitek2 Compact (BioMérieux, France). *Acinetobacter* was identified by Gram staining, and colony morphology, positive catalase test, negative oxidase test and absence of motility. Speciation of *Acinetobacter* was performed on the basis of glucose oxidation, gelatin liquefaction, beta hemolysis, growth at 37°C and 42°C, colorless on MacConkey agar and arginine hydrolysis.<sup>34</sup> *Pseudomonas* was also identified by Gram staining and colony morphology. Aerobically grow showing beta haemolysis in blood agar, colorless colonies on MacConkey. It was catalase, oxidase and citrase positive, whereas indole and urease negative.<sup>35</sup>

## Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing of *A. baumannii* and *P. aeruginosa* isolates was performed according to the criteria of Clinical and Laboratory Standard Institute (CLSI) using the Kirby-Bauer disk diffusion method on Mueller-Hinton Agar.<sup>36,37</sup> The antibiotic discs tested were: penicillin category including: amoxicillin (25µg; Oxoid<sup>®</sup>, Basingstoke, England) and amoxicillin-clavulanic acid (20/10µg; Oxoid<sup>®</sup>, Basingstoke, England). Cephalosporin category: cefotaxime (30µg; Oxoid<sup>®</sup>, Basingstoke, England), ceftazidime (30µg; Oxoid<sup>®</sup>, Basingstoke, England), ceftazidime (30µg; Oxoid<sup>®</sup>, Basingstoke, England). Carbapenem family: meropenem (10µg; Oxoid<sup>®</sup>, Basingstoke, England) and ertapenem (10µg; Oxoid<sup>®</sup>, Basingstoke, England). Fluoroquinolones category: ciprofloxacin (25µg; Oxoid<sup>®</sup>, Basingstoke, England), nitrofurantoin (300µg; Oxoid<sup>®</sup>, Basingstoke, England). Folate pathway inhibitors: trimethoprim-sulfamethoxazole (25µg; Oxoid<sup>®</sup>, Basingstoke, England). Aminoglycosides: gentamicin (10µg; Oxoid<sup>®</sup>, Basingstoke, England). These antimicrobial drug disks were selected based on CLSI guidelines and considering the availability and frequency of prescriptions of these drugs in the study area. The diameters of the zones of inhibition around the discs were measured using a digital caliper. The interpretation of the results of the antimicrobial susceptibility tests was based on CLSI criteria for resistance.<sup>23</sup>

## Detection of Extended-Spectrum $\beta$ -Lactamase and Carbapenemase Production

Initial screening for ESBL was done by considering the diameters of zones of inhibition produced by either ceftazidime (30 µg) or cefotaxime (30µg) from the antimicrobial susceptibility tests. After initial screening, ESBL production was confirmed with phenotypic combined disk method according to CLSI guidelines.<sup>23</sup> The organism to be tested was uniformly inoculated onto MHA plates. Ceftazidime (30 µg) and cefotaxime (30µg) disks were used alone and in combination with clavulanic acid (30 µg/10 µg) for phenotypic confirmation of the presence of ESBLs at the same time. After incubation at 37°C for 24 h, a  $\geq 5$ mm increase in diameter of zone of inhibition for either the ceftazidime-clavulanate and/or cefotaxime-clavulanate disk combination versus the zone diameter of the respective cephalosporin disk alone was considered positive and the isolate was interpreted as ESBL producer.<sup>23</sup>

Isolates resistant or intermediate for ertapenem (10µg) and/or meropenem (10µg) disk diffusion antimicrobial resistance screening was further tested for the production of carbapenemase by phenotypic modified carbapenem inhibitory method.<sup>23</sup> With this method, the bacterial isolates were emulsified in tryptic soy broth and meropenem disk (10 µg) was added, then incubated for 4 h. McFarland standard equivalent suspension carbapenem sensitive indicator organism (*E. coli* ATCC<sup>®</sup>25922) was evenly swabbed onto MHA, and then the meropenem in the tryptic soy broth was dispensed. After incubation for 24 h at 37°C, the zone of inhibition for meropenem was measured. If the zone of inhibition was between 6–15 mm or 16–18 mm with pin points at the inhibition zone, the bacterial isolate was considered as carbapenemase producer.<sup>23</sup>

## Quality Control

The sterility of the media was checked by incubating 5% of the batch at 35–37°C overnight. For antimicrobial sensitivity testing on MHA, American Type Culture Collection (ATCC) standard reference strains (*E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853) for carbapenem and *Escherichia coli* ATCC 35218 (for β-lactam/β-lactam inhibitor combination) were used as quality control strains for culture and susceptibility testing throughout the study.<sup>23</sup> For ESβL production, *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603, for carbapenemase production *K. pneumoniae* ATCC BAA1705 were used as positive controls and *K. pneumoniae* ATCC BAA 1706 as carbapenemase negative control according to CLSI guidelines.<sup>23</sup> All reference strains were obtained from APHI.

## Data Analysis

Data were checked, entered, and analyzed using Statistical Package for Social Sciences 25 (IBM Corp, Released 2011, IBM SPSS statistics, Armonk, NY). Descriptive statistics were used to describe relevant variables. Chi-squared test and Fisher's exact test were utilized to determine association between dependent and independent variables. P-value of < 0.05 was considered statistically significant.

## Results

Gram negative non-fermenters are known to cause different types of infections mainly in hospital settings. Due to the ubiquitous nature of these bacteria they can easily acquire resistant genes and become multidrug resistant. This study was done to determine the prevalence of ESβL and carbapenemase producing *A. baumannii* and *P. aeruginosa* isolated at different sites of infections by performing standard bacteriological methods.

A total of 384 study participants presumed to have BSI, UTI, LRTI and wound infections were screened for Gram negative non-fermenters. Gram negative non-fermenters recovered were phenotypically characterized in terms of susceptibility for commonly prescribed antibiotics and production of ESBL and carbapenemase. Overall, 20 (5.2) and 10 (2.6%) patients were culture positive for *A. baumannii* and *P. aeruginosa*, respectively and co-infection with the two species was not found. The frequency of isolation of *A. baumannii* and *P. aeruginosa* was 26 (4.9%) among inpatients and four (3.4%) among outpatients. Culture positivity was prominent in wound specimens: 12 (12.6%) followed by blood specimens: 10 (10.4). [Table 1](#) illustrated the isolation rate of *A. baumannii* and *P. aeruginosa*.

## Phenotypic Characteristics of the Recovered Isolates

Overall, 20 (66.7%) isolates, of which 14 (70%) and 6 (60%) was *A. baumannii* and *P. aeruginosa* isolates, were carbapenem resistant, respectively. ESβL production was found in 16 (53.3%) of the total isolates. The distribution was 8 (40%) and 8 (80%) among *A. baumannii* and *P. aeruginosa* isolates, respectively. Four (13.3%) of the non-fermenter isolates; two each *A. baumannii* and *P. aeruginosa* isolates were carbapenemase producers ([Table 2](#)).

Both *A. baumannii* and *P. aeruginosa* isolates were 100% resistant to chloramphenicol and cefoxitin. *Acinetobacter baumannii* isolates were 100% resistant to sulfamethoxazole-trimethoprim while *P. aeruginosa* isolates were 100% resistant to amoxicillin-clavulanic acid, gentamicin, nitrofurantoin and cefotaxime. *Acinetobacter baumannii* isolates revealed 90% resistance to third generation cephalosporins (cefotaxime and ceftazidime). It also revealed 60% and 50% resistance to meropenem and ertapenem, respectively. On the other hand, *P. aeruginosa* isolates revealed 80% resistance

**Table 1** Prevalence of *A. baumannii* and *P. aeruginosa* and Demographic Characteristics of Patients at Selected Hospitals of North East Ethiopia

Variables	Number of Participants N (%)	<i>A. baumannii</i> N (%)	<i>P. aeruginosa</i> N (%)	Total N (%)	P-value
<b>Age (years)</b>					
0.002 –5	57 (14.8)	8 (14)	0	8 (14)	NA
6 –18	45 (11.7)	4 (8.9)	2 (4.4)	6 (13.3)	
19–28	63 (16.4)	0	2 (3.2)	2 (3.2)	
29–38	81 (21.1)	4 (4.9)	2 (2.5)	6 (7.4)	
39–48	55 (14.3)	2 (3.6)	4 (7.3)	6 (11)	
49–58	45 (11.7)	0	0	0	
> 58	38 (9.9)	2 (5.3)	0	2 (5.3)	
<b>Sex</b>					0.09
Male	210 (54.7)	16 (7.6)	6 (2.8)	20 (10.6)	
Female	174 (45.3)	4 (2.2)	4 (2.2)	8 (4.4)	
<b>Residence</b>					0.08
Rural	225 (58.6)	4 (1.8)	8 (3.6)	12 (5.4)	
Urban	159 (41.4)	16 (10)	2 (1.3)	18 (11.3)	
<b>Site of infections</b>					NA
Urinary tract	96 (25)	2 (2)	0	2 (2)	
Blood stream	96 (25)	10 (10.4)	0	10 (10.4)	
Lower respiratory tract	96 (25)	4 (4.2)	2 (2)	6 (6.2)	
Wound	96 (25)	4 (4.2)	8 (8.4)	12 (12.6)	
<b>Hospital patient setting</b>					0.24
Outpatient	121 (31.5)	2 (1.6)	2 (1.6)	4 (3.2)	
Inpatient	263 (68.5)	18 (6.8)	8 (3.0)	26 (9.9)	
<b>Total</b>	<b>384 (100)</b>	<b>20 (5.2)</b>	<b>10 (2.6)</b>	<b>20 (7.8)</b>	

Abbreviation: NA, not applicable.

**Table 2** Distribution of ESBL and Carbapenemase Production and Carbapenem Resistance Among *A. baumannii* and *P. aeruginosa* Isolates from Patients at Selected Hospitals of North East Ethiopia

Type of Bacterial Isolates (n = 30)	ESBL Producer N (%)	Carbapenemase Producer N (%)	Carbapenem Resistance N (%)
<i>A. baumannii</i> (n = 20)	8 (40.0)	2 (10.0)	14 (70.0)
<i>P. aeruginosa</i> (n = 10)	8 (80.0)	2 (20.0)	6 (60.0)
<b>Total</b>	<b>16 (53.3)</b>	<b>4 (13.3)</b>	<b>20 (66.7)</b>

to both ceftazidime and ciprofloxacin. Moreover, *P. aeruginosa* isolates revealed 60% resistance to carbapenem drugs either meropenem or ertapenem (Table 3).

All *A. baumannii* and *P. aeruginosa* isolates were found to be MDR (100%) (Table 4). All *A. baumannii* isolates revealed resistance to antibiotics representatives of 5–10 different classes. All *P. aeruginosa* isolates revealed resistance to antibiotics representatives of nine different classes (Table 4). All carbapenem resistant isolates were MDR. Likewise, all ESBL and carbapenemase producers were MDR.

## Risk Factors of ESBL and Carbapenemase Production

No statistical difference was obtained for ESBL production in terms of sex, residence, and hospital patients setting. The proportion of ESBL production was significantly higher among patients with history of intravenous catheter for the last 12 months (8.7%) than their counterparts (2.7%) ( $p = 0.015$ ). Furthermore, ESBL production was significantly higher among patients with history of admission for the last 12 months than their counterparts ( $p = 0.007$ ). The proportion of

**Table 3** Antibiotic Resistance Profiles of *A. baumannii* and *P. aeruginosa* Isolates from Participants Presumed to have Bacterial Infections at Selected Hospitals of North East Ethiopia

Antimicrobials	<i>A. baumannii</i>		<i>P. aeruginosa</i>		Total	
	# T	R %	# T	R %	# T	R %
Amoxicillin- clavulanic acid	20	16 (80)	10	10 (100)	20	26 (86.7)
Nitrofurantoin	20	12 (60)	10	10 (100)	20	22 (73.3)
Sulfamethoxazole-trimethoprim	20	20 (100)	10	6 (60)	20	26 (86.7)
Gentamicin	20	16 (80)	10	20 (100)	20	26 (86.7)
Chloramphenicol	20	20 (100)	10	10 (100)	20	30 (100)
Ciprofloxacin	20	10 (50)	10	8 (80)	20	18 (60)
Cefotaxime	20	18 (90)	10	10 (100)	20	28 (93.3)
Ceftazidime	20	18 (90)	10	8 (80)	20	26 (86.7)
Cefoxitin	20	20 (100)	10	10 (100)	20	30 (100)
Meropenem	20	12 (60)	10	6 (60)	20	18 (60)
Ertapenem	20	10 (50)	10	6 (60)	20	16 (53.3)

Notes: # T: Number of isolates tested, R%: Percentage of resistant isolates.

**Table 4** Antibiogram of *A. baumannii* and *P. aeruginosa* Isolates from Patients Clinically Presumed for Different Clinical Sites of Infections at Selected Hospitals of North East Ethiopia

Bacterial species	Level of Antibiotic Resistance						Overall, MDR
	R5	R6	R7	R8	R9	R10	
<i>A. baumannii</i> (n = 20)	2 (1)	0	2 (1)	6 (30)	6 (30)	4 (20)	20 (100)
<i>P. aeruginosa</i> (n = 10)	0	0	0	0	10 (100)	0	10 (100)
<b>Total (n = 30)</b>	<b>2 (6.7)</b>	<b>0</b>	<b>2 (6.7)</b>	<b>6 (20)</b>	<b>16 (53.3)</b>	<b>4 (13.3)</b>	<b>30 (100)</b>

Notes: R5, 6, 7, 8, 9, 10 = Resistance to 5, 6, 7, 8, 9, 10 antibiotics in different classes; MDR = resistance to  $\geq 3$  antibiotics taken from different classes.

ESBL production was 14.3% among patients who had surgery than their counterparts (2.7%) ( $p = 0.006$ ) (Table 5). The proportion of carbapenem resistant isolates was significantly higher among patients with history of hospital admission for the last 12 months (12.7%) than their counterparts (2.8%) ( $p = 0.004$ ) (Table 5).

## Discussion

This study revealed the emergence of MDR strains of carbapenem resistant and beta-lactamases (CP and ESBL) producing *A. baumannii* and *P. aeruginosa* superbugs among patients with different sites of infections in a referral hospital, which is a major concern for patients and health care providers.

The prevalence of *A. baumannii* and *P. aeruginosa* infections was relatively higher than in a study in Jimma, Ethiopia,<sup>27</sup> but lower than in a study in Addis Ababa, Ethiopia.<sup>1</sup> However, the prevalence of *A. baumannii* and *P. aeruginosa* infection in the present study was lower than in studies from Uganda,<sup>28</sup> Madagascar,<sup>7</sup> Nepal,<sup>38</sup> and India.<sup>39</sup>

The prevalence of *A. baumannii* infection in the present study was lower than in studies in other parts of Ethiopia.<sup>40,41</sup> However, it was consistent with studies from other African countries,<sup>42–44</sup> and Asia.<sup>38</sup> *A. baumannii* was predominantly isolated from blood samples (5.2%) followed by sputum (2.1%), wounds (2.1%) and urine (1%) in the present study. This study corroborated a study from India at a tertiary care hospital,<sup>45</sup> and from Madagascar.<sup>7</sup> However; the finding of the

**Table 5** Distribution of ESBL Producing and Carbapenem Resistant *A. baumannii* and *P. aeruginosa* Infection According to Different Variables of Study Participants at Selected Hospitals of North East Ethiopia (n = 384)

Variables	Number of participants N (%)	ESBL Positive N (%)	P-value	Carbapenem resistance N (%)	P-value
<b>Sex</b>				Positive	
Female	174 (45.3)	6 (3.4)	0.238	4 (2.3)	0.119
Male	210 (54.7)	10 (4.8)		16 (7.6)	
<b>Residence</b>					
Rural	224 (58.4)	6 (2.7)	0.23	6 (2.7)	1.00
Urban	160 (41.6)	10 (6.3)		14 (8.8)	
<b>Hospital patient setting</b>					
Inpatient	263 (64.5)	12 (4.6)	0.35	18 (6.8)	0.18
Outpatient	121 (35.5)	4 (3.3)		2 (1.6)	
<b>Intravenous catheter in the last 12 months</b>					
Yes	92 (24)	8 (8.7)	0.015	8 (8.7)	0.225
No	292 (76)	8 (2.7)		12 (4.1)	
<b>Hospitalization in the last 12 months</b>					
Yes	97 (25.3)	10 (10.3)	0.007	12 (12.3)	0.04
No	287 (74.7)	6 (2.1)		8 (2.8)	
<b>Antibiotic use in the last 6 months</b>					
Yes	257 (66.9)	9 (3.5)	1.00	18 (7.0)	0.17
No	127 (33.1)	7 (5.5)		2 (1.6)	
<b>Surgery in the last 12 months</b>					
Yes	49 (12.8)	7 (14.3)	0.006	7 (14.3)	0.89
No	335 (87.2)	9 (2.7)		13 (3.9)	
<b>Chronic infection</b>					
Yes	64 (16.7)	4 (6.3)	0.69	3 (4.9)	0.32
No	320 (83.3)	12 (3.6)		17 (5.3)	

present study is not in agreement with a study from Ethiopia.<sup>1</sup> In this study, the highest number of *P. aeruginosa* was isolated from wound infection rather than other site infections. This is concurrent with the results of studies from Asia.<sup>38,45,46</sup> The predominance of *P. aeruginosa* in wound infections might be linked to contamination of the wound from health care workers' fomites, hands and hospital environments rather than other site of infections.

The current carbapenem resistance rate (66.7%) among non-fermenters is higher than other studies from Ethiopia,<sup>27</sup> Bangladesh (14.5%),<sup>25</sup> and USA (4.5%),<sup>26</sup> This shows the rising prevalence of carbapenem resistance among non-fermenter GNB isolates, which is a threat to clinical practices. This could be due to drug prescription with improper susceptibility testing and indiscriminate use of antibiotics. Widespread use of third generation cephalosporins might contribute to the problem of carbapenem resistance. Furthermore, data on carbapenem drug resistant isolates are limited in Ethiopia and there is no regular tracking of such resistance profiles using antimicrobial susceptibility testing.

The proportion of carbapenem resistant *A. baumannii* isolates in this study was consistent with a study in eastern India,<sup>45</sup> India,<sup>3</sup> Nepal<sup>7</sup> and Ethiopia,<sup>47</sup> India.<sup>45</sup> However, it was higher than a study from Uganda.<sup>28</sup> On the other hand, it was lower than a study from Ethiopia,<sup>27</sup> United States,<sup>26</sup> and Latin America.<sup>46</sup> The proportion of carbapenem resistant *P. aeruginosa* isolates in the present study is consistent with studies done in Egypt,<sup>42</sup> India,<sup>45</sup> and United States.<sup>26</sup> However, it was higher than a study from Ethiopia<sup>27</sup> and Libya (24%).<sup>18</sup> Moreover, both meropenem and ertapenem resistance was shown by maximum isolates of *P. aeruginosa*.

In the current study, 10% of *A. baumannii* isolates were carbapenemase producers. Slightly lower rates were reported from Ethiopia<sup>41</sup> and Japan.<sup>48</sup> Moreover, the proportion of carbapenemase producing *P. aeruginosa* isolates in the present study was

higher than studies from Ethiopia<sup>41</sup> and Japan.<sup>48</sup> This shows that there is an emergence of carbapenemase enzyme production among gram negative non-fermenters in the study area, which is one of the major resistance mechanisms for MDR.

The proportion of ESBL producing *P. aeruginosa* in the present study was 8 (80%). This is higher than rates reported from previous studies done in Ethiopia,<sup>1,47</sup> India,<sup>38</sup> and Nepal.<sup>7</sup> However, the prevailing proportion of ESBL producing [8 (40%)] *A. baumannii* in this study was consistent with reports from other parts of Ethiopia,<sup>1,47</sup> India,<sup>38</sup> and Nepal.<sup>7</sup> Thus, the occurrence of ESBL production on maximum isolates of non-fermenter might be linked to the extensive use of beta-lactams and heavy use of third generation cephalosporin antimicrobial drugs. This is because greater than 90% of *A. baumannii* and *P. aeruginosa* isolates were resistant to cefotaxime and ceftazidime in the present study. This showed that these two organisms are majorly resistant to most effective drugs (third generation cephalosporins) which makes it cumbersome to choose effective antibiotics for the treatment of these organisms.

The overall drug resistance profiles of *A. baumannii* and *P. aeruginosa* (commonly prescribed antibiotics) was high (86.7–100%). Similarly, the resistance profiles of *A. baumannii* and *P. aeruginosa* against cephalosporins were also high (93.3–100%). *A. baumannii* isolates' resistance to cefotaxime (90%) and ceftazidime (90%) in the present study was consistent with a previous study done in Ethiopia,<sup>1</sup> where 67.9% and 96.4% of isolates were resistant to ceftazidime and cefotaxime, respectively. Moreover, a study in Bithanda, India,<sup>38</sup> reported 96.6% resistant isolates of *A. baumannii* to ceftazidime. In a study from Ethiopia,<sup>47</sup> *A. baumannii* isolates were resistant to ceftazidime (63.1%) and cefotaxime (69.8%). Studies from eastern India<sup>45</sup> and Madagascar<sup>37</sup> reported 88.9% and 62% rate of resistance to ceftazidime, respectively.

The proportion of *P. aeruginosa* isolates resistant to ceftazidime (80%) and cefotaxime (100%) in the present study was higher than in other reports in Ethiopia and elsewhere in the world,<sup>1,37,47,49</sup> where 1.9–66.9% and 70.8–91.8% isolates were resistant to ceftazidime and cefotaxime, respectively. This shows the rising spread of resistance toward extended-spectrum cephalosporins, which may lead to increased prescription of more broad-spectrum and expensive drugs. Thus, restriction on antibiotic use is required to contain them.

The rate of resistance of *A. baumannii* isolates to ciprofloxacin in the current study was lower than studies in Ethiopia.<sup>1,47</sup> However, fewer and higher results were also documented in other parts of the world.<sup>7,37,45,49</sup> On the other hand, the frequency of *P. aeruginosa* isolates' resistance to ciprofloxacin (80%) in the present study was consistent with studies from Ethiopia,<sup>47</sup> and India.<sup>45</sup> But lower results were found in Ethiopia,<sup>1</sup> Madagascar,<sup>37</sup> and Nepal.<sup>7</sup>

All isolates of *A. baumannii* and *P. aeruginosa* were MDR (100%). This is consistent with previous studies in Ethiopia (100%).<sup>50</sup> Moreover, higher MDR proportions were documented in Addis Ababa, Ethiopia (92.9%) for *A. baumannii* and (91.8%) for *P. aeruginosa* isolates.<sup>1</sup> Furthermore, 62% and 81% of *A. baumannii* and *P. aeruginosa* were MDR in a similar study from Libya.<sup>18</sup>

The proportion of ESBL producing *A. baumannii* and *P. aeruginosa* infection was significantly higher among patients with prior intravenous catheterization, hospitalization, and surgery. This might be due to the increased colonization of resistant nosocomial strains in the hospital environment. Moreover, invasive procedures and hospitalization lower the immune status of patients which increases their susceptibility to hospital contaminants.<sup>51</sup> Furthermore, intravenous catheterization, hospitalization, and invasive procedures allow resistance determinant genes to be acquired among isolates of the same species or Enterobacteriaceae which are common in the clinical area.<sup>24,52</sup> According to CDC report, *Acinetobacter* infections typically occur in people in healthcare settings. People most at risk include patients in hospitals, especially those who have devices such as catheters and open wounds from surgery, are in intensive care units, and have prolonged hospital stays.<sup>24</sup>

## Conclusion

This study highlighted high prevalence of carbapenem and cephalosporins resistant *A. baumannii* and *P. aeruginosa* isolates in the study area. Moreover, there was a considerable emergence of ESBLs and CP, and all isolates were MDR and resistant to at least five antibiotics representative of different classes. This necessitates the restricted and wise use of commercially available antibiotics, and need for regular screening of these superbugs and continued infection control practices in the clinical area. To conclude, treatment of infections caused by non-fermenter gram negative bacilli should be guided by drug susceptibility testing. Furthermore, antimicrobial resistance testing studies on the drug resistant determining genes are recommended.



## Abbreviations

ATCC, American Type Culture Collection; AMR, Antimicrobial resistance; BSI, Blood stream infection; CLSI, Clinical and Laboratory Standards Institute; CP, Carbapenemase; ESβLs, Extended-Spectrum β- lactamases; GNNF, Gram negative non-fermentor; ICU, Intensive Care Unit; LRTI, Lower respiratory tract infection; MDR, Multi-drug resistance; UTI, Urinary tract infection.

## Data Sharing Statement

The finding of this study was generated from the data collected and analyzed based on the stated methods and materials. All of the data are already in the manuscript and there are no supplementary files. The original data supporting this finding will be available from the corresponding author any time upon request.

## Ethical Approval and Informed Consent

The study was approved by the Institutional Review Board (IRB) of College of Health Sciences, Woldia University with IRB no CHS/IRB/03-008. Prior to data collection, written informed consent was obtained from each participant. Written assent was also obtained from parents and/or surrogates to obtain information from children and those who cannot give data. Subject confidentiality and any special data security requirements were maintained and ensured by giving only codes for questionnaires. Results of the laboratory examinations that had a direct benefit to the health of the study participants were provided to physicians and the participants received their results and treatment duly as required. This study was in line with the Declaration of Helsinki.

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## Author Contributions

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

## Disclosure

The authors declare that they have no competing interests.

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