ORIGINAL ARTICLE

Surviving superbugs: Epidemiology, clinical impact, and resistance trends in carbapenem-resistant non-fermenters

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Abstract

Background: The worldwide spread of carbapenem-resistant non-fermentative gram-negative bacilli (CR-NFGNB) has posed an urgent public-health threat, especially in healthcare institutions. The purpose of this study was to define the epidemiological, clinical outcome and antimicrobial resistance pattern of infections caused by CR-NFGNB in a secondary care hospital. *Materials and Methods:* We retrospectively reviewed clinical isolates of CR-NFGNB from various clinical samples submitted to Sohar Hospital, Oman from January 2017–December 2021. Bacterial identification and antimicrobial susceptibility testing were done in accordance with Clinical and Laboratory Standards Institute (CLSI) standards. Univariate analyses determined risk factors for mortality through chi-square tests and Fisher's exact tests, with significance level of $p < 0.05$. *Results:* Among 1,201 NFGNB isolates, 233 (19.4%) demonstrated carbapenem resistance, predominantly hospital-acquired (76.0%). The isolates were recovered from 201 patients (61.2% male; median age 55 years). *Acinetobacter baumannii* exhibited the highest carbapenem resistance rate (59.3%, 144/243), followed by *Pseudomonas aeruginosa* (7.9%, 75/944). Carbapenem-resistant *A. baumannii* (CRAB) demonstrated extensive resistance to aminoglycosides (98.6%), fluoroquinolones (100%), and β-lactam/β-lactamase inhibitor combinations (100%), while maintaining susceptibility to colistin (100%) and tigecycline (93.3%). Significant mortality predictors included mechanical ventilation (OR: 4.8, $p<0.001$), central venous catheterization (OR: 3.7, $p < 0.001$), COVID-19 with secondary bacteremia ($p < 0.001$), hemodialysis ($p = 0.002$), and end-stage renal disease ($p = 0.025$). *Conclusion*: The high prevalence of carbapenem resistance, especially in *A. baumannii* in our hospital settings, coupled with limited therapeutic options and significant mortality in vulnerable populations, requires urgent implementation of robust antimicrobial stewardship, infection prevention strategies, and investment in therapeutic development to mitigate this emerging threat in secondary care facilities.

Keywords: carbapenem resistance, *Acinetobacter baumannii*, healthcare-associated infections, antimicrobial resistance, intensive care unit, mortality predictors

Introduction

Non-Fermentative Gram-Negative Bacilli (NFG-NB) have emerged as formidable nosocomial pathogens, particularly in intensive care settings where they cause severe infections in immuno-compromised and critically ill patients [1, 2]. These aerobic, non-spore-forming bacilli, characterized

by their inability to ferment glucose, include clinically significant species such as *Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*, and *Burkholderia cepacia complex* [3, 4]. The global dissemination of carbapenem-resistant NFGNB has reached pandemic proportions, with the World Health Organization designating Carbapenem-Resistant *A. Baumannii* (CRAB) and Carbapenem-Resistant *P. Aeruginosa* (CRPA) as critical priority pathogens requiring urgent research and development of new antibiotics [5]. Recent surveillance data indicate that CRAB prevalence ranges from 25% to 85% globally, with particularly high rates in the Middle East and North Africa (MENA) region [6].

The molecular mechanisms underlying carbapenem resistance in NFGNB (CR-NFGNB) are multifaceted, involving production of carbapenemases (particularly OXA-type β-lactamases in *A. baumannii* and metallo-β-lactamases in *P. aeruginosa*), efflux pump overexpression, porin loss, and target site modifications [7, 8]. The horizontal transfer of resistance determinants through mobile genetic elements facilitates rapid dissemination within healthcare facilities [7, 8].

The clinical impact of CR-NFGNB infections is substantial, with attributable mortality rates ranging from 30% to 70%, prolonged hospitalization, and increased healthcare costs [4, 9, 10]. Prior exposure to antibiotics, especially carbapenems and broad-spectrum antibiotics, recent Intensive Care Unit (ICU) admission, prolonged hospitalizations, and the presence of invasive medical devices such as mechanical ventilators or central venous catheters, and underlying medical conditions like immunocompromised or specific chronic diseases are important risk factors for CR-NFGNB infections [11]. The COVID-19 pandemic has further exacerbated this crisis, with several studies reporting increased incidence of CR-NFGNB infections, particularly in critically ill patients who have been subjected for surgical intervention, mechanical ventilation, and other invasive procedures [12].

Despite the critical nature of this threat, comprehensive epidemiological data from the MENA region remain limited. This study addresses this knowledge gap by providing a detailed analysis of CR-NFGNB epidemiology, resistance patterns, and clinical outcomes in a secondary care setting in Oman, contributing essential data for regional antimicrobial resistance surveillance and informing evidence-based infection control strategies.

Material and Methods

This retrospective cross-sectional study was conducted at Sohar Hospital, a secondary care facility serving the Al Batinah North Governorate of Oman, in collaboration with the College of Medicine and Health Sciences, National University, Oman. The study period spanned from January 1, 2017, to December 31, 2021. The study protocol was approved by the Research and Ethics Committee of the Ministry of Health, Sultanate of Oman (Approval No: MH/DGHS/NBG/RERA C10/2022). Patient confidentiality was maintained through data anonymization.

Patients with clinical signs and symptoms of infection with CR-NFGNB isolates that had shown resistant to both imipenem and meropenem confirmed by laboratory investigations as per CLSI guidelines were included in the study. Moreover, isolation of CR-NFGNB from sterile sites such as blood and cerebro-spinal fluid even in asymptomatic patients were considered significant and

included in the study. Patients lacking clinical signs or symptoms whose isolates from non-sterile sites were deemed contaminants or colonizers, as well as those with incomplete medical records or duplicate isolates, were excluded from the study.

Comprehensive clinical data of patients were extracted from hospital's electronic health records and entered into Excel sheet. The data included demographics, comorbidities (diabetes mellitus, hypertension, cardiovascular disease, chronic kidney disease), hospitalization details, invasive procedures (mechanical ventilation, central venous catheterization, urinary catheterization, hemodialysis), and 30-day mortality.

Bacterial identification

Clinical specimens were processed according to standard microbiological protocols [13]. Samples were inoculated onto MacConkey agar and 5% sheep blood agar (Oxoid Ltd., UK) and incubated at 37°C for 18-24 hours. NFGNB identification was performed using conventional biochemical tests including oxidase test, triple sugar iron agar, motility testing, and growth at 42°C, supplemented by automated identification using VITEK 2 Compact system (bioMérieux, France) when necessary.

Antimicrobial susceptibility testing

Antimicrobial susceptibility was determined using the Kirby-Bauer disk diffusion method on Mueller-Hinton agar or by Epsilometer (E) test in ambiguous cases, as per CLSI guidelines [14]. The antibiotic panel included: amikacin (30µg), gentamicin (10µg), ciprofloxacin (5µg), levofloxacin (5µg), ceftazidime (30µg), ceftriaxone (30µg), piperacillin-tazobactam (100/10µg), trimethoprim-sulfamethoxazole (1.25/23.75µg), imipenem (10µg), and meropenem (10µg). Colistin and tigecycline Minimum Inhibitory Concentrations (MICs) were determined using broth microdilution method according to CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines, respectively [14, 15]. Quality control was performed using *P. aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922.

Definitions

Hospital-acquired infections: Infection occurring > 48 hours after hospital admission or within 30 days of discharge, with no evidence that the infection was present or incubating at the time of admission.

Community acquired infection: Infection present at admission or developing within 48 hours of admission, with no recent healthcare exposure such as no hospitalization, surgery, dialysis, or residence in long-term care facility within 90 days.

Colonization: Presence of CR-NFGNB without clinical signs and symptoms. Typically identified through surveillance cultures (from sites such as nasal, rectal, skin swabs) without associated fever, elevated WBC, or local/systemic inflammatory signs.

Statistical analysis

Data analysis was performed using STATA version 14.0 (StataCorp, College Station, TX, USA). Continuous variables were expressed as mean ± standard deviation or median with Interquartile Range (IQR) based on distribution normality (Shapiro-Wilk test). Categorical variables were presented as frequencies and percentages. Univariate analysis using chi-square or Fisher's exact tests identified factors associated with mortality. All tests were two-tailed with significance set at $p < 0.05$.

Results

Epidemiological characteristics

During the five-year study period, 233 (19.4%) of 1,201 NFGNB isolates demonstrated carbapenem resistance. These isolates were recovered from 201 patients with a male predominance (61.2%, n=123). The median age was 55 years (IQR: 36-68), with 39.3% of patients aged > 60 years. The majority of CR-NFGNB were hospital-acquired (76.0%), while 2.6% were community-acquired and 21.4% had undetermined origin (Table 1).

Table 1: Base line characteristics of study population

Characteristics	Number (%)
Total no. of patients	201
Gender	
Male	123 (61.2)
Female	78 (38.8)
Age	
10-20 years	26 (12.9)
21-40	42 (20.9)
41-60	54 (26.9)
> 60 years	79 (39.3)
Total no. of CR-NFGNB isolated	233 (19.4)
Place of acquisition of resistant strains Hospital acquired Community acquired Undetermined	 177 (76.0) 6 (2.6) 50 (21.4)
Comorbidities/risk factors*	
Respiratory disease (COPD, Asthma)	22 (13.7)
Cardiovascular diseases	50 (31.1)
Chronic neurological diseases	51 (31.7)
Chronic renal diseases	49 (30.8)
Diabetes mellitus	65 (40.4)
Hypertension	75 (46.6)
Length of hospital stay (mean ± SD) in days	33.5443 (50.4364)
Mechanical ventilation	116 (72.0)
Central venous catheterization	74 (46.8)
Hemodialysis	31 (19.4)
Urinary catheterization	132 (82.0)

**Comorbidity/risk factors data was available only in 162 patients*
CR-NFGNB: carbapenem resistant non-fermentative gram-negative bacilli; COPD: chronic obstructive pulmonary disease; SD: standard deviation

Distribution of clinical specimens and bacterial species

CR-NFGNB were most frequently isolated from respiratory specimens (endotracheal aspirates: 28.8%; sputum: 5.2%), followed by urine (23.6%), blood (19.3%), and wound/pus samples (10.3%) (Figure 1). *A. baumannii* was the predominant species (61.8%, n=144), followed by *P. aeruginosa* (32.2%, n=75), *S. maltophilia* (4.3%, n=10), *Elizabethkingia meningoseptica* (1.3%, n=3), and *B. cepacia* (0.4%, n=1) (Table 2).

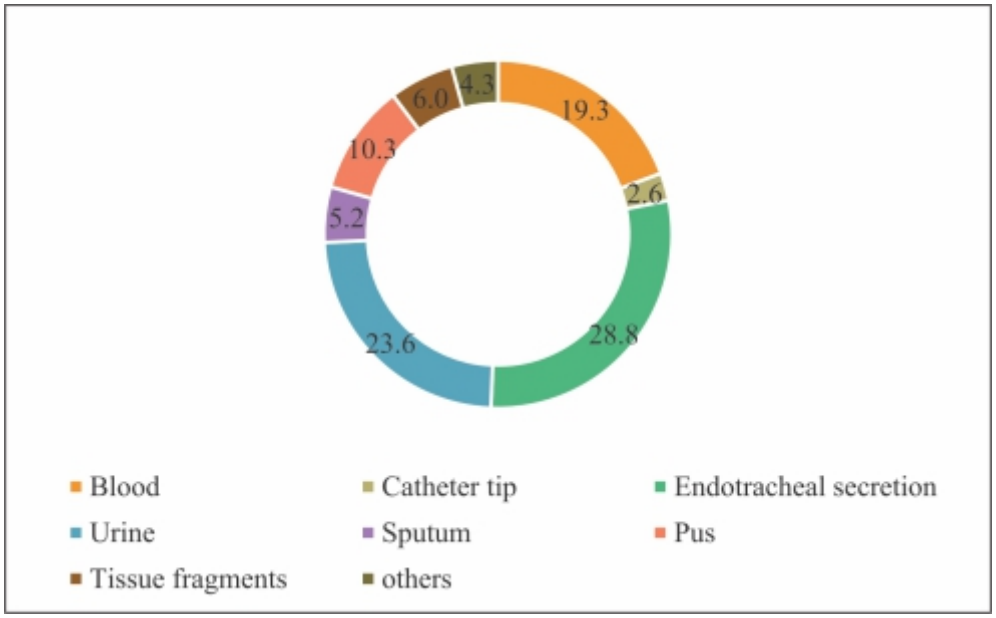

Figure 1: Sample-wise distribution of NFGNB isolates (%)

Table 2: Carbapenem-resistant NFGNB isolated from clinical samples of studied population.

Bacterial isolate	n (%)
Acinetobacter baumannii (CRAB)*	144 (61.8)
Pseudomonas aeruginosa (CRPA)*	75 (32.2)
Elizabethkingia meningoseptica	3 (1.3)
Stenotrophomonas maltophilia	10 (4.3)
Burkholderia cepacia	1 (0.4)

CRAB: Carbapenem-resistant A. baumannii, CRPA: Carbepenem-resistant P. aeruginosa

Species-specific carbapenem resistance rates

Among individual species, *A. baumannii* exhibited the highest carbapenem resistance rate (59.3%, 144/243), while P. aeruginosa showed significantly lower resistance (7.9%, 75/944). *S. maltophilia* and *E. meningoseptica*, which possess intrinsic carbapenem resistance, demonstrated 100% resistance as expected (Figure 2).

Antimicrobial resistance patterns

Carbapenem-resistant *A. baumannii*

CRAB isolates exhibited Extensive Drug Resistance (XDR) phenotypes with resistance rates exceeding 90% for most antimicrobial classes: aminoglycosides (amikacin: 98.6%, gentamicin: 98.6%), fluoroquinolones (ciprofloxacin: 100%), cephalosporins (ceftazidime: 100%, ceftriaxone: 100%), and β-lactam/β-lactamase inhibitor combinations (piperacillin-tazobactam: 100%). Notably, colistin retained excellent activity (100% susceptibility), while tigecycline resistance was 6.7% (Table 3).

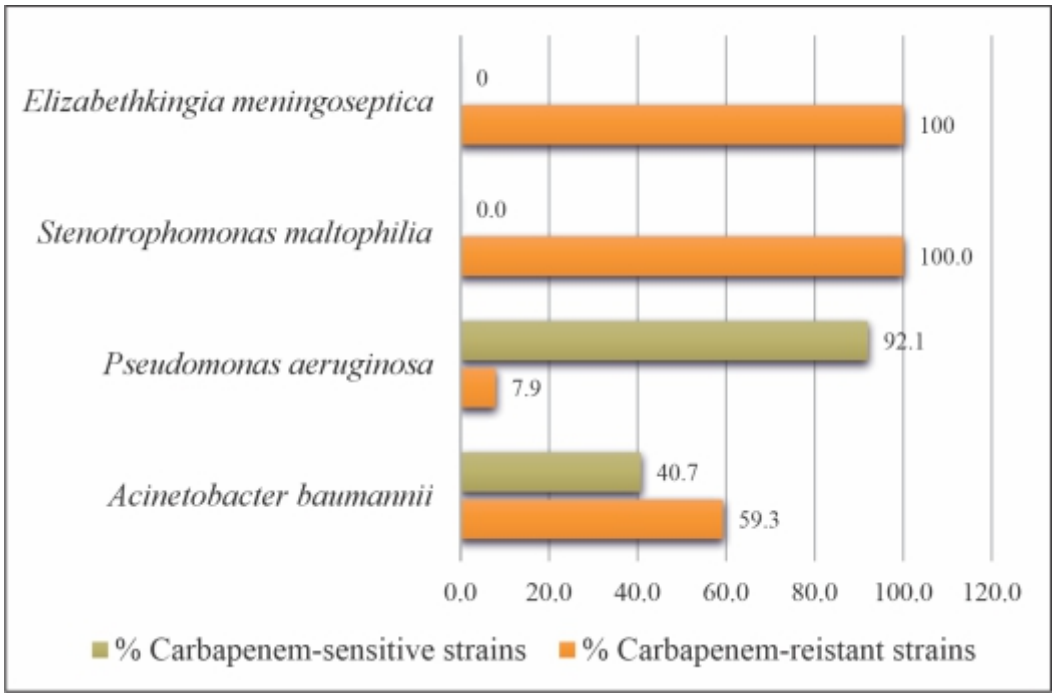

Figure 2: Organism-wise percentage of carbapenem resistance among NFGNB isolates

Table 3: Antimicrobial resistance (%) pattern of carbapenem resistance NFGNB isolates

Antimicrobial resistance (%)				
Bacterial isolate	*A. baumannii*	*P. aeruginosa*	*E. meningoseptica*	*S. maltophilia*
Amikacin	98.6	36.0	100	40
Ciprofloxacin	100	49.3	**66.6**	**10**
Colistin	**0**	**3.6**	100	**---**
Trimethoprim sulfamethoxazole	92.1	---	**0**	**0**
Ceftriaxone	100	---	---	---
Ceftazidime	100	62.7	100	40
Gentamicin	98.6	58.7	100	40
Piperacillin-tazobactam	100	44.0	**66.6**	80
Tigecycline	**6.7**	---	---	---
Levofloxacin	---	---	---	**0**

Carbapenem-resistant *P. aeruginosa*

CRPA isolates demonstrated more heterogeneous resistance patterns compared to CRAB, with moderate resistance to aminoglycosides (amikacin: 36.0%, gentamicin: 58.7%), fluoroquinolones (ciprofloxacin: 49.3%), ceftazidime (62.7%), and piperacillin-tazobactam (44.0%). Colistin resistance remained low at 3.6% (Table 3).

Other CR-NFGNB

S. maltophilia maintained susceptibility to trimethoprim-sulfamethoxazole (100%) and levofloxacin (100%), its primary therapeutic options. *E. meningoseptica* showed universal susceptibility to trimethoprim-sulfamethoxazole despite high-level resistance to other agents (Table 3).

Clinical outcomes and risk factor analysis

The 30-day mortality rate was 49.3%, with significant predictors including invasive procedures like mechanical ventilation, central venous catheterization, hemodialysis, and urinary catheterization. Comorbidities like hypertension and end-stage renal disease were also significant. COVID-19 complications like secondary bacteremia were also significant. The mean hospital stay was 33.5 ± 50.4 days, with no significant difference between survivors and non-survivors (Table 4).

Table 4: Correlation between risk factors and outcome of infection

Variable		Survival (recovery)	Non-survival (death)	*p*
Number		76	74	
Age, median (IQR)		50 (29.5, 66)	55.5 (43, 68)	0.085
Gender	Female	33 (43%)	26 (35%)	0.30
	Male	43 (57%)	48 (65%)	
Diabetes	No	48 (63%)	37 (51%)	0.12
	Yes	28 (37%)	36 (49%)	
Hypertension	No	47 (62%)	30 (41%)	**0.011**
	Yes	29 (38%)	43 (59%)	
Cardiovascular	No	55 (72%)	46 (63%)	0.22
	Yes	21 (28%)	27 (37%)	
Respiratory	No	62 (82%)	65 (89%)	0.20
	Yes	14 (18%)	8 (11%)	
Central Nervous System	No	48 (63%)	53 (73%)	0.22
	Yes	28 (37%)	20 (27%)	
Renal	No	52 (70%)	47 (64%)	**0.45**
	Yes	22 (30%)	26 (36%)	
COVID-19 with secondary bacterial pneumonia	No	65 (86%)	55 (74%)	0.086
	Yes	11 (14%)	19 (26%)	
COVID-19 with secondary bacterial septicaemia	No	67 (88%)	46 (62%)	**<0.001**
	Yes	9 (12%)	28 (38%)	
COVID-19 with other secondary bacterial infection	No	72 (95%)	71 (96%)	0.73
	Yes	4 (5%)	3 (4%)	

Continued...

End stage renal disease	No	71 (93%)	74 (100%)	**0.025**
	Yes	5 (7%)	0 (0%)	
LOS, mean (SD)		33.698 (37.729)	31.301 (62.511)	0.78
Mechanical ventilation/Intubation	No	33 (43%)	10 (14%)	**<0.001**
	Yes	43 (57%)	63 (86%)	
Central venous catheterization	No	50 (66%)	24 (34%)	**<0.001**
	Yes	26 (34%)	46 (66%)	
Haemodialysis	No	68 (89%)	50 (69%)	**0.002**
	Yes	8 (11%)	22 (31%)	
Urinary catheterization	No	20 (26%)	7 (10%)	**0.008**
	Yes	56 (74%)	66 (90%)	

IQR: inter-quartile range; LOS: length of stay

Discussion

This comprehensive analysis reveals an alarming prevalence of carbapenem resistance among NFGNB in our institution, with nearly one-fifth of isolates demonstrating resistance. The predominance of CRAB (59.3% resistance rate) aligns with global surveillance data indicating *A. baumannii* as the leading carbapenem-resistant pathogen in many regions [16, 17]. A study by Nieto-Saucedo et al. found that 32.5% of non-fermenters were carbapenem resistant [16]. Bahrami et al. found a frequency of 53.5% and 5.8% in *A. baumannii* and *P. aeruginosa*, respectively [17]. In another Indian study, high-level carbapenem resistance in *A. baumannii* (90.54%) and *P. aeruginosa* (52%) was observed [18]. Geographic variations in resistance rates were partly due to local antibiotic prescription policies, adequacy of infection control practices, and the extent of use of carbapenems [19]. The extensive resistance profile of CRAB isolates, with > 90% resistance to most antimicrobial classes, reflects the global crisis of XDR *A. baumannii*. Recent molecular epidemiological studies have identified the international clonal lineages IC1, IC2, and IC7 as primary drivers of CRAB dissemination, often harboring multiple carbapenemase genes including blaOXA-23, blaOXA-24, and blaNDM [20, 21]

Our study found that carbapenem-resistant isolates were primarily recovered from endotracheal secretions, urine, blood, and pus. This higher rate of isolation is partly due to patients' exposure to medical or surgical interventions such as mechanical ventilation, central-venous catheterization, and urinary catheterization in critical care settings. Furthermore, critically ill patients are immunocompromised and the frequent use of carbapenems in these critically ill patients in intensive care

settings promotes rapid carbapenem resistance due to selective antibiotic pressure. Rapid emergence and dissemination of carbapenem-resistant NFGNB severely limits the treatment option, and causes frequent treatment failures and increased mortality, especially in critically ill and immunocompromised patients [18, 22]. In the present study, the majority of the patients were old age people with one or more comorbidities and were exposed to medical or surgical interventions. In a study by Park *et al*., mechanical ventilation, central venous catheterization, and bacteremia were independent risk factors significantly related to CRAB infection and mortality [23]. Similarly, we found in our study, COVID-19 with secondary bacterial septicemia, use of mechanical ventilation, central-venous catheterization, hemodialysis, and renal complication with end-stage renal disease, as independent risk factors for increased mortality (p-value < 0.05). The significant association between invasive procedures and mortality underscores the importance of device-associated infections in CR-NFGNB transmission [24].

CRAB pose a significant challenge to physicians as they often resist commonly prescribed antibiotics. Tafreshi et al. from Iran, demonstrated high percentage of resistance of CRAB to ciprofloxacin, ampicillin, ceftazidime, gentamicin, and amikacin, while colistin remained the most effective antibiotic [25]. In another similar study by Soni et al., 2.3% *A. baumannii* were resistant to colistin [26]. Similarly, in our study, CRAB demonstrated high-level resistance (92-100%) to amikacin, gentamicin, ceftazidime, ceftriaxone, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, while colistin and tigecycline remained the most effective antibiotics. Polymyxins and tigecycline are the current antimicrobials for CRAB, however, there is a lack of clinically relevant data about in-vivo susceptibility breakpoints, which could result in unfavorable clinical outcomes. Furthermore, polymyxins have a narrow therapeutic spectrum and are associated with serious side effects like neurotoxicity and nephrotoxicity. In these dire circumstances, the need for the discovery of new therapeutic agents is indispensable. The recent approval of novel β-lactam/β-lactamase inhibitor combinations such as sulbactam-durlobactam and cefiderocol offers hope for CRAB treatment, though accessibility remains limited in many regions [27, 28].

S. maltophilia and *E. meningoseptica* are intrinsically resistant to carbapenems and other beta-lactams, but they still show greater susceptibility to trimethoprim-sulfamethoxazole, a first-line drug [29, 30]. Levofloxacin, an alternative drug, has shown higher effectiveness against *S. maltophilia*. Congruently, in our study, *S. maltophilia* showed 100% in-vitro susceptibility towards levofloxacin and trimethoprim-sulfamethoxazole making them as good choice for therapy.

Limitations

Several limitations merit consideration. The retrospective design precluded collection of detailed clinical data including severity scores, prior antibiotic exposure, and time to appropriate therapy. The single-center nature limits generalizability, though our findings likely reflect regional patterns. Molecular characterization of resistance mechanisms was not performed, limiting understanding of clonal relationships and resistance determinants. Finally, the relatively small sample sizes for less common species (*S. maltophilia, E.*

meningoseptica) limit conclusions about their resistance patterns. Therefore, a multicenter study with a larger sample size is recommended to better generalize our findings.

Conclusion

The study suggests multifaceted approach for managing CR-NFGNB infections. These include routine screening for CR-NFGNB colonization in high-risk units, molecular typing for outbreak investigation, and participation in regional/global surveillance networks. A combination therapy with high-dose ampicillin-sulbactam and additional agents should be considered for CRAB infections. The findings also highlight the urgent need for comprehensive antimicrobial resistance containment strategies, including, improving infection prevention through enhanced environmental cleaning protocols, monitoring hand hygiene, antimicrobial stewardship programs, and investment in novel therapeutic development, and contact precautions for colonized patients. Effective antimicrobial stewardship for CR-NFGNB rods demands institutional committees that monitor carbapenem consumption, guide empirical therapy using local antibiograms, promote de-escalation practices, and provide continuous prescriber education with real-time feedback. This integrated approach ensures optimal patient treatment while preserving our limited therapeutic arsenal against these formidable pathogens.

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