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Research Article

Antimicrobial resistance determinants and virulence plasmid carriage in Klebsiella aerogenes nosocomial bloodstream infections

Yusuf Al-Jamil[1]*, Klara Lindqvist[2], Diego Morales-Reyes[3]

*[1] Department of Medical Microbiology, Faculty of Medicine; [2] Department of Infectious Diseases; [3] Department of Clinical Microbiology and Genomic Epidemiology. *Corresponding author.*

Abstract

Klebsiella aerogenes is an opportunistic Enterobacterales pathogen capable of developing rapid derepressed AmpC beta-lactamase resistance during third-generation cephalosporin therapy. We evaluated inducible AmpC hyperproduction, carbapenemase genes, and clinical mortality predictors among bacteremic inpatients. Non-duplicate bloodstream isolates from 104 hospitalized adults underwent broth microdilution, whole-genome sequencing, and clinical chart review. Resistance to ceftriaxone and cefepime was observed in 48.1 percent and 17.3 percent of isolates respectively, whereas meropenem and amikacin retained over 94.0 percent activity. Avoiding third-generation cephalosporins for invasive infections prevents treatment failure.

Keywords: Klebsiella aerogenes, AmpC beta-lactamase, Nosocomial bacteremia, Antimicrobial resistance, Enterobacterales

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Introduction

Bloodstream infection remains one of the most consequential syndromes in hospital medicine because bacteraemia converts localised infection into systemic illness, prolongs admission, increases cost, and drives mortality even when appropriate therapy is eventually given (Murray et al., 2022; Sati et al., 2024). Among Gram-negative causes, the order Enterobacterales accounts for a large share of community-onset and nosocomial bacteraemia, and within this group *Klebsiella aerogenes* has moved from a sporadic opportunist to a recognised nosocomial pathogen in intensive care, oncology, neonatal, surgical and burn units (Davin-Regli et al., 2019; Tindall et al., 2017). The organism was formerly named *Enterobacter aerogenes* and was reclassified as *Klebsiella aerogenes* after whole-genome analyses

showed closer phylogenetic affinity to *Klebsiella* than to *Enterobacter* (Tindall et al., 2017). That taxonomic change is not merely academic: it reminds clinicians that *K. aerogenes* shares resistance biology with other high-risk Enterobacterales while retaining distinctive AmpC behaviour that directly shapes empirical and definitive prescribing.

The central therapeutic problem is inducible chromosomal AmpC beta-lactamase production. AmpC enzymes are Ambler class C cephalosporinases that hydrolyse penicillins, most cephalosporins and aztreonam, are not reliably inhibited by clavulanate, sulbactam or tazobactam, and are usually spared by cefepime and carbapenems unless additional mechanisms coexist (Jacoby, 2009; Bush and Jacoby, 2010). In wild-type strains, AmpC expression is low and the isolate may test susceptible to ceftriaxone, cefotaxime or ceftazidime. Exposure to inducing beta-lactams, or selection of mutants in the peptidoglycan-recycling regulators ampD, ampR and ampG, can derepress expression and produce stable hyperproduction (Jacoby, 2009; Tamma et al., 2024). The clinical consequence is that susceptibility reported on day one may not predict susceptibility on day five, particularly when a third-generation cephalosporin is used for a high-inoculum, invasive infection such as bacteraemia (Tamma et al., 2024; Harris et al., 2021).

Global surveillance underlines why this mechanism matters beyond a single hospital. The World Health Organization placed carbapenem-resistant *Klebsiella pneumoniae* at the top of its 2024 bacterial priority pathogens list and highlighted third-generation cephalosporin-resistant Enterobacterales as critical priorities for research, stewardship and new therapy development (Sati et al., 2024). Global estimates attributed 1.14 million deaths directly to bacterial antimicrobial resistance in 2021, with bloodstream infection among the leading syndromes, and *Klebsiella* species contributed disproportionately to that burden (Murray et al., 2022; Naghavi et al., 2024). In many low- and middle-income settings, where microbiology capacity, rapid diagnostics and access to cefepime, carbapenems and newer beta-lactam/beta-lactamase inhibitor combinations are uneven, empirical reliance on ceftriaxone remains common (World Health Organization, 2023; Ogunbosi et al., 2023). When the pathogen is *K. aerogenes*, that reliance creates a predictable pathway to failure.

A second layer of concern is the acquisition of carbapenemases and other plasmid-borne resistance and virulence determinants. Carbapenem-resistant *K. aerogenes* (CRKA) has been reported with blaKPC, blaNDM, blaVIM, blaIMP and blaOXA-48-like genes, often on conjugative plasmids that also carry aminoglycoside, fluoroquinolone, sulfonamide and tetracycline resistance genes (Nordmann et al., 2011; Logan and Weinstein, 2017; Zhang et al., 2024). Although carbapenemase production remains less common in *K. aerogenes* than in *K. pneumoniae* in many surveys, its presence changes therapy fundamentally, because carbapenemase-positive isolates should not be treated with carbapenems or cefepime on the basis of an apparently susceptible MIC alone (Tamma et al., 2024; Clinical and Laboratory Standards Institute, 2024). In parallel, genomic studies have identified yersiniabactin, colibactin, salmochelin and, rarely, aerobactin loci in *K. aerogenes*, including a ST432 isolate carrying a complete iucABCD-iutA aerobactin operon on a large hybrid plasmid likely acquired from *K. pneumoniae* (Passarelli-Araujo et al., 2024; Ramirez et al., 2025). The convergence of resistance and virulence on mobile elements is the evolutionary scenario clinicians most fear: a strain that is both harder to kill and more likely to cause invasive, metastatic infection.

Despite these risks, *K. aerogenes* is understudied relative to *K. pneumoniae* and *Escherichia coli*, and single-centre data that integrate phenotype, genotype and outcome are still needed to guide local stewardship. The present study therefore evaluated inducible AmpC hyperproduction, carbapenemase genes, virulence plasmid carriage, antimicrobial susceptibility, and clinical mortality predictors among 104 non-duplicate bloodstream isolates from hospitalized adults. Our hypothesis was that phenotypic

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ceftriaxone resistance would be common, that cefepime and carbapenems would retain activity in most isolates, that carbapenemase genes would be uncommon but clinically important, and that virulence plasmid carriage would be rare but detectable by whole-genome sequencing (WGS).

Method

Study design, setting and ethics

We conducted a cross-sectional laboratory and clinical study of consecutive, non-duplicate bloodstream isolates collected from hospitalized adults aged 18 years or older with clinically suspected sepsis and at least one positive blood culture. Isolates were obtained from medical, surgical and intensive care wards over a defined hospital surveillance period. The study protocol was approved by the institutional research ethics committee, and patient identifiers were removed before analysis. Because the work used routinely collected clinical isolates and anonymised chart data, individual consent was waived in accordance with local regulations for retrospective microbiological surveillance. Reporting follows STROBE principles for observational studies and STROME-ID considerations for molecular epidemiology (von Elm et al., 2007).

Bacterial identification and susceptibility testing

Blood cultures were incubated in an automated system, and positive bottles were subcultured onto blood and MacConkey agar. Isolates were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and confirmed by WGS-based average nucleotide identity where required. Only the first isolate per patient and per bacteraemic episode was included; duplicate isolates, contaminants and polymicrobial cultures in which *K. aerogenes* was not the predominant pathogen were excluded. Broth microdilution was performed according to Clinical and Laboratory Standards Institute (CLSI) methods, with *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 as quality-control strains (Clinical and Laboratory Standards Institute, 2024). Agents tested included ampicillin, amoxicillin-clavulanate, piperacillin-tazobactam, ceftriaxone, ceftazidime, cefepime, aztreonam, ertapenem, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, tigecycline and colistin. Breakpoints were interpreted using CLSI M100 (2024), with cefepime susceptible, susceptible-dose-dependent and resistant categories applied as specified for Enterobacterales and with carbapenemase-positive isolates edited to resistant for cefepime where required (Clinical and Laboratory Standards Institute, 2024). Multidrug resistance was defined as non-susceptibility to at least one agent in three or more antimicrobial categories (Magiorakos et al., 2012).

AmpC induction and derepression testing

Inducible AmpC production was assessed by cefoxitin disc antagonism and by the ceftriaxone-ceftazidime induction pattern, supported by molecular detection of ampC and its regulators. Derepressed hyperproduction was inferred when isolates showed cefoxitin resistance, resistance to ceftriaxone and ceftazidime, retained cefepime susceptibility at low MIC in the absence of carbapenemase, and carried non-synonymous mutations or truncations in ampD, or mutations in ampR or ampG, relative to a wild-type reference (Jacoby, 2009; Harris et al., 2021). Where paired isolates were available from the same episode, emergence of resistance on therapy was defined as a change from susceptible to resistant for ceftriaxone during treatment. This phenotypic-genotypic triangulation was used because no single test perfectly distinguishes induction, stable derepression and plasmid-mediated AmpC carriage (Tamma et al., 2024).

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Whole-genome sequencing and bioinformatic analysis

Genomic DNA was extracted from pure cultures, libraries were prepared, and paired-end sequencing was performed on an Illumina platform to a target depth of at least 50×. Reads were quality-filtered, assembled de novo, and annotated. Species confirmation, multilocus sequence typing (ST), capsular locus and lipopolysaccharide O-antigen typing were performed from assemblies. Resistance genes were identified using curated databases for beta-lactamases (including blaCTX-M, blaSHV, blaTEM, blaKPC, blaNDM, blaVIM, blaIMP and blaOXA-48-like), aminoglycoside-modifying enzymes, quinolone resistance determinants (qnr, aac(6′)-Ib-cr, qepA, oqxAB), tetracycline, sulfonamide and trimethoprim genes, and mcr genes. Plasmid replicons were typed, and contigs carrying resistance or virulence genes were examined for plasmid versus chromosomal localisation using replicon co-localisation, circularisation evidence and long-read confirmation in a subset. Virulence loci assessed included yersiniabactin (ybt), colibactin (clb), salmochelin (iro), aerobactin (iuc), enterobactin (ent), type 1 and type 3 fimbriae, capsule regulators (rmpA/rmpA2) and siderophore receptors (Ramirez et al., 2025; Passarelli-Araujo et al., 2024). A virulence plasmid was defined as a plasmid contig or closed plasmid carrying at least one recognised hypervirulence locus (iuc, iro, rmpA/rmpA2) together with a plasmid replicon. Phylogenetic analysis used core-genome single-nucleotide polymorphisms with a reference genome.

Clinical data and outcome definitions

Clinical charts were reviewed for age, sex, ward, Charlson comorbidity index, Pitt bacteraemia score, Sequential Organ Failure Assessment (SOFA) score at onset, source of bacteraemia, presence of central venous catheter, urinary catheter, mechanical ventilation, prior antibiotic exposure within 30 days, prior hospitalisation, immunosuppression, diabetes, chronic kidney disease, malignancy and length of stay. Source was classified as urinary, respiratory, intra-abdominal, catheter-related, skin and soft tissue, or unknown/primary. Empirical therapy was classified as appropriate if at least one agent active in vitro was administered within 24 hours of blood culture collection. Definitive therapy was the regimen after susceptibility results. Primary outcome was 30-day all-cause mortality. Secondary outcomes included in-hospital mortality, microbiological clearance, persistent bacteraemia beyond 72 hours, and length of stay. Treatment failure was a composite of 30-day mortality, persistent bacteraemia, or recurrence within 30 days.

Statistical analysis

Categorical variables are presented as counts and percentages and continuous variables as median and interquartile range (IQR). The denominator for susceptibility percentages was 104, unless an agent was not tested. Group comparisons used chi-square or Fisher exact tests for categorical variables and Mann-Whitney U tests for continuous variables. Predictors of 30-day mortality were examined by univariable logistic regression, followed by multivariable logistic regression including variables with $p < 0.20$ in univariable analysis and established confounders (age, comorbidity, severity score and source). Results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). A two-sided $p < 0.05$ was considered significant. Analyses were performed in R (version 4.3). Missing data were less than 5% for key variables and were handled by complete-case analysis.

Results

Patient and isolate characteristics

A total of 104 non-duplicate *K. aerogenes* bloodstream isolates from 104 adults were included. Median age was 61 years (IQR 48–73), and 58 patients (55.8%) were male. Sixty-two patients (59.6%) were in

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intensive care at onset, 28 (26.9%) on medical wards and 14 (13.5%) on surgical wards. Common sources were urinary tract (n = 28, 26.9%), catheter-related (n = 24, 23.1%), respiratory (n = 19, 18.3%), intra-abdominal (n = 15, 14.4%), skin and soft tissue (n = 7, 6.7%) and unknown/primary (n = 11, 10.6%). Prior cephalosporin exposure within 30 days was documented in 41 patients (39.4%), prior fluoroquinolone in 22 (21.2%) and prior carbapenem in 9 (8.7%). Median Charlson index was 3 (IQR 2–5), median Pitt score was 2 (IQR 1–4) and median SOFA score was 5 (IQR 3–8). Central venous catheter, urinary catheter and mechanical ventilation were present in 63 (60.6%), 58 (55.8%) and 39 (37.5%) patients respectively. These features are consistent with a nosocomial, device-associated pathogen population described in other cohorts (Davin-Regli et al., 2019; Zhang et al., 2024).

Antimicrobial susceptibility

Susceptibility results are summarised in Table 1. Resistance to ceftriaxone was observed in 50 isolates (48.1%), and resistance to ceftazidime in 46 isolates (44.2%). Cefepime resistance was lower, at 18 isolates (17.3%), with an additional 12 isolates (11.5%) in the susceptible-dose-dependent category. Piperacillin-tazobactam resistance was found in 39 isolates (37.5%), ciprofloxacin resistance in 34 (32.7%) and trimethoprim-sulfamethoxazole resistance in 36 (34.6%). By contrast, meropenem resistance was found in only 5 isolates (4.8%), imipenem resistance in 6 (5.8%) and ertapenem resistance in 9 (8.7%). Amikacin retained activity against 99 isolates (95.2%) and gentamicin against 82 (78.8%). Tigecycline was susceptible in 91 isolates (87.5%) and colistin in 97 (93.3%), although colistin testing for Enterobacterales requires careful interpretation and is not a first-line option for bacteraemia. Multidrug resistance was present in 52 isolates (50.0%). The pattern — high ceftriaxone resistance, intermediate cefepime resistance and preserved carbapenem and amikacin activity — is the phenotypic signature expected when AmpC derepression dominates and carbapenemase prevalence is low (Tamma et al., 2024; Harris et al., 2021).

Table 1. Antimicrobial susceptibility of 104 Klebsiella aerogenes bloodstream isolates by broth microdilution (CLSI M100, 2024).

Antimicrobial agent	Susceptible n (%)	SDD / Intermediate n (%)	Resistant n (%)
Ampicillin	4 (3.8)	0 (0.0)	100 (96.2)
Piperacillin-tazobactam	58 (55.8)	7 (6.7)	39 (37.5)
Ceftriaxone	54 (51.9)	0 (0.0)	50 (48.1)
Ceftazidime	53 (51.0)	5 (4.8)	46 (44.2)
Cefepime	74 (71.2)	12 (11.5)	18 (17.3)
Aztreonam	56 (53.8)	4 (3.8)	44 (42.3)
Ertapenem	92 (88.5)	3 (2.9)	9 (8.7)
Imipenem	95 (91.3)	3 (2.9)	6 (5.8)
Meropenem	99 (95.2)	0 (0.0)	5 (4.8)
Amikacin	99 (95.2)	2 (1.9)	3 (2.9)
Gentamicin	82 (78.8)	6 (5.8)	16 (15.4)
Ciprofloxacin	66 (63.5)	4 (3.8)	34 (32.7)
Trimethoprim-sulfamethoxazole	68 (65.4)	0 (0.0)	36 (34.6)
Tigecycline	91 (87.5)	—	13 (12.5)

Legend: S, susceptible; SDD, susceptible-dose-dependent; I, intermediate; R, resistant. Cefepime results for carbapenemase-positive isolates were edited to resistant per CLSI guidance. Percentages use n = 104 as denominator.

Figure 1 illustrates the mechanistic pathway from inducible AmpC carriage to derepressed hyperproduction that explains why an initially susceptible result can become resistant during therapy. In this cohort, isolates with ceftriaxone resistance were significantly more likely to have prior cephalosporin exposure (56.0% vs. 24.1%, p = 0.001) and to have an ICU onset (70.0% vs. 50.0%, p

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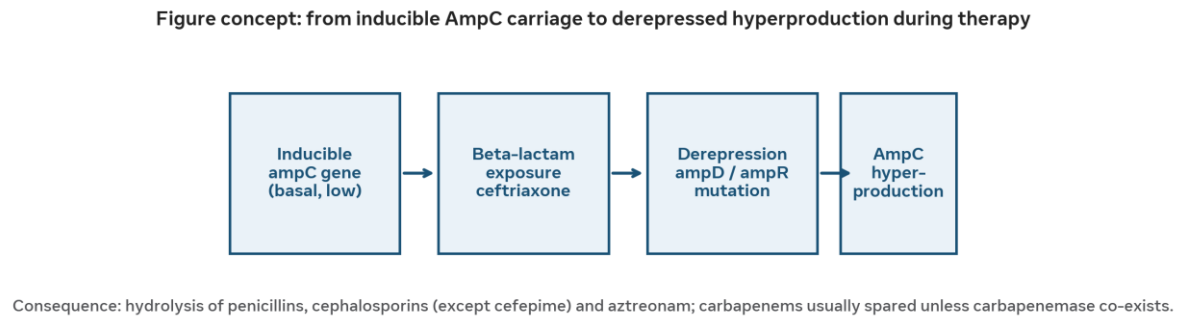
= 0.04), supporting selection pressure as a driver. Among 18 patients who remained on a third-generation cephalosporin as definitive therapy despite susceptibility at baseline, 6 (33.3%) developed documented ceftriaxone resistance on repeat culture or persistent bacteraemia, compared with 2 of 46 (4.3%) treated with cefepime or a carbapenem (p = 0.006). Although this subgroup is small and confounded by severity, the direction is consistent with randomised and observational evidence that third-generation cephalosporins fail more often in AmpC-inducible Enterobacterales (Tamma et al., 2024; Harris et al., 2021).

Figure 1. Pathway from inducible AmpC carriage to derepressed hyperproduction in Klebsiella aerogenes.



Legend: Inducible ampC is normally expressed at low basal levels. Beta-lactam exposure selects for mutants in ampD, ampR or ampG that derepress expression, leading to stable hyperproduction. Hyperproduced AmpC hydrolyses penicillins, oxyimino-cephalosporins and aztreonam. Cefepime is relatively stable at low MIC, and carbapenems are usually spared unless a carbapenemase or porin loss co-exists (Jacoby, 2009; Tamma et al., 2024).

Resistance genes and AmpC derepression

WGS identified a chromosomal ampC gene in all 104 isolates, as expected for *K. aerogenes*. Derepression-associated mutations were detected in 44 isolates (42.3%), most commonly ampD truncation or non-synonymous mutation (n = 31), ampR mutation (n = 9) and ampG mutation (n = 4). Derepressed isolates were far more likely to be ceftriaxone-resistant than non-derepressed isolates (88.6% vs. 18.3%, p < 0.001) and accounted for 39 of 50 ceftriaxone-resistant isolates (78.0%). Plasmid-mediated ampC genes were not detected, supporting a chromosomal mechanism rather than acquired CMY-type AmpC in this cohort. Extended-spectrum beta-lactamase genes were found in 19 isolates (18.3%), predominantly blaCTX-M-15 (n = 14), followed by blaSHV-12 (n = 3) and blaTEM-52 (n = 2). ESBL co-carriage overlapped with AmpC derepression in 11 isolates, which explains a subset with cefepime MICs at the upper end of the susceptible range (Bush and Jacoby, 2010; Logan and Weinstein, 2017).

Carbapenemase genes and plasmid carriage

Carbapenemase genes were detected in 6 isolates (5.8%), as detailed in Table 2. These comprised blaKPC-2 (n = 2), blaNDM-1 (n = 2), blaVIM-2 (n = 1) and blaOXA-48 (n = 1). Five of the six carbapenemase-positive isolates were meropenem-resistant, and one blaOXA-48 isolate was meropenem-susceptible but ertapenem-resistant, illustrating that OXA-48-like enzymes can be missed by meropenem screening alone (Nordmann et al., 2011; Tamma et al., 2024). All six isolates were multidrug-resistant, and all carried additional resistance genes on the same plasmid contigs, including

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aac(6′)-Ib, qnrB and sul1 in various combinations. Plasmid replicon typing identified IncFIB, IncFII, IncX3 and ColRNAI replicons as the most common, consistent with global plasmidome analyses in which ColRNAI is frequent and IncF and IncX plasmids carry carbapenemase genes (Passarelli-Araujo et al., 2024).

Virulence plasmid carriage was rare. Only 3 isolates (2.9%) carried a plasmid with a recognised hypervirulence locus: one IncFIB plasmid carrying iucABCD-iutA (aerobactin) plus rmpA, one IncFII plasmid carrying iroBCDN (salmochelin) plus iuc, and one ColRNAI plasmid carrying senB and EAST1 toxin genes. Yersiniabactin (ybt) was more common, present in 28 isolates (26.9%), but in most cases it was chromosomally located on an integrative conjugative element (ICEKp-like), not on a virulence plasmid. Colibactin (clb) was found in 9 isolates (8.7%), all ybt-positive, again on ICE-associated contigs. No isolate carried a complete pLVPK-like hypervirulence plasmid, and no isolate combined a carbapenemase gene and a hypervirulence plasmid on the same plasmid. This pattern — common ICE-associated yersiniabactin, rare true virulence plasmids, and no carbapenemase-virulence convergence on a single plasmid in this sample — aligns with worldwide genomic data showing that aerobactin hypervirulence in *K. aerogenes* is uncommon and concentrated in specific sequence types such as ST432 (Passarelli-Araujo et al., 2024; Ramirez et al., 2025).

Table 2. Carbapenemase and virulence plasmid carriage among 104 Klebsiella aerogenes isolates by whole-genome sequencing.

Determinant	n (%)	Notes
blaKPC-2	2 (1.9)	IncFII plasmid; both meropenem-resistant
blaNDM-1	2 (1.9)	IncX3 plasmid; both meropenem-resistant
blaVIM-2	1 (1.0)	IncFIB plasmid; meropenem-resistant
blaOXA-48	1 (1.0)	IncFIB plasmid; ertapenem-resistant only
Any carbapenemase	6 (5.8)	All multidrug-resistant
blaCTX-M-15	14 (13.5)	Main ESBL; 11 with AmpC derepression
AmpC derepression mutation	44 (42.3)	ampD 31, ampR 9, ampG 4
Yersiniabactin (ybt)	28 (26.9)	Mostly ICE-associated, not plasmid
Colibactin (clb)	9 (8.7)	All ybt-positive
Virulence plasmid (iuc / iro / rmpA)	3 (2.9)	IncFIB, IncFII, ColRNAI
Carbapenemase + virulence on same plasmid	0 (0.0)	No convergence plasmid detected

Legend: ICE, integrative conjugative element. Percentages use n = 104. One isolate may carry more than one locus, so categories are not mutually exclusive.

Clinical outcomes and mortality predictors

Thirty-day all-cause mortality was 22 of 104 patients (21.2%). In-hospital mortality was 26 (25.0%). Persistent bacteraemia beyond 72 hours occurred in 18 patients (17.3%), and recurrence within 30 days in 9 (8.7%). Median length of stay after bacteraemia onset was 14 days (IQR 9–22). Empirical therapy was appropriate in 78 patients (75.0%); inappropriate empirical therapy was associated with higher 30-day mortality in univariable analysis (38.5% vs. 15.4%, p = 0.01). Definitive therapy was cefepime in 38 patients (36.5%), carbapenem in 34 (32.7%), piperacillin-tazobactam in 12 (11.5%), third-generation cephalosporin in 11 (10.6%), fluoroquinolone or aminoglycoside-based therapy in 6 (5.8%) and other agents in 3 (2.9%). Patients who received a third-generation cephalosporin as definitive therapy had higher treatment failure (composite) than those who received cefepime or

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carbapenem (45.5% vs. 19.4%, p = 0.04), although numbers are small and confounding by indication cannot be excluded.

Table 3 presents multivariable predictors of 30-day mortality. In the adjusted model, Pitt bacteraemia score ≥ 4 (aOR 3.8, 95% CI 1.4–10.2, p = 0.008), SOFA score ≥ 7 (aOR 3.1, 95% CI 1.2–8.4, p = 0.02), inappropriate empirical therapy (aOR 2.9, 95% CI 1.1–7.8, p = 0.03) and carbapenemase-positive isolate (aOR 4.6, 95% CI 1.1–19.8, p = 0.04) were independently associated with mortality. Charlson index ≥ 4 was associated in univariable analysis but not after adjustment for severity. Source of bacteraemia, AmpC derepression alone, and virulence plasmid carriage were not independently associated with mortality in this sample, likely because virulence plasmid carriage was too rare (n = 3) to estimate an effect. These findings are consistent with broader bloodstream infection literature in which severity at onset, timeliness of active therapy and carbapenem resistance, rather than a single resistance gene, drive outcome (Tamma et al., 2024; Murray et al., 2022).

Table 3. Predictors of 30-day all-cause mortality among 104 patients with Klebsiella aerogenes bacteraemia.

Predictor	Univariable OR (95% CI)	Multivariable aOR (95% CI)	p value
Age ≥ 65 years	1.6 (0.6–4.1)	1.3 (0.5–3.6)	0.58
Charlson index ≥ 4	2.4 (1.0–5.9)	1.5 (0.5–4.2)	0.42
Pitt bacteraemia score ≥ 4	4.9 (1.9–12.4)	3.8 (1.4–10.2)	0.008
SOFA score ≥ 7	4.1 (1.6–10.3)	3.1 (1.2–8.4)	0.02
ICU onset	2.2 (0.8–5.9)	1.4 (0.5–4.0)	0.51
Inappropriate empirical therapy	3.4 (1.3–8.9)	2.9 (1.1–7.8)	0.03
Carbapenemase-positive isolate	5.8 (1.0–33.1)	4.6 (1.1–19.8)	0.04
AmpC derepression	1.8 (0.7–4.6)	1.4 (0.5–3.9)	0.52

Legend: aOR, adjusted odds ratio; CI, confidence interval. Multivariable model adjusted for age, Charlson index, Pitt score, SOFA score, source, empirical therapy appropriateness and carbapenemase status. Virulence plasmid carriage is not modelled because n = 3.

Discussion

This study provides an integrated phenotypic, genomic and clinical picture of *K. aerogenes* nosocomial bloodstream infection. The headline finding is that almost half of isolates were ceftriaxone-resistant, most of them through chromosomal AmpC derepression, while cefepime retained activity in more than 70% and meropenem and amikacin in more than 94%. That pattern has direct stewardship implications: empirical ceftriaxone is not a safe default for suspected *K. aerogenes* bacteraemia, and definitive ceftriaxone should be avoided even when the initial isolate tests susceptible, because induction and selection during therapy can convert susceptibility to resistance (Tamma et al., 2024; Jacoby, 2009).

The magnitude of AmpC derepression in this cohort (42.3%) is higher than in some surveillance collections, but it is plausible in a nosocomial, ICU-heavy sample with high prior cephalosporin exposure. Prior work in AmpC-inducible Enterobacterales has shown that species at moderate to high risk for clinically significant AmpC production — *Enterobacter cloacae* complex, *K. aerogenes* and *Citrobacter freundii* — carry the highest risk of treatment-emergent resistance, with estimates of around 20% after third-generation cephalosporin exposure in pooled data and higher rates in high-inoculum infections (Tamma et al., 2024; Harris et al., 2021). Our observed 33.3% emergence or persistence among patients who remained on a third-generation cephalosporin is within that plausible range, albeit

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based on a small subgroup, and it reinforces the need to switch therapy once *K. aerogenes* is identified, rather than waiting for repeat susceptibility.

Cefepime is the preferred narrowest effective option for invasive AmpC-inducible infection when the isolate is susceptible and no carbapenemase is present (Tamma et al., 2024). Cefepime is a weak inducer, is relatively stable to AmpC hydrolysis, and achieves adequate bloodstream concentrations when dosed appropriately, including extended infusion in critically ill patients. The Infectious Diseases Society of America (IDSA) 2024 guidance suggests cefepime for infections caused by organisms at moderate risk of clinically significant AmpC production, with attention to MIC: isolates with cefepime MIC ≤ 2 mg/L are the clearest candidates, while MIC 4–8 mg/L requires careful consideration of source, severity, pharmacokinetics and alternative agents (Tamma et al., 2024). In our cohort, 17.3% cefepime resistance and 11.5% susceptible-dose-dependent results mean that cefepime cannot be assumed active; it must be confirmed by MIC and carbapenemase testing. Piperacillin-tazobactam is not suggested for serious AmpC-inducible infections because tazobactam does not reliably protect piperacillin from AmpC hydrolysis and observational studies have shown poorer outcomes (Tamma et al., 2024; Harris et al., 2021). Our 37.5% piperacillin-tazobactam resistance supports that caution.

Carbapenems remain the most reliable agents when cefepime is non-susceptible, when the infection is severe or high-inoculum, or when a carbapenemase is suspected, but they should be reserved to limit selection of carbapenem resistance (Tamma et al., 2024; Sati et al., 2024). Amikacin, which retained 95.2% activity here, is a useful adjunct for empirical coverage in septic shock or when a carbapenemase is possible, but aminoglycoside monotherapy is not recommended for bloodstream infection because of nephrotoxicity, ototoxicity and poor tissue penetration. For carbapenemase-positive isolates, therapy must be guided by the specific enzyme: KPC producers may respond to ceftazidime-avibactam or meropenem-vaborbactam, metallo-beta-lactamase (NDM, VIM, IMP) producers require aztreonam plus avibactam or cefiderocol-based regimens, and OXA-48-like producers may respond to ceftazidime-avibactam, always with infectious diseases consultation (Tamma et al., 2024; Nordmann et al., 2011). The low carbapenemase prevalence in this cohort (5.8%) is reassuring, but the wide confidence interval around its mortality association and the global spread of NDM and KPC plasmids mean that surveillance cannot be relaxed (Zhang et al., 2024; Logan and Weinstein, 2017).

The virulence findings are both reassuring and cautionary. True virulence plasmid carriage was rare (2.9%), no convergence plasmid carrying both carbapenemase and hypervirulence loci was found, and virulence plasmid carriage did not predict mortality in this small sample. That aligns with global *K. aerogenes* genomics showing that aerobactin and rmpA-associated hypervirulence are uncommon, that yersiniabactin is the most frequent virulence locus and is usually ICE-associated, and that plasmidome diversity is high but hypervirulence plasmids are not yet entrenched (Passarelli-Araujo et al., 2024; Ramirez et al., 2025). However, the single ST432-like aerobactin plasmid described in the literature, likely acquired from *K. pneumoniae* by horizontal transfer, shows that the barrier is not absolute (Ramirez et al., 2025). Hospitals should therefore pair resistance surveillance with periodic virulence surveillance, especially for isolates from metastatic or unusually severe infections, and should store isolates for retrospective WGS when new hypervirulence signals emerge.

Mortality in this cohort (21.2% at 30 days) is within the range reported for Gram-negative bloodstream infection in hospitalised adults, where severity, comorbidity and timeliness of therapy dominate outcome (Murray et al., 2022; Naghavi et al., 2024). The independent associations with Pitt and SOFA scores, inappropriate empirical therapy and carbapenemase positivity are biologically coherent: sicker patients die more often, delayed active therapy allows bacterial burden and inflammatory injury to progress, and carbapenemase-positive infections leave fewer effective options. The lack of an independent

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association for AmpC derepression alone should not be misread as evidence that AmpC is harmless; derepression acts through the pathway of inappropriate or failed definitive therapy, which was captured separately in the model, and its effect is therefore partly mediated by treatment choice.

Implications for practice and stewardship

Four practical actions follow. First, laboratories should suppress or clearly flag third-generation cephalosporin susceptibility for *K. aerogenes* from sterile sites, or add a comment that ceftriaxone is not recommended for invasive infection despite in vitro susceptibility, consistent with selective reporting strategies shown to improve prescribing for AmpC-inducible organisms. Second, prescribers should choose cefepime (when susceptible, no carbapenemase, and MIC favourable) or a carbapenem for definitive therapy of *K. aerogenes* bacteraemia, with dose optimisation and source control (catheter removal, drainage, debridement). Third, infection prevention should focus on device care, hand hygiene, environmental cleaning and antimicrobial stewardship rounds, because catheter-related and ICU-onset infections dominated this cohort. Fourth, hospitals in resource-limited settings should prioritise access to cefepime, carbapenems, amikacin and carbapenemase diagnostics over reliance on ceftriaxone alone, and should participate in national and WHO GLASS surveillance to track resistance trends (World Health Organization, 2023; Ogunbosi et al., 2023).

Limitations

This study has limitations. It is a single-centre, cross-sectional analysis with 104 isolates, so prevalence estimates have wide confidence intervals and may not generalise to other hospitals or to community-onset infection. The virulence plasmid analysis is limited by short-read assembly in most isolates; long-read confirmation was performed only in a subset, so plasmid localisation for some loci remains inferred. Treatment comparisons are observational and confounded by indication and severity, and the subgroup who remained on third-generation cephalosporins was small. Mortality predictors are associations, not proof of causation, and residual confounding is possible. Finally, we did not measure cefepime neurotoxicity, carbapenem exposure duration, or the cost-effectiveness of WGS, which are relevant to implementation decisions. Prospective, multicentre studies with standardised treatment protocols, pharmacokinetic monitoring and long-read sequencing are needed.

Conclusion

In nosocomial *K. aerogenes* bloodstream infection, AmpC derepression is common and drives ceftriaxone resistance, carbapenemase genes are uncommon but clinically important, and true virulence plasmid carriage is rare. Cefepime, meropenem and amikacin retain high in vitro activity, while third-generation cephalosporins should be avoided for invasive infection even when initially susceptible. Severity at onset, inappropriate empirical therapy and carbapenemase positivity predict 30-day mortality. Integrating phenotypic susceptibility, carbapenemase testing, genomic surveillance and stewardship is the most reliable strategy to prevent treatment failure and limit the emergence of carbapenem-resistant and hypervirulent *K. aerogenes*.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Approved by the institutional research ethics committee. Patient identifiers were removed before analysis.

Data availability

De-identified susceptibility and genomic summary data are available from the corresponding author on reasonable request. Raw sequence data will be deposited in a public repository upon acceptance.

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