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Quantifying aminoglycoside resistance in extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales clinical isolates: a retrospective cohort study

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Summary

AIMS: Aminoglycoside resistance is frequently detected in extended-spectrum-beta-lactamase (ESBL)-producing Enterobacterales (ESBL-PE), questioning the appropriateness of aminoglycosides as empiric therapy in patients with suspected ESBL-PE infections. Therefore, we aimed to evaluate the frequency of aminoglycoside resistance in patients harbouring ESBL-PE and identify patient-related risk factors associated with aminoglycoside resistance to facilitate early detection of at-risk patients.

METHODS: This retrospective single-centre cohort study included hospitalised patients aged ≥18 years with an ESBL-PE-positive sample between January 2016 and December 2018. Aminoglycoside resistance was defined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for Enterobacterales for the current year of testing.

RESULTS: Five hundred forty-four patients met the eligibility criteria, of which 240 (44.1%) harboured aminoglycoside-resistant ESBL strains. Identification of ESBL-*Klebsiella pneumoniae* was significantly associated with aminoglycoside resistance (odds ratio [OR] = 2.64, 95% confidence interval [CI] = 1.65–4.21, p <0.001) and an international travel history within the past 12 months was marginally associated with aminoglycoside resistance (OR = 1.51, 95% CI = 0.95–2.42, p = 0.084).

CONCLUSIONS: In a low ESBL endemicity setting, aminoglycoside resistance in patients harbouring ESBL-PE is common, especially ESBL-*K. pneumoniae*, and needs to be considered in clinicians' decision-making regarding empiric therapy regimens.

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Introduction

Aminoglycosides are frequently administered empirically in combination with beta-lactam agents to treat severe sepsis, aiming to provide broad coverage for multidrug-resistant Gram-negative bacteria [1, 2], including extended-spectrum beta-lactamase producing Enterobacterales (ESBL-PE). While a number of host-related risk factors, such as immunosuppressive therapy or haematologic malignancies, have been identified as risk factors for carrying ESBL-PE [3], knowledge of their associations with aminoglycoside resistance is incomplete. In Europe, the prevalence of aminoglycoside resistance varies between countries, ranging from 0% to 67% for *Klebsiella pneumoniae* and 5% to 34% for *Escherichia coli* (https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc, accessed on 9th July 2022). These findings question the value of empiric aminoglycoside therapy in patients with suspected ESBL-PE infections, possibly enhancing their risk of adverse outcomes such as acute kidney injury without necessarily improving clinical outcomes. Our study aimed to identify patient-related risk factors associated with aminoglycoside resistance in ESBL-PE carriers to optimise empiric antibiotic decision-making.

Methods

Setting and participants

This retrospective cohort study was conducted at the University Hospital Basel, a tertiary care centre in Basel, Switzerland. It included hospitalised patients aged ≥18 years with ESBL-PE detected in any screening or clinical sample between January 2016 and December 2018. Its sample size and study period were determined based on a preexisting cohort in the ESBL-Infect study [4]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.

Data collection and outcomes

Pertinent clinical and microbiological data were extracted from electronic medical records and entered into a secure REDCap® database [5]. The data were collected retrospec-

tively, and missing data were categorised as absent. The assessed variables were

- demographics;
- previous hospitalisations, defined as >1 night stay in an acute-care facility within the past 12 months;
- comorbidities based on the Charlson Comorbidity Index (CCI);
- travel history, defined as stay outside of Switzerland within the past 12 months, and whether patients were hospitalised abroad;
- surgical interventions within the prior three months and chronic wounds (defined as ulcers or decubitus);
- indwelling hardware (transurethral or suprapubic urinary catheterisation) within 30 days prior to the index sample detecting ESBL-PE and vascular hardware (defined as a central venous catheter) in place for at least seven days prior to the index sample;
- microbiologic data;
- treatment data (antibiotic therapies, defined as any antibiotic medication within three months prior to the index ESBL-PE-positive sample, immunosuppressive therapy within the prior 12 months [e.g. long-term steroids, cytostatics, biologicals/antibody therapies, mechanistic target of rapamycin kinase (mTOR) inhibitors and calcineurin inhibitors] and concomitant medication).

Infections within the relevant hospitalisation were defined according to the Centres for Disease Control and Prevention (CDC) guidelines [6]. The primary study outcome was the frequency of aminoglycoside resistance, defined as resistance to at least one of the tested aminoglycosides in patients with ESBL-PE isolates.

Microbiological testing

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for Enterobacterales were used for minimal inhibitory concentration (MIC) breakpoints for the current year of testing (www.eucast.org). Patients were categorised as aminoglycoside resistant when ESBL-PE tested as "R – resistant" or "I – intermediate" for tobramycin or amikacin, respectively. If multiple species of ESBL-PE were isolated from the same patient, patients were categorised according to the more resistant strain.

ESBL-PE testing was conducted as previously described in the ESBL-Infect study at the University Hospital Basel, which was part of the same cohort [4]: Samples were plated onto selective chromogenic agar plates (chromID® ESBL; bioMérieux, Marcy-l'Étoile, France) while species were identified using either matrix-assisted laser desorption-ionisation time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Bremen, Germany) or the Vitek 2™ System (bioMérieux, Durham, NC, USA), which was also used for susceptibility testing. ESBL production was suspected based on the detection of resistance to cefpodoxime, ceftriaxone or ceftazidime and the ESBL-PE was phenotypically confirmed using Etest® strips (bioMérieux, Marcy-l'Etoile, France) for cefotaxime, ceftazidime or cefepime, each tested with and without clavulanic acid or with disks using the Extended Spectrum β Lactamase Set (Mast Diagnostika, Reinfeld, Germany). Indeterminate results were further evaluated using the eazyplex Superbug CRE panel (AmplexDiagnostics, Gars-Bahnhof, Germany), including the *bla* $_{\text{CTX-M-1}}$ and *bla* $_{\text{CTX-M-9}}$ genes, based on our local epidemiology. If these genes were not present, isolates were considered ESBL negative.

Statistical analyses

The overall distribution of numeric data was compared using Fisher's exact test and the Mann-Whitney-U test. Patients with and without detected aminoglycoside-resistant ESBL-PE were compared using univariable and multivariable logistic regression analyses. Variables differing significantly in the multivariable analyses (except the outcome measures) were included in the multivariable model, which was checked using the Hosmer-Lemeshow goodness-of-fit test. Statistical analyses were performed using STATA (version 16.1; StataCorp, College Station, TX, USA). A p-value of <0.05 was considered statistically significant.

Ethics approval

This study was approved by the local ethics committee (EKNZ-2017-00100).

Results

Five hundred forty-four patients met the eligibility criteria, of which 240 (44.1%) harboured aminoglycoside-resistant ESBL-PE strains. Their baseline characteristics are provided in table 1. Their median age was 70 (interquartile range [IQR] = 56–81) years, and 49.3% were male. In addition, 369 (67.8%) had a history of at least one prior hospitalisation within the past 12 months. Moreover, 88 (16.2%) had a documented stay outside of Switzerland, of which 35 (6.4%) were also hospitalised abroad. Furthermore, 258 (47.4%) had been administered antibiotic therapy within the previous three months, of which 18 had received aminoglycosides (3.3%).

Proportions of aminoglycoside resistance in patients harbouring ESBL-PE did not differ significantly within the study period ($p = 0.374$; figure 1).

The distribution of aminoglycoside resistance patterns is summarised in table 2. Of the 240 patients harbouring aminoglycoside-resistant ESBL-PE strains, amikacin-intermediate and tobramycin-resistant strains were the most common (n = 117, 21.5%), followed by amikacin-susceptible and tobramycin-resistant strains (n = 102, 18.8%), with 3.5% (n = 19) testing as resistant to both amikacin and tobramycin.

The univariable analysis identified international travel within the past 12 months as the only risk factor associated with aminoglycoside resistance in patients with ESBL-PE colonisations (table 3). Overall, 55.7% (n = 49) of patients travelled within Europe, 19.5% (n = 26) within Asia, 6.8% (n = 6) within North and Central America, 2.3 % (n = 2) within South America and 9.1% (n = 8) within Africa.

Colonisation with ESBL-*K. pneumoniae* was associated with an increased probability of aminoglycoside resistance than colonisation with ESBL-*E. coli* (odds ratio [OR] = 2.74, 95% confidence interval [CI] = 1.71–4.36, $p < 0.001$; table 1). In multivariable analyses including travel history

Table1:
Baseline characteristics of the study cohort (n = 544).

		n (%) or median (IQR)
Age (years)		70 (56–81)
Male sex		268 (49.3)
Stay in an intensive care unit		141 (25.9)
History of hospitalisation*		369 (67.8)
Travel history*		88 (16.2)
Hospitalisation abroad*		35 (6.4)
Charlson Comorbidity Index		2 (0–3)
Open wounds**		60 (11.0)
Surgery***		154 (28.3)
Vascular hardware#		22 (4.0)
Dialysis		10 (1.8)
Urinary catheterisation##		160 (29.4)
Solid organ transplantation		26 (4.8)
Allogenic stem cell transplantation		16 (2.9)
Antibiotic therapy***		258 (47.4)
– Duration (days)		14 (6–34)
– Aminoglycosides		18 (3.3)
– Aminoglycosides: duration (days)		3 (1–11)
Immunosuppressive therapy*		144 (26.5)
Proton pump inhibitor*		295 (54.2)
Death		32 (5.9)
Length of hospital stay (days)		13 (8-23)
ESBL-PE species	ESBL-*Escherichia coli*	475 (87.3)
	ESBL-*Klebsiella pneumoniae*	93 (17.1)
ESBL-PE Infection		296 (54.4)
non-ESBL-PE-Infection		293 (53.8)

ESBL-PE: extended-spectrum-beta-lactamase (ESBL)-producing Enterobacterales; IQR: interquartile range.

* Within 12 months prior to the index hospitalisation

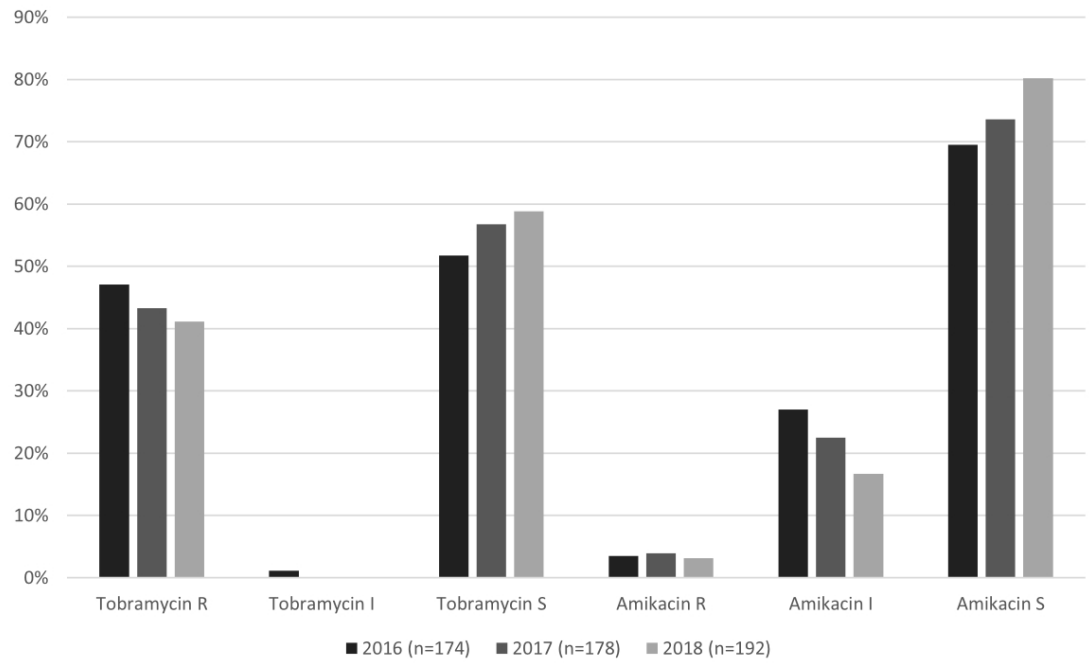
** Decubitus, ulcers

*** Within three months prior to ESBL-PE detection

In place for at least seven days prior to the index sample

Transurethral or suprapubic catheterisation within 30 days prior to the index sample

Figure 1: The proportions of tobramycin and amikacin resistance within the study period (01/2016-12/2018). The proportions of susceptible isolates were compared between study years using Fisher's exact test: amikacin (p = 0.058), tobramycin (p = 0.374), and overall (p = 0.374).



and ESBL-PE species, colonisation with ESBL-*K. pneumoniae* remained associated with aminoglycoside resistance (OR = 2.64, 95% CI = 1.65–4.21, p <0.001), while travel history only showed a trend towards an association (OR = 1.51, 95% CI = 0.95–2.42, p = 0.084). The Hosmer-Lemeshow goodness-of-fit test revealed adequate model fit (Hosmer-Lemeshow chi-square = 0.86, p = 0.649).

Discussion

Aminoglycosides are commonly administered to patients with ESBL-PE infections. However, ESBL-PE infections are at risk of aminoglycoside resistance. Understanding the patients at greatest risk of aminoglycoside-resistant ESBL-PE is important to optimise patient outcomes. In a cohort of 544 Swiss patients with ESBL-PE colonisation or car-

Table 2:
Distribution of aminoglycoside resistance patterns in patients colonised with ESBL-PE.

Amikacin	Tobramycin	n = 544	%
S	S	304	55.9
R	R	19	3.5
I	R	117	21.5
S	R	102	18.8
I	I	2	0.4

ESBL-PE: extended-spectrum-beta-lactamase (ESBL)-producing Enterobacterales; I: intermediate; R: resistant; S: sensitive.

Table 3:
Comparison of patients colonised with aminoglycoside-resistant and aminoglycoside-susceptible ESBL-PE.

		Patients with aminoglycoside-resistant ESBL-PE (n = 240)	Patients with aminoglycoside-susceptible ESBL-PE (n = 304)	Univariable analysis	
		n (%) or median (IQR)	n (%) or median (IQR)	p-value	OR (95% CI)
Age (years)*		60 (56–77)	71 (57–81.5)	0.075	0.99 (0.98–1.00)
Male sex		112 (46.7)	156 (51.3)	0.282	1.20 (0.85–1.69)
Admission from another acute healthcare facility		47 (19.6)	48 (15.8)	0.248	1.30 (0.83–2.02)
Admission from a long-term care facility		25 (10.4)	36 (11.8)	0.601	0.86 (0.50–1.49)
History of hospitalisation**		163 (67.9)	206 (67.8)	0.970	1.01 (0.7–1.44)
Travel history**		48 (20.0)	40 (13.2)	**0.032**	**1.65 (1.04–2.61)**
Hospitalisation abroad**		20 (8.3)	25 (8.2)	0.112	1.75 (0.88–3.45)
Charlson Comorbidity Index		2 (0–3)	2 (0–3)	0.971	1.00 (0.92–1.08)
Active open wounds***		29 (12.1)	31 (10.2)	0.486	1.21 (0.71–2.07)
Surgery		68 (28.3)	86 (28.3)	0.991	1.00 (0.69–1.46)
Indwelling vascular hardware****		12 (5.0)	10 (3.3)	0.318	1.55 (0.66–3.65)
Dialysis		6 (2.5)	4 (1.3)	0.315	1.92 (0.54–6.89)
Urinary catheterisation[#]		75 (31.3)	85 (28.0)	0.403	1.17 (0.81–1.70)
Solid organ transplantation		10 (4.2)	16 (5.3)	0.553	0.78 (0.35–1.76)
Allogenic stem cell transplantation		6 (2.5)	10 (3.3)	0.590	0.75 (0.27–2.10)
Antibiotic therapy[##]		118 (49.2)	140 (46.1)	0.470	1.13 (0.81–1.59)
	Duration (days)	14 (6–39)	13 (6.5–29)	0.370	1.00 (0.99–1.01)
	Aminoglycosides	10 (4.2)	8 (2.6)	0.324	1.61 (0.62–4.14)
	Aminoglycosides duration (days)	1.5 (1–14)	3.5 (2.5–9)	0.607	1.04 (0.90–1.19)
Immunosuppressive therapy**		64 (26.7)	80 (26.3)	0.927	1.02 (0.69–1.49)
Proton pump inhibitor**		129 (53.8)	166 (54.6)	0.842	0.97 (0.69–1.36)
Micriobiological data					
ESBL-PE species[###, ####]	*Escherichia coli*	195 (81.3)	280 (92.1)	**<0.001**	**0.37 (0.22–0.63)**
	Klebsiella pneumoniae	60 (25.0)	33 (10.9)	**<0.001**	**2.74 (1.71–4.36)**
	Other	6 (2.5)	6 (2.0)	0.679	1.27 (0.41–4.00)
Outcomes					
Death		15 (6.3)	17 (5.6)	0.746	0.89 (0.43–1.81)
Death attributable to ESBL-PE infection		9 (60.0)	11 (64.7)	0.784	0.82 (0.20–3.43)
Intensive care unit stay		68 (28.3)	73 (24.0)	0.254	1.25 (0.85–1.83)
Length of hospital stay (days)		13 (8–25)	13 (7–22)	0.232	1.00 (0.99–1.01)

ESBL-PE: extended-spectrum-beta-lactamase (ESBL)-producing Enterobacterales; IQR: interquartile range; OR: odds ratio; 95% CI: 95% confidence interval.

* Increment for crude OR = per one year increase

** Within 12 months prior to the index hospitalisation

*** Decubitus and ulcers

**** In place for at least seven days prior to the index sample

[#] Transurethral or suprapubic catheterisation within 30 days prior to the index sample

[##] Within three months prior to ESBL-PE detection

[###] 36 patients (21 with aminoglycoside resistant ESBL-PE, 15 with aminoglycoside susceptible ESBL-PE) were colonised with multiple ESBL-PE species, explaining the total of >100% in both groups

[####] Comparison of *Escherichia coli* vs all others, *Klebsiella pneumoniae* vs all others, others vs *Escherichia coli* and *Klebsiella pneumoniae*

riage identified in clinical cultures, we found that 44% of isolates were aminoglycoside resistant. Colonisation or infection with *Klebsiella pneumoniae* was associated with 2.7 times greater odds of aminoglycoside resistance than colonisation or infection with *Escherichia coli*. Moreover, while not statistically significant, a travel history outside of Switzerland trended towards being associated with aminoglycoside-resistant ESBL-PE infections.

Our findings highlight the importance of considering local antibiotic resistance patterns when adopting international treatment guidelines. The European Conference on Infections in Leukemia (ECIL) and Infectious Diseases Society of America (IDSA) guidelines recommend adding aminoglycosides to empiric therapy for neutropenic fever in severely ill patients, patients with a known history of colonisation with multidrug-resistant Enterobacterales, or patients at increased risk of multidrug-resistant bacteria infection [1, 2]. A 2021 propensity-matched cohort study found that combination therapy with beta-lactam/aminoglycoside was associated with improved survival in patients with hematologic malignancies and Gram-negative blood infections [7]. However, with up to 44% aminoglycoside resistance among those infected with ESBL-PE in our setting, empiric therapy including an aminoglycoside might risk inadequate empirical antibacterial treatment, leading to poor clinical outcomes, while also unnecessarily exposing patients to toxicities such as acute kidney injury. This issue is particularly important because beta-lactam agents commonly used in combination with aminoglycosides, such as piperacillin-tazobactam or cefepime, are generally considered inadequate for treating invasive ESBL-PE infections, potentially leaving vulnerable patients with several days of inadequate coverage against ESBL-PE.

Colonisation with ESBL-*K. pneumoniae* was independently associated with aminoglycoside resistance in our cohort compared to colonisation with ESBL-*E. coli*. While high levels of aminoglycoside resistance in ESBL-*K. pneumoniae* isolates have been previously reported in Taiwan [8], to our knowledge, its frequency has not been compared to that of ESBL-*E. coli*. However, our results are consistent with a previous report indicating greater resistance to aminoglycosides for *Klebsiella pneumoniae* compared to *Escherichia coli* among European isolates [9]. Travel history was the only host factor identified in our cohort that may increase the odds of aminoglycoside-resistant ESBL-PE infections. This finding appears to agree with a previous study reporting an 8%–40% increase in gentamicin resistance in *Escherichia coli* in returning travellers [10]. We did not find an association between prior aminoglycoside exposure and aminoglycoside resistance. Interestingly, aminoglycoside resistance has been described as infrequently identified after aminoglycoside therapy, unlike with other antibiotic agents, where previous exposure is generally a key resistance determinant [11].

This was a single-centre observational study, potentially introducing biases and limiting its generalisability. Its data collection was limited to the years 2016–2018; however, since the resistance rates of Gram-negative bacteria, analysed annually by our microbiology laboratory, remained consistent since 2016, we believe that incorporating more recent data would not significantly alter the outcomes of our study. Missing data might have led to underestimating associations for some parameters with aminoglycoside resistance in ESBL-PE carriers. Since collecting information on the included variables is standard practice, we consider the respective impact on our findings minor. Furthermore, this limitation is unlikely to have biased our results since it affects both patients with aminoglycoside-resistant and aminoglycoside-susceptible ESBL-PE colonisation. These limitations notwithstanding, our study indicates that aminoglycoside resistance is frequently detected in ESBL-PE, especially ESBL-*K. pneumoniae*. Estimating the risk of carrying ESBL-PE based on risk scores validated for local epidemiology might help guide clinicians' decision-making on empiric therapy regimens [12], along with infection severity.

Availability of data and materials

The dataset used and analysed during this study is available from the corresponding author upon reasonable request.

Author contributions: IV collected and analysed data, interpreted the results and wrote the manuscript. LAB, NK, EWW and PDT critically revised the manuscript. AE described the microbiological analyses and critically revised the manuscript. STS conceived and supervised the study, analysed data, interpreted the results and critically revised the manuscript.

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Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix: Definitions

History of hospitalisation: Hospitalisation lasting ≥2 days within the past 12 months prior to index hospitalisation.

Travel history: A stay outside of Switzerland within 12 months prior to the index hospitalisation.

Hospitalisation abroad: Hospitalisation outside of Switzerland within 12 months prior to the index hospitalisation.

Active open wounds: Decubitus or ulcers.

Surgery: Within three months prior to index hospitalisation.

Vascular hardware: Central venous catheters in place for at least seven days prior to index sample.

Urinary catheterisation: Suprapubic or transurethral catheterisation within 30 days prior to the index sample detecting ESBL-PE.

Antibiotic therapy: Any antibiotic medication within three months prior to the index sample detecting ESBL-PE.

Duration of antibiotic therapy: Cumulative duration (days) of any antibiotic therapy within the three months prior to the index sample detecting ESBL-PE.

Immunosuppressive therapy: Within 12 months prior to index sample (e.g. long-term steroids, cytostatics, biologicals/antibody therapies, mTOR-Inhibitors and calcineurin-inhibitors).

Proton pump inhibitor: Within 12 months prior to the index sample.

Infections: Acute infection within the relevant hospitalisation, defined according to the CDC guidelines.