Insights into multidrug-resistant *K. pneumoniae* urinary tract infections: From susceptibility to mortality

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Abstract. The incidence of urinary tract infections (UTIs) caused by *Klebsiella pneumoniae* has exhibited an increasing trend and has become a high burden for many public health systems, especially in hospital settings. Multidrug resistance associated with the production of extended-spectrum β-lactamases (ESBL) among *K. pneumoniae* isolates is endemic in Southeastern Europe. We retrospectively analyzed 75 cases admitted to 'St. Parascheva' Clinical Hospital of Infectious Diseases in Iasi, Romania, during the first 6 months of 2019 (January 1 to June 30), who had a confirmed diagnosis of *K. pneumoniae* UTI at discharge. From a total of 75 patients, 34 (45.3%) presented ESBL⁺ *K. pneumoniae*. The mean age was 66 years (70.1 for the ESBL⁺ patients vs. 62.6 for the ESBL⁻ patients, P=0.0365). There was a symmetrical sex distribution (37 men vs. 38 women). Of these, 22 men had ESBL⁺ *K. pneumoniae* UTIs, compared to only 15 with an ESBL⁻ strain, P=0.0087. Another risk factor for ESBL⁺ *K. pneumoniae* UTIs was the presence of hospitalization in the past 6 months; 20 (58.82%) patients with ESBL⁺ infections were previously hospitalized, compared to only 5 (12.19%) patients with ESBL⁻ strains, P<0.0001. The urinary catheter carriers presented an increased prevalence of ESBL⁺ infections (15/34 vs. 5/41, P=0.0012). Regarding mortality, ESBL⁺ infections caused 6 fatalities, compared to only 1 death in the ESBL⁻ group, P=0.0166. ESBL⁺ *K. pneumoniae* strains represent an important cause of healthcare-related UTIs, with a significantly higher mortality rate compared to ESBL⁻ strains. Early identification and adequate management of the risk factors incriminated in ESBL⁺ UTIs should be a priority for physicians in order to limit the dissemination of the ESBL-producing strains and thus to improve the outcome of these patients.

Introduction

Klebsiella pneumoniae (KP) is a relatively common component of the normal microbiota, having the capacity to colonize various tissues and anatomical structures (e.g., distal urethra, upper respiratory tract, or the gastrointestinal tract). It is considered an opportunistic pathogen, being incriminated in the etiology of severe infections in hospitalized patients, especially in those immunocompromised or who present severe comorbidities (1,2).

The multidrug-resistance of KP, in particular to carbapenems due to the production of carbapenemases, has increased dramatically over the past 10 years and has become an important worldwide burden for the public health systems (3,4). First recognized almost four decades ago, extended-spectrum β-lactamases (ESBL) are enzymes produced by multiple gram-negative bacteria, being significantly involved in the resistance of these bacteria to almost all β-lactam antibiotics, except for cephamycins and carbapenems (5,6).

The ESBL mechanism of action is based upon their capacity to hydrolyze the β-lactam ring of the third-generation cephalosporins and aztreonam, but are inhibited by clavulanic acid (7).

The ESBL producers can also develop co-resistance to other classes of antibiotics, such as fluoroquinolones, cotrimoxazole or aminoglycosides, which are frequently used in the treatment of urinary tract infections (UTIs), thus inducing a severe limitation to their therapeutic approach (8,9). This

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aspect is due to the coexistence, on large plasmids, of the genes that encode ESBL with similar genes for resistance to other antimicrobial agents, subsequently creating a multidrug-resistant phenotype that is more and more associated with ESBL-producing *Enterobacteriaceae* (10). As a result, the judicious choice of empirical antibiotic therapy for UTI treatment is of paramount importance as it must be approached in accordance to the risk factors for infections due to ESBL-producing *K. pneumoniae* (ESBL⁺ KP), such as recurrent UTIs, diabetes mellitus (DM), previous antibiotic usage, female sex or urinary catheterization (11).

The epidemiological magnitude determined by ESBL-producing KP (ESBL⁺ KP) isolates is based on their significantly increased morbidity and mortality rates, prolonged hospitalization, and important financial burden (12). Additionally, there is a major concern regarding the increasing prevalence of ESBL⁺ KP's; a multicenter study conducted over a period of 10 years revealed a worldwide prevalence of 16%, with higher rates among patients hospitalized in intensive care units (ICU) (13). A similar increasing trend over time was noted in the case of colonization with ESBL⁺ KP, with rates in ICU patients ranging from 2.6% in the US to almost 50% in India (14). However, is it likely that the real prevalence is higher than the reported numbers, due to the paucity of reported data and difficulties in laboratory assessment as many testing kits fail to detect all ESBL producers.

In this challenging context, healthcare providers aim to find the ideal, thin balance between an effective antibiotic treatment against ESBL⁺ KP and to avoid the selection of new multidrug-resistant strains, the current paradigm being focused on preventing their spread both in the community and in healthcare facilities.

Patients and methods

Study design and population. We conducted this retrospective study aiming to assess the incidence, risk factors and antibiotic susceptibility of *K. pneumoniae* urinary strains isolated from patients admitted to the 'St. Parascheva' Clinical Hospital of Infectious diseases in Iasi, Romania, a University Clinic with 300 beds, between January 1, 2019 and June 30, 2019.

We performed a comparative assessment between patients with ESBL⁺ KP infections and the ESBL-negative (ESBL⁻) ones, by dividing them into two distinct cohorts: group 1, patients with ESBL⁺ KP UTIs and group 2, patients with non-ESBL producing KP (ESBL⁻ KP) UTIs. The main objectives were to assess the individual epidemiological characteristics, risk factors for antibiotic resistance and overall patient mortality.

In the present study, we included all hospitalized patients presenting with UTIs, with the following additional inclusion criteria: i) suggestive clinical syndrome (dysuria, pollakiuria); ii) pyuria [≥10 white blood cell count (WBC)/mm³]; iii) isolation of *K. pneumoniae* in urine culture [≥10⁵ colony forming units (CFU)/ml)]. We excluded patients with *K. pneumoniae* colonization and those with a urinary CFU count <10⁵/ml.

Study and laboratory measurements. The following antimicrobial agents were tested by disk diffusion method: Ampicillin + sulbactam, cefixime, cefuroxime, cefotaxime, cefepime, ceftazidime, cefuroxime, cefoxitin, gentamicin,

amikacin, ciprofloxacin, imipenem, meropenem, ertapenem, and colistin. EUCAST clinical breakpoint table v8.0 (15) was used for the interpretation of the minimal inhibitory concentrations and zone diameters.

We analyzed several parameters from the patient medical hospital records. Demographic characteristics (including age, sex), a full medical history, previous conditions (hospitalizations in the past 6 months, history of antibiotic use within the previous 30 days), clinical aspects (underlying diseases, invasive procedures) were fully recorded. Important comorbidities (e.g., chronic renal failure, cardiovascular diseases, diabetes mellitus, malignancy, chronic liver diseases, neurological pathologies) were previously documented or diagnosed during the current hospitalization. Charlson comorbidity index was used for assessing the overall mortality risk, based on patients coexisting comorbidities. Recurrent UTI in adults is defined as 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dl, a HbA1c ≥6.5% or current consumption of antidiabetic medication. Obesity was established in all patients presenting a body mass index ≥30 kg/m².

Routine investigations as part of the admission approach (complete blood count, inflammatory markers), assessment of the antibiotic susceptibility, hospitalization length, therapeutic management (including inappropriate empirical antibiotics and targeted single therapy/association of antibiotics) and clinical outcome were registered as well.

Statistical analysis. Categorical variables are presented as numbers and percentages, with continuous variables being presented as means and standard deviations. We used the 95% confidence interval in parameter estimation. Independent t-tests were used to compare continuous variables, while Chi-squared tests were used to compare categorical variables. Mann-Whitney U test was used for abnormally distributed categorical variables. A P-value of <0.05 was considered statistically significant for all of the analyses. Statistical analysis was performed with SPSS v20 (IBM Corp.) and EpiInfo v7.2 softwares (developer: Centers for Disease Control and Prevention).

Results

A total of 75 patients met the inclusion criteria for the study. Group 1 was comprised of 34 patients (45.3%) who had an ESBL⁺ KP UTI, while group 2 was made up of 41 patients (54.7%) with an ESBL⁻ KP UTI. Out of the 34 ESBL⁺ KP cases, 6 (17.6%) were OXA48-producers.

Mean age of the total participants was 66±17.72 years (70.1±18.68 for group 1 vs. 62.6±7.21 for group 2; P=0.0365). The mean age of patients infected with OXA48⁺ strains was 69.3 years. We found a symmetrical sex distribution in the entire cohort (37 males and 38 females), but with a significant difference concerning the sex distribution in the two groups: (64.7% males in group 1 vs. 36.5% in group 2, P=0.087) (Table I). Out of the 6 OXA48-producing cases, 4 were males.

The baseline patient characteristics are summarized in Table II. In addition to the demographic aspects, we also found statistically significant differences between the two groups concerning the underlying conditions, such as the recurrent

Table I. Age distribution of the patients with *K. pneumoniae* UTI.

Age interval	ESBL$^+$ KP (n=34)	ESBL$^-$ KP (n=41)	P-value	OR (95% CI)
0-20 years	1 (2.9%)	5 (12.1%)	0.0855	0.218 (0.024-1.966)
21-50 years	3 (8.8%)	4 (9.7%)	0.4528	0.895 (1.186-4.307)
51-70 years	10 (29.4%)	17 (41.4%)	0.1464	0.588 (0.224-1.543)
≥71 years	20 (58.8%)	15 (36.5%)	**0.0303**	2.476 (0.974-6.294)
Mean age	70.1	62.6	**0.0365**	

All data are expressed as n (%). UTI, urinary tract infections; KB, *Klebsiella pneumoniae;* ESBL, extended-spectrum β-lactamase; ESBL$^+$ KP, ESBL-producing *K. pneumoniae;* ESBL$^-$ KP, non-ESBL producing KP. OR, odds ratio; CI, confidence interval. Significant P-values are presented in bold print.

Table II. Baseline characteristics of the patients with *K. pneumoniae* UTI.

Characteristics	ESBL$^+$ KP (n=34)	ESBL$^-$ KP (n=41)	P-value	OR (95% CI)
Demographics				
Age, median (IQR)	70.1	62.6	**0.0365**	
Male sex	22 (64.7%)	15 (36.5%)	**0.0080**	3.177 (1.231-8.200)
Previous conditions				
Hospitalizations in the past 6 months	20 (58.8%)	5 (12.1%)	**<0.0001**	10.285 (3.23-32.752)
Antibiotic treatment in the last 30 days	9 (26.4%)	4 (9.7%)	**0.0340**	3.330 (0.923-12006)
Underlying conditions				
Chronic kidney disease	8 (23.5%)	3 (7.31%)	**0.0296**	3.897 (0.944-16.085)
Recurrent UTIs	12 (35.2%)	7 (17.0%)	**0.0404**	2.694 (0.903-7.765)
Cardiovascular diseases	24 (70.5%)	20 (48.7%)	**0.0309**	2.520 (0.966-6.573)
Diabetes mellitus	10 (29.4%)	13 (31.7%)	0.4180	0.897 (0.334-2.411)
Chronic liver disease	6 (17.6%)	13 (31.7%)	0.0880	0.461 (0.153-1.386)
Malignancy	11 (32.3%)	5 (12.1%)	**0.0203**	3.443 (1.058-11.201)
Cerebrovascular disease	11 (32.3%)	9 (21.9%)	0.1630	1.700 (0.606-4.768)
Obesity	7 (20.5%)	9 (21.9%)	0.4470	0.921 (0.303-2.804)
Charlson comorbidity index, median (IQR)	5.7	3.5	**0.0005**	
Urinary catheterization	15 (44.1%)	5 (12.1%)	**0.0011**	5.684 (1.791-18.036)
Laboratory findings				
Hemoglobin <11.7 g/dl	16 (47.0%)	11 (26.8%)	**0.0385**	2.424 (0.923-6.361)
White blood cells >10,000/mm^3	19 (55.8%)	19 (46.3%)	0.2113	1.466 (0.588-3.657)
Erythrocyte sedimentation rate >12 mm/h	24 (32.0%)	36 (48.0%)	**0.0372**	0.333 (0.101-1.097)
Treatment				
Inappropriate empirical therapy	18 (52.9%)	19 (46.3%)	0.3334	1.226 (0.496-3.025)
Targeted therapy	17 (47.0%)	22 (53.6%)		

All data are expressed as n (%). UTI, urinary tract infections; KB, *Klebsiella pneumoniae;* ESBL, extended-spectrum β-lactamase; ESBL$^+$ KP, ESBL-producing *K. pneumoniae;* ESBL$^-$ KP, non-ESBL producing KP. IQR, interquartile range; OR, odds ratio; CI, confidence interval. Significant P-values are presented in bold print.

UTIs, chronic kidney disease, cardiovascular pathologies and malignancies, which were more commonly associated with ESBL$^+$ KP. This aspect was furtherly confirmed by an increased Charlson comorbidity index among patients with ESBL$^+$ KP UTI (5.7 vs. 3.5, P=0.0005). Moreover, both the presence of an indwelling urinary catheter (15 vs. 5, P=0.0011) and previous hospitalizations in the past six months (20 vs. 5, P<0.0001) or a history of antibiotic use within the last 30 days (9 vs. 4, P=0.034) were significant predictors for the presence of ESBL$^+$ KP (Table II).

Another important aspect of the study was to highlight the relationship between the incidence of ESBL$^+$ KP and the use of specific antibiotics. Noteworthy, we observed that patients without ESBL-producing strains were more commonly treated

Table III. Antibiotic treatment of the enrolled patients with *K. pneumoniae* UTI.

Variables	ESBL⁺ KP (n=34) (%)	ESBL⁻ KP (n=41) (%)	P-value	OR (95% CI)
Single antibiotic therapy	7 (20.5)	16 (39.0)	**0.0462**	0.405 (0.143-1.147)
2 antibiotic therapy	16 (47.0)	18 (43.9)	0.3949	1.135 (0.455-2.830)
≥3 antibiotic therapy	11 (32.3)	7 (17.0)	0.0683	2.323 (0.784-6.877)
Most commonly used antibiotics				
Ciprofloxacin	6 (17.6)	21 (51.2)	**0.0014**	0.204 (0.069-0.597)
Ampicillin + sulbactam	6 (17.6)	13 (31.7)	0.0882	0.461 (0.153-1.386)
3rd generation cephalosporins	6 (17.6)	21 (51.2)	**0.0014**	0.204 (0.069-0.597)
Carbapenems	18 (52.9)	6 (14.6)	**0.0002**	6.562 (2.190-19.657)
Amikacin	19 (55.8)	7 (17.0)	**0.0002**	6.152 (2.135-17.728)
Trimethoprim/sulfamethoxazole	5 (14.7)	8 (19.5)	0.302	0.711 (0.209-2.417)
Colistin	6 (17.6)	1 (2.4)	**0.0166**	8.571 (0.977-75.178)

UTI, urinary tract infections; KB, *Klebsiella pneumoniae;* ESBL, extended-spectrum β-lactamases; ESBL⁺ KP, ESBL-producing *K. pneumoniae;* ESBL⁻ KP, non-ESBL producing KP. OR, odds ratio; CI, confidence interval. Significant P-values are presented in bold print.

Table IV. Evolution of the patients with *K. pneumoniae* UTI.

Variables	ESBL⁺ KP (n=34)	ESBL⁻ KP (n=41)	P-value	OR (CI)
Length of hospital stay (IQR)	13.1 days	9.4 days	**0.0012**	
Mortality	6 (17.6%)	1 (2.4%)	**0.0166**	8.571 (0.977-75.178)

UTI, urinary tract infections; KB, *Klebsiella pneumoniae;* ESBL, extended-spectrum β-lactamases; ESBL⁺ KP, ESBL-producing *K. pneumoniae;* ESBL⁻ KP, non-ESBL producing KP; IQR, interquartile range; OR, odds ratio; CI, confidence interval. Significant P-values are presented in bold print.

with one single antibiotic (P=0.046), the use of regimens consisting of multiple antibiotic molecules (≥3 antibiotics) being observed in the lot infected with ESBL⁺ KP (32.3 vs. 17%, P=0.0683). Keeping in mind the resistance profile of ESBL⁺ KP, we identified a positive correlation between the administration of ciprofloxacin, amikacin, colistin or 3rd generation cephalosporins and the absence of ESBL producers. Contrary, the presence of ESBL⁺ KP was significantly associated with the large-scale use of carbapenems, indirectly reflecting both the susceptibility profile and the severity of infection (Table III).

In terms of evolution, the patients with ESBL⁺ KP presented a severe prognosis, characterized both by prolonged hospitalization (13.1 vs. 9.4 days, P=0.0012) and by a much higher mortality rate compared to those without ESBL-producing strains (17.6 vs. 2.4%, P=0.0166; Table IV).

The differences between ESBL and non-ESBL susceptibility profiles are illustrated in Fig. 1, revealing the quasi-total resistance of ESBL⁺ KP to cephalosporins, but also to certain other classes of antibiotics, such as fluoroquinolones (ciprofloxacin) or aminoglycosides (gentamicin).

Furthermore, our study aimed to identify the risk factors for a poor outcome among the included patients. In this regard, we performed a comparative analysis between the surviving patients and the ones who were deceased. When assessing certain data from the personal history, we observed

that elderly patients >70 years present a high risk for a fatal outcome (P=0.019), a similar negative evolution being also associated with previous antibiotic therapy (P=0.008) or other hospitalizations in the past six months (P=0.021). Very importantly, even if the share of severe comorbidities (except for diabetes mellitus) was higher among the deceased patients, the differences did not reach the threshold of statistical significance.

Evaluating the classic risk factors for UTIs, we found a significant association between the mortality rate and the presence of an indwelling urinary catheter (P=0.044) or a prolonged hospitalization (P=0.033). Moreover, a severe course of the infection, translated as the initiation of an aggressive antibiotic treatment (e.g., carbapenems) was significantly correlated with an increased fatality rate (P=0.018). Finally, when analyzing the ESBL production among deceased patients, we noted that 6 out of 7 fatalities presented an ESBL⁺ KP infection (P=0.016), suggesting the important negative prognostic value of these strains in the outcome of patients with UTI (Table V).

Discussion

The current situation of antimicrobial resistance has reached a crucial point since 2005. In UTIs, multidrug-resistant *Enterobacteriaceae*, including ESBL-producing microorganisms, can be readily encountered, emerging as a growing

Table V. Risk factors for in-hospital mortality of the patients with *K. pneumoniae* UTI.

Factors	Deceased N=7	Surviving N=68	P-value	OR (95% CI)
Demographics				
Age >70 years	6 (85.7%)	29 (42.6%)	**0.019**	8.069 (0.95-75.734)
Age, median (IQR)	75.8	65	0.142	
Male sex	3 (42.8%)	34 (50.0%)	0.370	0.750 (0.155-3.607)
Previous conditions				
Hospitalizations in the past 6 months	5 (71.4%)	20 (29.4%)	**0.021**	6.000 (1.073-33.534)
Previous antibiotic therapy	4 (57.1%)	9 (13.2%)	**0.008**	8.740 (1.673-45.656)
Comorbidities				
Chronic kidney disease	2 (28.5%)	9 (13.2%)	0.165	2.622 (0.44-15.604)
Cardiovascular pathology	5 (71.4%)	39 (57.3%)	0.256	1.859 (0.336-10.266)
Diabetes mellitus	2 (28.5%)	22 (32.3%)	0.838	0.836 (0.15-4.655)
Chronic liver disease	2 (28.5%)	17 (25.0%)	0.836	1.200 (0.212-6.763)
Malignancy	2 (28.5%)	15 (22.0%)	0.695	1.413 (0.248-8.029
Cerebrovascular disease	2 (28.5%)	18 (26.4%)	0.904	1.111 (0.197-6.242)
Obesity	2 (28.5%)	14 (20.5%)	0.623	1.542 (0.27-8.808)
Charlson comorbidity index, median (IQR)	6	4.3	0.153	
Urinary catheterization	4 (57.1%)	16 (23.5%)	**0.044**	4.333 (0.876-21.429)
Length of hospital stay (IQR)	15.2	10.6	**0.033**	
Carbapenem treatment after laboratory diagnosis	5 (71.4%)	19 (27.9%)	**0.018**	6.447 (1.15-36.124)
ESBL production				
ESBL⁺	6 (17.6%)	28 (82.3%)	**0.0166**	8.571 (0.977-75.178)
ESBL⁻	1 (2.4%)	40 (97.5%)		

UTI, urinary tract infections; KB, *Klebsiella pneumoniae*; ESBL, extended-spectrum β-lactamases; ESBL⁺ KP, ESBL-producing *K. pneumoniae*; ESBL⁻ KP, non-ESBL producing KP; IQR, interquartile range; OR, odds ratio; CI, confidence interval. Significant P-values are presented in bold print.
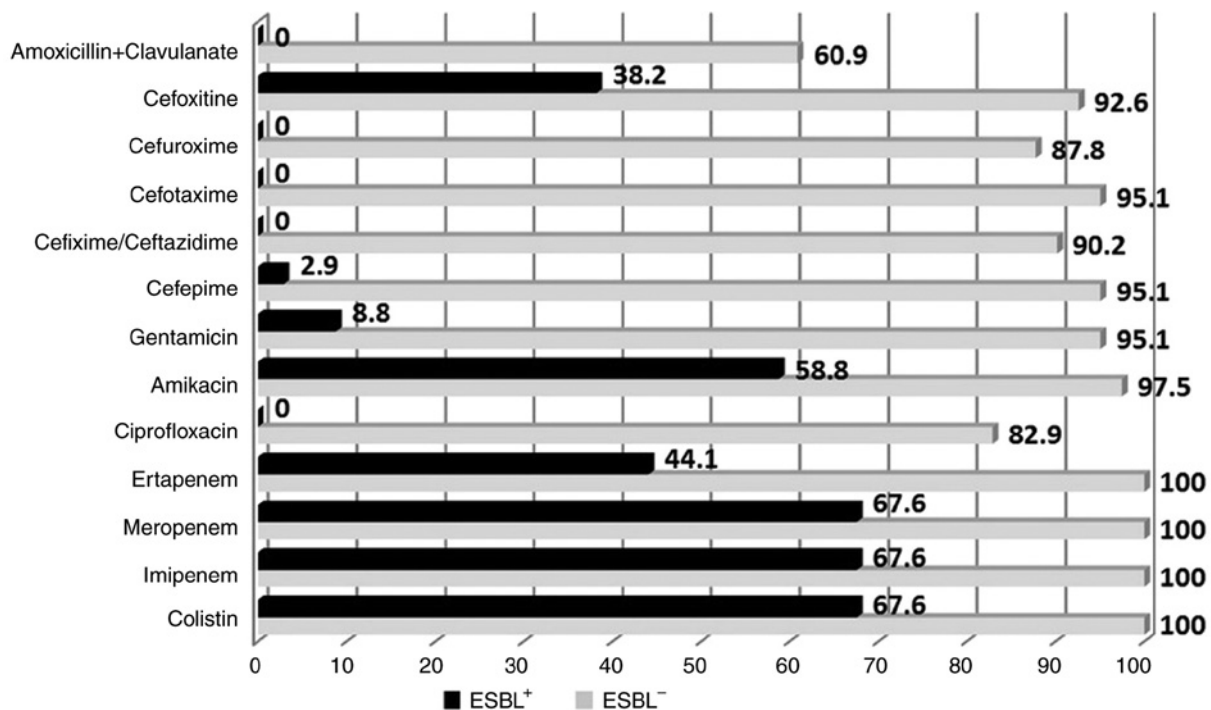

Figure 1. ESBL⁺ and ESBL⁻ KP susceptibility profiles (%) to various classes of antibiotics. KB, *Klebsiella pneumoniae*; ESBL, extended-spectrum β-lactamase; ESBL⁺ KP, ESBL-producing *K. pneumoniae*; ESBL⁻ KP, non-ESBL producing KP.

challenge in many infectious disease clinical setups (16). In addition to the fact that patients with ESBL-producing bacteria are generally prone to a more severe course of infection compared to those without ESBL isolates, another serious issue is represented by the paucity of antibiotics that can be used for the treatment of multidrug-resistant *K. pneumoniae* (KP) UTIs. The persistent and often inappropriate exposure of KP strains to various β-lactam antibiotics has created the background for dynamic mutations and enhanced synthesis of β-lactamases in these bacteria, thus inducing multidrug resistance even against the extremely useful, broad-spectrum, 3rd generation cephalosporins (17,18).

Previous studies have reported a variable, geographic-related incidence of ESBL[+] KP. This regional variability is explained by several factors, ranging from the specific, local pattern of resistance to some socio-economic aspects, such as healthcare access or household income, with higher rates being prevalent in developing, low-income countries from Asia or Eastern Europe (19-21). Given the scarce data in the literature concerning ESBL-producing strains in the North East region of Romania (22), our study aimed to unravel the local resistance profile in an area with certain socio-epidemiological particularities (23,24).

We found a very high prevalence of ESBL-producing isolates (45.3%) among all *K. pneumoniae* strains detected in urinary specimens from a university hospital serving a region with ~4 million inhabitants.

Urinary catheterization is a well-known risk factor for UTIs, this aspect being confirmed by multiple previous studies, starting from Platt *et al* study in 1986, when about 20% of UTIs were associated with Foley catheterization, due to contamination at the insertion of the catheter (25). Additionally, Lee *et al* (26) found that ESBL-producing bacteria were approximately 2.4 times more frequent in patients with Foley catheterization. In line with these findings, our study revealed that 20 patients (26.6%) had an indwelling urinary catheter, which was significantly associated with the presence of ESBL[+] KP (15 ESBL[+] KP vs. 5 ESBL[-] KP, P=0.0011).

A past history of exposure to antibiotics and hospitalizations in the last 6 months may represent another risk factor for the emergence of ESBL-producing strains. In the literature, particularly the use of cefaclor and cefminox was incriminated for the emergence of resistant strains (26). In our study, we identified a previous antibiotic exposure in 26.4% of the patients with ESBL[+] KP, compared to only 9.7% with an ESBL[-] KP (P=0.0340). Regarding recent contact with healthcare facilities, we also found a noteworthy difference among the two groups, 20 (58.8%) for the ESBL producers vs. 5 (12.1%) for the non-ESBL producers (P<0.0001) presenting a documented hospitalization in the last six months. Similarly, Yilmaz *et al* (27) found that 90% of the patients with an ESBL producer had a history of previous hospitalization in the past three months vs. only 16.7% for the ESBL-negative ones.

Basically, when reviewing the literature (28-30), we noted a plethora of risk factors for infection with ESBL-producing bacteria that were also identified in our research, such as recent antibiotic use, residence in long-term care facilities, recent hospitalization, old age and male sex. In our study, elderly patients (>70 years), male sex, hospitalization in the past 6 months, previous antibiotic treatment, chronic renal failure, recurrent UTIs, urinary catheterization, longer hospital stay, underlying cardiovascular pathologies, malignancies, and anemia were considerably more prevalent among the patients with ESBL[+] KP UTIs. The latter aspects may be explained by the mutual and dynamic relationship between serious comorbidities and the occurrence and severity of KP infections. Frail patients with impaired immunity due to a severe associated pathology are more prone to develop a KP infection, and vice versa, the KP infection may negatively influence the outcome of such a patient. For example, a recent study highlighted the significant incidence and poor prognosis of carbapenemase-producing KP infections among patients with hematological malignancies or aplastic anemia (31).

Antimicrobial susceptibility was investigated for all isolates. Our results demonstrate that, among the ESBL[+] KP patients, susceptibility rates to ciprofloxacin, gentamicin, amikacin, imipenem, meropenem and colistin were extremely low: 0, 8.9, 58.9, 67.7, 67.7 and 67.7%, respectively. On the other hand, the ESBL[-] KP strains showed lower susceptibility to amoxicillin + clavulanic acid (61%), ciprofloxacin (83%) and cefuroxime (87.8%), while high susceptibility was identified for carbapenems (100%), amikacin (97.6%), gentamicin (95.1%), cefepime (95.1%), ceftazidime (90.3%), cefotaxime (95.1%), cefixime (90.3%) and cefoxitin (92.7%), these findings being in accordance with other results that have identified a similar resistance pattern, thus raising awareness both on the adequate therapeutic approach and nosocomial or community spread of ESBL[+] KP (32). It is noteworthy to point out that the antibiotic combination between a β-lactam and an aminoglycoside is synergistic and is widely used as a first-line therapy prior to antibiogram results, especially in patients with established risk factors for multidrug-resistant infections. Given the local susceptibility profile, in addition to a β-lactam, in our setting we prefer the use of amikacin instead of gentamicin given the higher resistance rate associated with the latter.

However, despite the similarities, there are also some susceptibility-related differences, mainly due to particular local factors. Even if some of the results from a Pakistani study (33) were similar to ours concerning the susceptibility profile of ciprofloxacin, amikacin, imipenem and meropenem they also found a significantly lower susceptibility to gentamicin for the ESBL[-] KP (63.1 vs. 95.1% in our study). A more recent multicentric study from the same country furtherly confirmed this regional pattern of resistance, thus bringing attention to the geographical polymorphism of ESBL[+] KP (34). Coinciding results were found in another study performed by Müller-Schulte *et al* (35) regarding the differences between the susceptibility profiles depending on the ESBL production in a sub-Saharan country; for the ESBL[+] KP the susceptibility to ciprofloxacin, gentamicin, meropenem, cefuroxime, ceftazidime and cefotaxime was 38, 21, 100, 0, 0 and 0%, respectively, while for the ESBL[-] KP the susceptibility was 88, 94, 100, 100, 100 and 100%, respectively.

Numerous studies have examined whether ESBL production has an adverse effect on clinical outcomes. Although most of the reported data revealed an association between unfavorable outcome and infections with ESBL[+] KP (36-40), other studies have failed to demonstrate such a link (41). In

our patients we identified a significant association between the presence of ESBL$^+$ KP and the morality rate (P=0.016). Noteworthy, of the six patients with OXA48-producing *K. pneumoniae* UTI, we recorded two deaths.

Furthermore, we found that the risk factors for all-cause mortality were similar to those for ESBL$^+$ KP infection and included: Age >70 years (P=0.019), hospitalizations in the past 6 months (P=0.024), previous antibiotic treatment (P=0.003), urinary catheterization (P=0.044), length of hospital stay (P=0.033), carbapenem treatment based on antibiogram result (P=0.018) and ESBL production (P=0.0166).

In terms of therapeutic approach, we could not quantify accurately the superiority of any particular antibiotic regimen in the prognosis of *K. pneumoniae* UTI mainly due to the heterogenicity of the regimens (often consisting of at least 3 different antibiotics), but also due to some patient-related specific aspects which led to the use of only certain antibiotics. As a general algorithm, before initiating antibiotic treatment in ESBL$^+$ patients, of paramount importance, is to assess the *in vitro* susceptibilities, the degree of the infection's source control and, finally, the clinical condition of each patient (7).

Carbapenems exhibit the broadest spectrum of β-lactam antibiotics, presenting the highest potency against Gram-negative bacteria, but being also characterized by stability to hydrolysis by the majority of β-lactamases. The majority of available data have demonstrated that carbapenem treatment is associated with improved outcomes in patients with severe ESBL$^+$ KP infections and remains the 'gold standard' especially in critically ill patients (7,42,43). The research spectrum of ESBL$^+$ KP has focused mainly on meropenem or imipenem, although a recently published multicentric study also assessed the efficacy of ertapenem (44), finding similar cure rates (90.6% with ertapenem and 75.5% with other carbapenems in empiric and 89.8 and 82.6% in targeted treatment), without significant differences concerning mortality rates. Importantly, in our study we observed a rather low ESBL$^+$ KP susceptibility rate to ertapenem (44.1%), compared to imipenem or meropenem (67.6% each), thus outlining bleak future prospects when compared to a 100% susceptibility rate to both ertapenem and imipenem reported less than two decades ago (45,46).

Our study has limitations related to the relatively small size of the research group and the retrospective nature. Given the continuously increasing trend of ESBL$^+$ KP prevalence, this means that our results could underestimate the actual burden of these strains, therefore requiring careful interpretation of the data. Despite these limitations, our study provides several insights on the association between the ESBL$^+$ KP and the outcome of the UTI patients with this etiology, as well as the implications regarding susceptibility profiles and local risk factors from the Northeast region of Romania. In conclusion, our data may have a significant impact for further antibiotic prescription in patients with community- and/or hospital-acquired UTIs, mainly focusing on the early identification or even prevention of certain risk factors associated with ESBL-producing KP.

Availability of data and materials

Data used in this original study were obtained from the patient personal medical records admitted to the 'St. Parascheva' Clinical Hospital of Infectious Diseases in Iasi, Romania. Any further information regarding the present study is available from the corresponding authors upon reasonable request.

Authors' contributions

All authors presented an equal contribution to this paper. ILM, OSD and EGM designed the study and collected data from the included patients. OSD, CL and LSI performed the susceptibility tests and other laboratory determinations. DTAP, EVN, IIC and CSS analyzed data and performed the statistics. ILM, OSD and RSM analyzed and wrote the Results and Discussion sections including the literature review. RSM and EVN prepared the manuscript, translated it and managed all the correspondence for publishing. All authors were actively involved in conceiving the paper and they read and approved the final version of the manuscript for publication.

Ethics approval and patient consent

This study was approved by the local Ethics Commission of 'St. Parascheva' Clinical Hospital of Infectious Diseases in Iasi, Romania (approval no. 8/2019) and it was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki Principles. Patient consent was not required due to the retrospective character of the study.

Patient consent for publication

Not applicable.

Competing interests

There are no competing interests regarding the authors of this research.

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