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Impact of infection control measures and antibiotic stewardship programs on multidrug-resistant *Klebsiella pneumoniae* prevalence in Intensive Care Unit

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ABSTRACT:

– ***Objective:*** Studies show that 30% to 60% of antibiotics prescribed in Intensive Care Units (ICUs) are unnecessary and inappropriate. Tailored antibiotic stewardship, infection control, and prevention measures should be implemented based on their own local epidemiology and healthcare possibilities.
– ***Materials and Methods:*** We conducted an observational retrospective study in the General and Neurosurgery ICUs in Ospedale "dell'Angelo", Venice. We collected microbiological data about *Klebsiella pneumoniae* from our local microbiology analysis laboratory and antibiotic consumption from the local pharmacy ward from January 2021 to December 2023.
– ***Results:*** 377 *K. pneumoniae* strains were isolated: 225 (59.7%) in 2021, 108 (28.6%) in 2022 and 44 (11.7%) in 2023. Extended-spectrum β-lactamases (ESBL) isolates were 201/225 (89.8%) in 2021, 98/108 (90.7%) in 2022 and 24/44 (54.5%) in 2023. Meropenem (MEM)-resistant *K. pneumonae* were 121/225 (54.0%) in 2021, 69/108 (64.0%) in 2022, and 3/44 (9.0%) in 2023. In 2021, 94 patients tested positive for carbapenem-resistant *K. pneumoniae* (CRKp), 32/94 (34.0%) at admission, and 62/94 (66.0%) during the hospitalization. In 2022 and 2023, 68 patients were colonized by CRKp: 26/68 (38.2%) at admission and 42/68 (61.8%) during the recovery. Carbapenems consumption decreased from 1,536.5 defined daily dose (DDD) in 2021 to 744.9 DDD in 2023. From 2021 to 2023, Fluoroquinolones (F.Q.) decreased from 345.0 DDD to 145.0 DDD.
– ***Conclusions:*** Our study shows that tailored and implemented infection control and antibiotic stewardship measures could profoundly impact CRKp transmission in the ICU.

– ***Keywords:*** *Klebsiella pneumoniae*, Antibiotic Stewardship, Intensive Care Unit, Carbapenem-sparing strategies.

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INTRODUCTION

Increasing antimicrobial resistance (AMR) rates and limited antibiotic options, particularly for Gram-negative pathogens, have led to a worldwide medical crisis[1]. Antibiotics are commonly prescribed in intensive care units (ICUs). More than 70% of patients in this setting receive antibiotics during hospitalization. The antimicrobial consumption in ICUs is ten times higher than in other hospital wards[2,3].

Excessive antibiotic use in ICUs contributes to the emergence of AMR, especially in Gram-negative microorganisms. The higher incidence of infections caused by multi-drug resistant microorganisms (MDRO) in ICUs depends on numerous factors associated with infectious risk and critically ill patients, such as the use of medical devices, aging, the presence of immunosuppression, the prolonged period of hospitalization and the consumption of broad-spectrum antibiotic therapies[4]. Carbapenems are often used as last-resort antimicrobials for treating seriously ill patients with Gram-negative infections. *Pseudomonas aeruginosa*, *Acinetobacter* species (spp.), and carbapenem-resistant *Enterobacterales* (CRE) isolates are frequently isolated in the ICUs and constitute an essential clinical problem, with the necessity of prompt new antibiotic therapeutical strategies[5,6].

A multidisciplinary approach could minimize the risk of developing AMR[7]. Appropriate antimicrobial stewardship needs rapid microbiological identification and treatment based on pharmacokinetic/pharmacodynamic properties, using narrow-spectrum drugs for the shortest possible time, and reducing patients treated with unnecessary antibiotics[8]. Microbiologic surveillance, local epidemiologic-based antibiotic practice guidelines, and a multidisciplinary approach with a specialized antibiotic team (ICU specialist, infectious diseases consultant, microbiologist, and clinical pharmacologist) could improve an early diagnosis and initial appropriate antibiotic treatment of infections in critical settings[9]. Prompt infection-related consultations in ICUs could positively impact the quality of care and clinical outcomes[10].

Infection prevention and control measures are an evidence-based and cost-effective approach that can optimize antimicrobial usage and reduce the incidence of MDRO[11]. The primary endpoint of infection control programs is to decrease the incidence of hospital-acquired infections to zero. Standard and transmission-based precautions can prevent any infectious agent from transmitting to susceptible hosts and should be tailored to the level of care provided in the different healthcare settings[12,13].

MATERIALS AND METHODS

We conducted an observational retrospective surveillance in the General and Neurosurgery ICUs in Ospedale "dell'Angelo" in Venice. We collected indiscriminately all microbiological data about *Klebsiella pneumoniae* from our local microbiology analysis laboratory and antibiotic consumption from the local pharmacy ward from January 2021 to December 2023.

The study aimed to describe the evolution of local *K. penumoniae* ecological and pharmacological data in the ICU ward. Moreover, we tried to find if implementing ordinary and routine clinical antibiotic stewardship practices could impact the transmission of AMR in *K. pneumoniae*.

Microbiology Data

Different samples (blood culture, urine, cerebrospinal fluid, pleural liquid, peritoneal liquid, bronco-lavage, skin, and rectal swab) were collected as part of the hospital's standard diagnostic procedures without any additional intervention on patients specifically for this study. Blood-colture were incubated in BD Bactec (bioMerieux, Florence, Italy). The blood was processed according to this protocol for direct identification *via* Matrix-assisted laser desorption/ionization (MALDI)-TOF/MS (Bruker, Bremen, Germany). Antibiotic susceptibility tests (AST) were performed using broth microdilution Microscan (Beckman Coulter, Brea, CA, USA). The clinical breakpoint and susceptibility interpretations were based on EUCAST Jan 1, 2024 criteria[14]. Real-time PCR Xpert® Carba-R (Cepheid, Sunnyvale, CA, USA) identified Carbapenem resistance.

Extended-spectrum β-lactamases (ESBL) were defined as resistant to the third generation of cefalosporin (3CEF), including Ceftriaxone (CTX) and Ceftazidime (CAZ).

Excluding criteria were if the antibiotic phenotype was incomplete or beta-lactams minimal inhibitory concentration (MIC) was missing. In the case of repetition of *K. pneumonae* isolates in the same patient within 30 days, the sample was dropped out of the study.

Carbapenem-resistant *K. pneumoniae* (CRKp) colonized patients were considered in case of the presence of CRKp in one of the following samples: blood culture, urine, cerebrospinal fluid, pleural liquid, peritoneal liquid, bronco-lavage, skin and rectal swab.

Pharmacological Data

Antibiotic consumption was measured according to the defined daily dose (DDD). The antibiotics evaluated were Amikacin (AMK), Cefepime (FEP), Cefiderol (FDC), CTX, CAZ, Piperacillin/Tazobactam (TZP), Fosfomycin (FOS), Colisitn (COL), Fluoroquinolones (F.Q.) (such as Levofloxacin and Ciprofloxacin), Carbapenems (such as Meropenem (MEM), Imipenem cilastatin and Ertapenem), Cefiderocol (FDC) and new β-lactam/β-lactam inhibitors (BL/BLI), such as Ceftazidime/Avibactam (CZA), Imipenem cilastatin/Relebactam (IPR) and Meropenem/Vaborbactam (VBM), Ceftolozane/Tazobactam (C/T).

Infectious Control Measures and New Antibiotic Stewardship Program

From January 2021 to December 2021, no specific intervention was implemented. Routine infectious control protocol was applied, such as active surveillance cultures with baseline rectal swabs and weekly control of rectal colonization in non-colonized patients, contact precautions for all the hospitalized patients in the ICU, isolation in a single room, and disinfection and sterilization.

At the beginning of January 2022, our Hospital decided to implement infectious control measures and applied for a new antibiotic stewardship program. The new internal policy included:

1. Continuing the infection control baseline measures.
2. Antibiotic stewardship programs:
   a. Active infectious disease (ID) consultant implementation.
   b. Target bundles interventions for intravascular catheter-related infection and catheter-associated urinary tract infection (i.e., changing the intravascular catheter and the urinary catheter every 14 days and changing it anyway in case of admission from another ICU. Reduce the positioning of the femoral catheters, preferring the jugular or subclavian access. In the case of discharge, the vascular catheter had been changed the day before).
   c. Local epidemiological-based antibiotic guidelines and cumulative antibiograms based on local isolates (the ID team developed cumulative antibiograms on Gram-negative and Gram-positive microorganisms MICs data yearly. Local sepsis guidelines were introduced in 2022 and reevaluated every year. The guidelines considered international antibiotic treatment recommendations and were contextualized and based on local microorganism frequency and their phenotypes).
   d. Active surveillance and prompt communications of CRE carriers and positive blood cultures (initially with direct call communication and at the end of 2023 with an active computerized signal).
3. Infection control measures:
   a. Simplification of MDRO signs of colonized patients.
   b. Implementation of disinfection and sterilization protocol (including for device).
   c. Educational program for ICU staff.
4. Monitoring data:
   a. The microbiology communicated the AMR trends to the ICU ward every six months.
   b. The pharmacy showed data about drug consumption, carbapenem, and F.Q. using trends every year.

Ethical Issues

Ethical approval was not needed for this study, which does not involve patients and is based on microbiological and pharmacological surveillance data. All data were anonymized.

Statistical Analysis

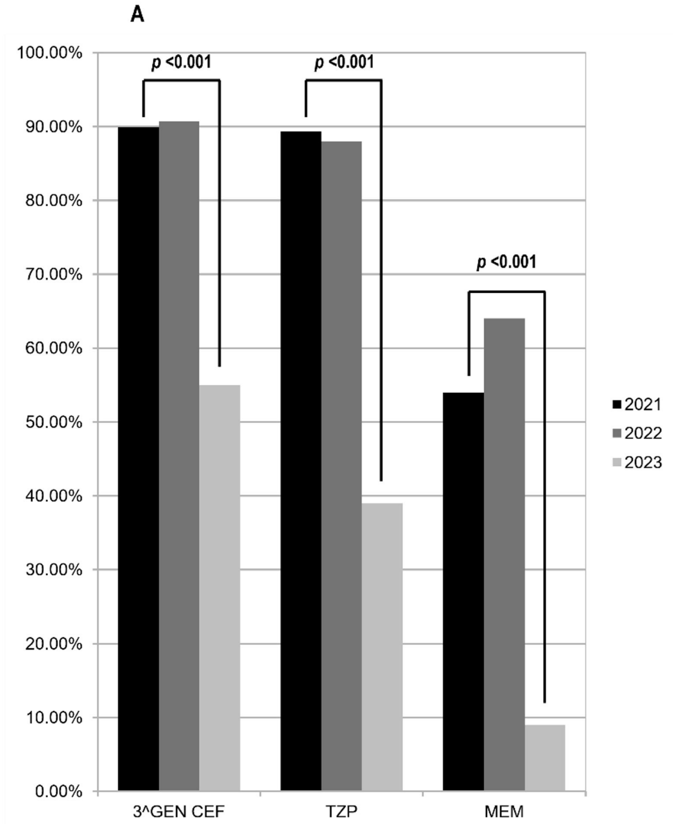
Data were collected with Excel (Microsoft, Redmond, WA, USA). Discrete variables were summarised as frequency (%). The percentage of resistance (%R) was defined as the proportion of resistant strain on all isolates. Categorical variables were compared using the χ^2 test or Fisher's *t*-test, as appropriate. A *p*-value ≤ 0.05 was considered statistically significant. Statistical analysis was conducted with STATA version 16 (StatsCorp, Lakeway, TX, USA).

RESULTS

During the observational period, we sampled 6,140 isolates from 2021 to 2023. After excluding non-*K. pneumoniae* and repetitive isolates within a 30-days period, we collected 377 *K. pneumoniae* isolates: 225 (59.7%) in 2021, 108 (28.6%) in 2022 and 44 (11.7%) in 2023. The percentage of ESBL isolates were 201/225 (89.8%) in 2021, 98/108 (90.7%) in 2022 and 24/44 (54.5%) in 2023. The resistance to TZP was 200/224 (89.3%) in 2021, 95/108 (89.0%) in 2022 and 17/44 (38.6%). MEM-resistant isolates were 121/225 (54.0%) in 2021, 69/108 (64.0%) in 2022, and 3/44 (9.0%) in 2023. The phenotypic profile resistance of 3CEF, TZP and MEM was reported in Figure 1.

From January 2021 to December 2021, 94 patients tested positive for CRKp, and 32/94 (34.0%) individuals tested positive at admission to the ICU. Instead, 62/94 (66.0%) became positive during the hospitalization. In 2022 and 2023, 68 patients were colonized by CRKp stains; 26/68 (38.2%) were positive at admission and 42/68 (61.8%) during recovery. Figure 2 summarizes the distribution of carbapenem-resistant *K. pneumoniae* colonization cases.

At the antibiotic consumption data, Carbapenems showed a reduction from 1,536.5 DDD in 2021 to 744.9 DDD in 2023. TZP DDD rose from 751.5 DDD in 2021 to 1,325.6 DDD in 2023. C/T prescription increased from 180.0 DDD in 2022 to 363.3 DDD in 2023 (in 2021, C/T was unavailable). New BL/BLI treatments fell from 652.6 DDD in 2021 to 258.1 DDD in 2023. F.Q. prescription was marginal, but from 2021 to 2023, we observed a significant reduction in their prescription (from 345.0 DDD to 145.0 DDD). Instead, FOS showed an increased usage, according to its essential role in carbapenem-sparing strategies (165.0 DDD from 2021 to 665.0 DDD in 2023). Figure 3 shows all principal Gram-negative antibiotic consumption per year.



B

MEM	Kp2021	Kp2022	Kp2023
<=0.125	18.5%	13.0%	70.5%
0.25	0.4%	0.0%	0.0%
0.5	0.4%	0.0%	0.0%
1	0.9%	0.0%	2.3%
2	0.9%	5.6%	2.3%
4	3.1%	4.6%	6.8%
8	21.1%	13.0%	9.1%
16	29.1%	13.0%	4.5%
32	3.1%	3.7%	2.3%
64	6.2%	34.3%	2.3%
128	16.3%	13.0%	

Figure 1. A, Phenotypic resistance profile of *K. pneumoniae* per year. **B**, Meropenem MIC distribution per year. 3CEF: third generation of cefalosporin, TZP: Piperacillin/Tazobactam, MEM: Meropenem.

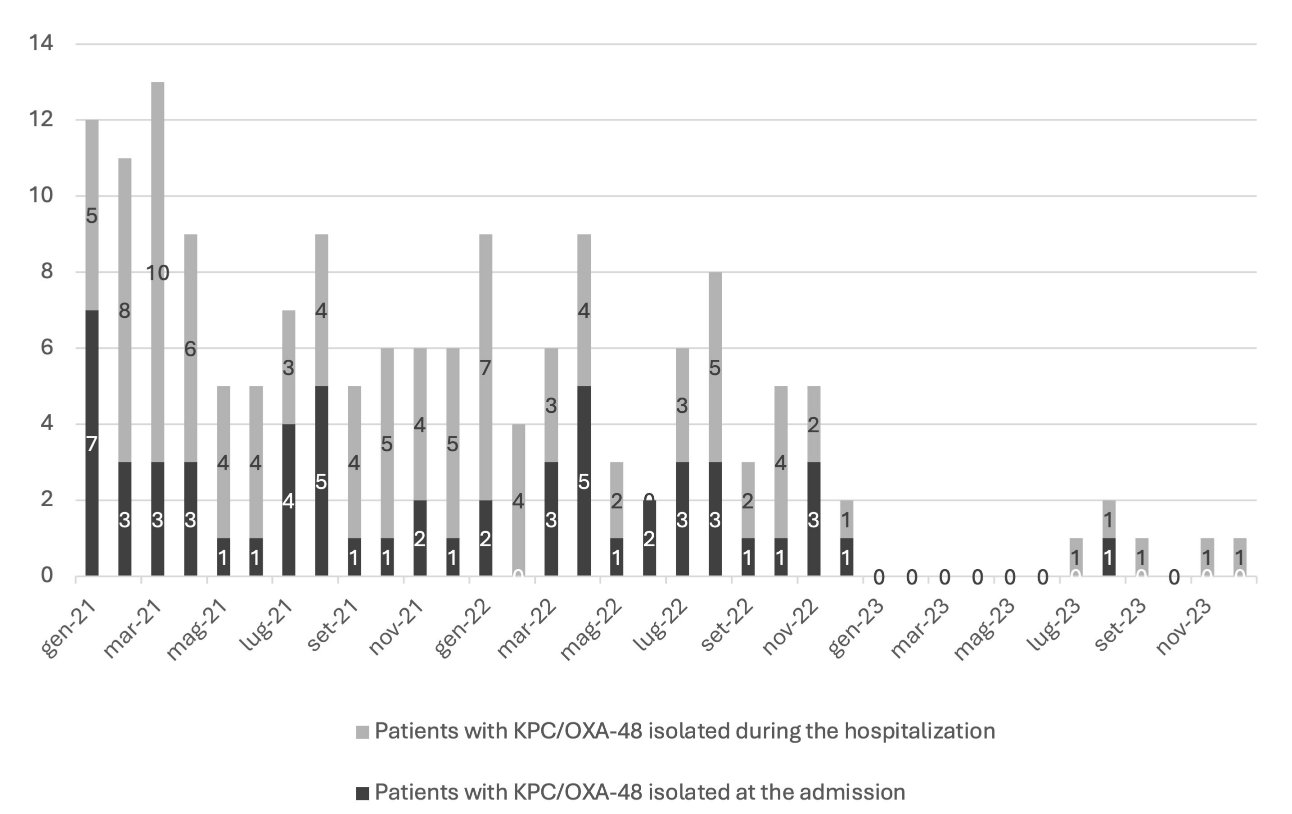
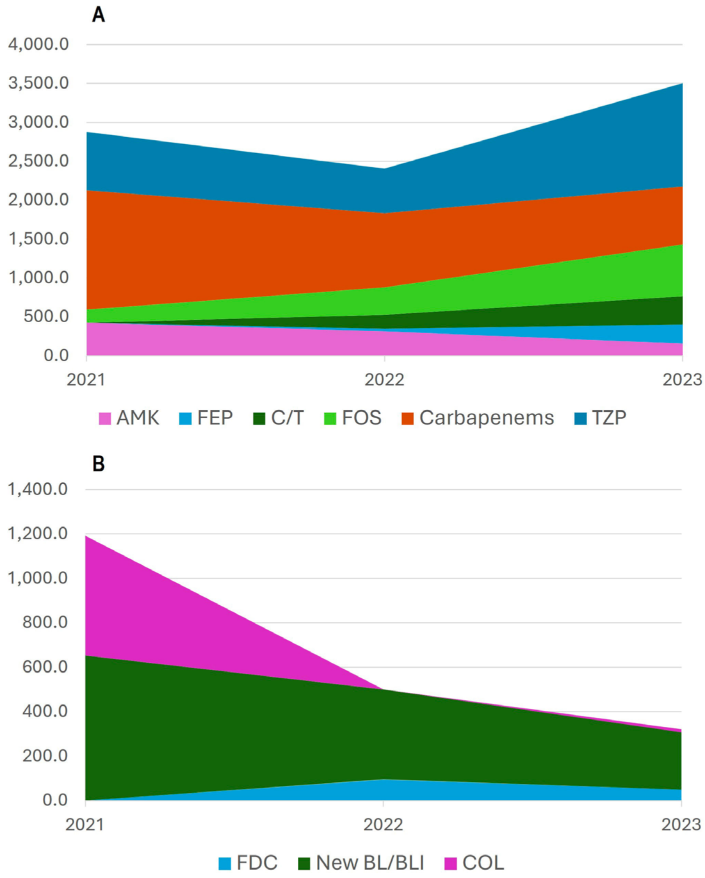


Figure 2. Carbapenem-resistant *K. pneumoniae* cases per year.



Antibiotics	2021	2022	2023
AMK	425.0	315.0	155.0
FEP	0.0	28.5	247.5
FDC	0.0	95.0	50.0
New BL/BLI	652.6	404.6	258.1
CTX or CAZ	1,018.5	1,227.3	757.5
C/T	0.0	180.0	363.3
FQ	345.0	222.5	145.0
COL	539.9	0.0	13.3
FOS	165.0	355.0	665.0
Carbapenems	1,536.5	953.2	744.9
TZP	751.5	571.4	1,325.6

Figure 3. Antibiotic DDD per year. **A**, Drugs usually used for Enterobacterales ESBL. **B**, Drugs of choice for CRE. AMK: Amikacina, FEP: Cefepime, FDC: Cefiderocol, BL/BLI: β-lactam/β lactam inhibitors, CTX: Ceftriaxone, CAZ: Ceftazidime, C/T: Ceftolozane/Tazobactam, FQ: Fluoroquinolones, Col: Colistin, FOS: Fosfomycina, TZP: Piperacilline/Tazobactam.

DISCUSSION

Tailored antimicrobial therapy is complex, especially in severe settings where the risk of AMR is much higher. Furthermore, AMR infection and the critical issues of many patients could be associated with inappropriate antibiotic treatments[15]. The principal goal of any antibiotic stewardship program is to reduce the incidence of MDRO. Antimicrobial stewardship and infection control measures should be personalized and conducted in the clinical setting where the intervention is intended[2]. The importance of microbiological data for implementing a rationale for empirical therapy has been evaluated in many studies[16,17], demonstrating its usefulness. Local epidemiology is essential to provide basic information regarding the most frequently isolated microorganism and their presumptive resistance patterns.

Infection prevention is fundamental to reducing the spread of MDRO. The primary goal is to decrease antibiotic use and, consequently, antibiotic pressure[18]. Additional standard strategies, such as surveillance and MDRO alert protocol, should be implemented to achieve this result[19]. In our study, structural infection control measures were implemented to reduce CRKp colonization frequency. Moreover, the reduction of CRKp was probably related to a most permissive antibiogram, with a decrease of *K. pneumoniae* ESBL from 89.9% to 55.0% (p<0.001). Additionally, TZP (from 89.3% to 39.0%, p<0.001) and MEM (from 54.0% to 9.0%, p<0.001) susceptibility drastically increased.

The AMR epidemiology, the availability of diagnostic tools, and antibiotics regimens can widely differ among countries, regions, and hospitals within the same country[20]. Tailoring facility-specific guidelines is essential for reducing AMR and implementing effective antimicrobial stewardship[21]. Cumulative susceptibility data track resistance changes over time and modify the local guidelines. Epidemiology data should be collected to undertake drug-resistant organism surveillance and suggest areas for intervention[22]. Furthermore, specific bundles should be implemented to manage the most common healthcare-associated infections. For example, using a bundle for central venous catheter (CVC) management has been documented in many studies to decrease rates of CVC-bloodstream-related infections[23].

Numerous studies[24] have shown the association between antimicrobial use and increasing AMR.

Monitoring antibiotic consumption is crucial to improving correct prescription perception and optimizing usage[25]. The literature indicates that previous antibiotic use was the most frequent risk factor associated with CRE infections. Of all specific antibiotic classes, prior use of carbapenems was highly reported as the most common drug associated with CRE[26]. Reduction of MEM consumption is fundamental in many antibiotic stewardship programs, and it has been associated with a decrease in the incidence of OXA-48-producing *K. pneumoniae*[27]. Not only were carbapenems related to an increasing risk of CRE, but prior F.Q. and 3CEF prescriptions also impacted the risk for isolation of KPC-producing *K. pneumoniae*[28]. For these reasons, the primary aim of antibiotic stewardship programs should consider carbapenem and F.Q.-sparing strategies, which are fundamental to implement. A multidisciplinary team approach involving microbiologists, ID consultants, pharmacists, and ICU specialists is often required[27,29,30]. Our cohort reduced carbapenem (from 1,536.5 DDD in 2021 to 744.9 DDD in 2023) and F.Q. prescription (from 345.0 DDD in 2021 to 145.0 DDD in 2023). Implementing local epidemiology-based guidelines and active ID consultants was fundamental to improving our antibiotic stewardship strategies. However, it is essential to remember that alternative agent choice and carbapenem reduction in clinical practice should be tailored according to local existing susceptibility patterns.

Our study presents some limitations. Firstly, no demographical data were collected. The clinical history and patient characteristics could impact the development and transmission of CRKp infection. Patients with previous recovery, subjected to invasive procedures, with previous extended-spectrum antibiotic therapy, or with long ICU stays could be more susceptible to CRKp colonization and consequently easily develop CRKp infections. Secondly, our surveillance does not consider the impact of the Coronavirus disease 2019 (COVID-19) pandemic on the possibility of *K. pneumoniae* transmission. In particular, 2021 represents a transmission year where antibiotic stewardship programs, infection control measures, and ID activity were progressively rebuilt after the COVID-19 pandemic. Thirdly, new antibiotic drugs were available in the last observational period, such as C/T, which were missing in 2021. New carbapenem and FQ-sparing strategies could be implemented thanks to new molecules, probably reducing extended anti-infective molecules prescription that can create ecological pressure in *K. pneumoniae* and other Gram-negative microorganisms in developing AMR.

CONCLUSIONS

Optimal antibiotic use is critical in ICUs. Studies show that 30% to 60% of antibiotics prescribed in ICUs are unnecessary and inappropriate[30]. Tailored antibiotic stewardship, infection control, and prevention measures should be implemented based on their own local epidemiology and healthcare possibilities. Carbapenem and FQ-sparing strategies could be essential in reducing antibiotic-resistant selective pressure.

Informed Consent:
Not applicable.

Authors' Contribution:
Conceptualization, N.G.; methodology, N.G.; validation, S.P.; investigation, N.G., L.T., G.F.; data curation, N.G.; writing-original draft preparation, N.G. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflicts of interest.

Data Availability:
Data will be available upon specific request to the corresponding author.

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Ethics Approval:
Not applicable.

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