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FULL PAPER

Antimicrobial resistance changing trends of *Klebsiella pneumoniae* isolated over the last 5 years

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SUMMARY

The aim of this study was to describe the prevalence and epidemiology distribution of *K. pneumoniae* isolated at University Hospital of Campania "Luigi Vanvitelli," including the susceptibility evolution profile. Data on resistant phenotype strains, such as extended-spectrum-β-lactamase (ESBL) producers and carbapenem-resistant *K. pneumoniae* (CRE) isolates, were also reported. *K. pneumoniae* strains were collected at the Complex Operative Unit (UOC) of Virology and Microbiology from different colonization and infection sites from January 2016 to December 2020.
The highest rates of isolation were in urinary samples and in respiratory and wound swabs. Antibiotics susceptibility patterns showed more than 50% of the isolates resistant to cephalosporins, fluoroquinolones and penicillin. On the other hand, from 20% to 40% of *K. pneumoniae* strains were resistant to carbapenems and aminoglycosides. Based on our analysis, fosfomycin, ceftazidime/avibactam and ceftolozane/tazobactam are still therapeutic alternatives. Data analysis on carbapenem class evolution in 2016-2020 showed a significant increase in resistance rates ($p<0.05$). Increased rates in CRE and ESBL producing *K. pneumoniae* since 2017 were reported. Providing information on clinical characteristics and epidemiology data on contemporary *K. pneumoniae* evolution could help mitigate the spread of these isolates in our hospital and avert the endemic levels that have been observed in Southern Italy and in other European countries.

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INTRODUCTION

Klebsiella pneumoniae is a major human pathogen that has been implicated in infections in healthcare settings over the past few decades. Antimicrobial treatment of *K. pneumoniae* infections has become increasingly difficult as a consequence of the emergence and spread of strains that are resistant to multiple antimicrobials [Moradigaravand *et al*., 2017). *Klebsiella species* are opportunistic pathogens found ubiquitously in nature and are responsible for human infection in the urinary tract, respiratory tract, wound sites, as well as in blood in individuals with debilitating diseases such as hospitalized or immunocompromised patients. A study conducted by Magill *et al.* in 2014 [Magill *et al*., 2014) estimated that *K. pneumoniae* was the third largest cause of hospital-acquired infections because of its ability to colonize the skin of patients, medical staff as well as the hospital environment [Khairy *et al*., 2020). Some antibiotics, such as cephalosporins and carbapenems, have played a key role in treating severe *K. pneumoniae* infections, but over time efficacy was compromised by the widespread acquisition of genes coding for enzymes (extended spectrum lactamases and carbapenemase) which mediate respective resistance to these critical drugs [De Oliveira *et al*., 2020). Often lacking effective antimicrobial options, it has been necessary to use drugs with higher risk of toxicity (e.g., aminoglycosides, polymyxins) or other safety concerns (e.g., tigecycline), and further resistance to these drugs has also been selected. The rise of carbapenem resistance isolates is a serious concern for the management of *K. pneumoniae* infections because the treatment alternative is limited. Therefore, investigating the incidence of nosocomial *K. pneumoniae* infection, but principally providing information on antimicrobial

Key words:
Klebsiella pneumoniae, epidemiology, antibiotics susceptibility, antimicrobial diagnostic stewardship, carbapenem-resistant, extended-spectrum beta-lactamases.

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resistance and development of genetic resistance of *K. pneumoniae*, are of paramount importance [Messaoudi *et al*., 2019). Infection control measure and procedure in all admitted patients was performed in our hospital swab for *Enterobacteria* Multi Drug Resistant Organisms (MDRO) colonization. We conducted a study in the Naples university hospital by characterizing a collection of non-repetitive isolates recovered during a 5-year period (January 2016-December 2020). Changes of pathogen distribution, demographics and antimicrobial resistance in accordance with an antimicrobial diagnostic stewardship program may affect epidemiology. Therefore, continuous worldwide monitoring of trends in pathogen microbiology is essential and a microbiological exam can help diagnostic approaches, treatment strategies and prevention programs [Foglia *et al*., 2022). We provide an update of the epidemiologic data on contemporary *K. pneumoniae* isolates to assess prevalence, the susceptibility profile, but also carbapenemase-producing *K. pneumoniae* (CPE) and extended-spectrum beta-lactamases producing *K. pneumoniae* (ESBL-*KP*) profiles. Our findings emphasize the emerging role in the dissemination of CPE and other resistance profiles such as ESBL. Considering the increasing identification of CPE and ESBL-*KP* isolates in this hospital, systematic carriage screening at the hospital admission, surveillance studies, an antimicrobial stewardship program, and early detection of these isolates are implemented to limit their further spread.

METHODS

This study was performed from January 2016 to December 2020. Within this frame time, 988 *K. pneumoniae* strains were isolated from patients admitted to University Hospital of Campania "Luigi Vanvitelli," Italy. *K. pneumoniae* clinical isolates were collected at the UOC of Virology and Microbiology from different colonization and infection sites: urine, respiratory tract, blood cultures, medical devices, and wound swabs. The study population was arbitrarily divided into four groups as follow: <20 years, 21-40, 41-60, >60 years.

All samples were plated on different culture media, according to the current procedures of the laboratory, and incubated at 37°C for 24/48 h in aerobic condition; the colonies grown on MacConkey agar (Becton Dickinson, NJ, USA) and on selective media for carbapenem-resistant K. pneumoniae (CHROMID Carba, Biomèrieux, Marcy l'Étoile, France) were identified via matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany) (Pignataro *et al*., 2020). The determination of antibiotic susceptibility of all K. pneumoniae isolates was performed using the Phoenix BD (Becton Dickinson, NJ, USA). The Epicenter software version 7.22A (Becton Dickinson, NJ, USA) was utilized to analyze the results after 16 h of incubation. The tested antibiotics were ampicillin, amoxicillin/clavulanic acid, ceftazidime, cefotaxime, cefepime, cefuroxime, piperacillin, piperacillin/tazobactam, ciprofloxacin, levofloxacin, gentamicin, amikacin, ertapenem, imipenem, meropenem, trimethoprim/sulfamethoxazole, fosfomycin, tigecycline, ceftazidime-avibactam, and ceftolozane-tazobactam. The minimum inhibitory concentration (MIC) values of antibiotics were assessed following breakpoint tables for interpretation of MICs and zone diameters Version 9.0, valid since 2019-01-02 (http://www.eucast.org/clinical_breakpoints). Further confirmation tests were performed for MDR organisms: Xpert CARBA-R (Cepheid, Sunnyvale, CA, USA) for carbapenemase producer organisms, NG-Test CTX-M (D.I.D. Diagnostic Distribution, Milan, Italy) for ESßL rapid detection.

Statistical analysis was performed using IBM SPSS 22.0 for IOS (SPSS Chicago, IL, USA). Category variables were presented as frequencies and percentages. Continuous variables were expressed as median and interquartile range (IQR). Age was classified into a categorical variable for data analysis. A Chi-square test was used to evaluate the relationship between two groups of categorical variables. A p-value of ≤0.05 was considered statistically significant.

RESULTS

In this study a total of 988 *K. pneumoniae* were isolated from different clinical samples. The study population was 53.3 % female and 46.7% male with no

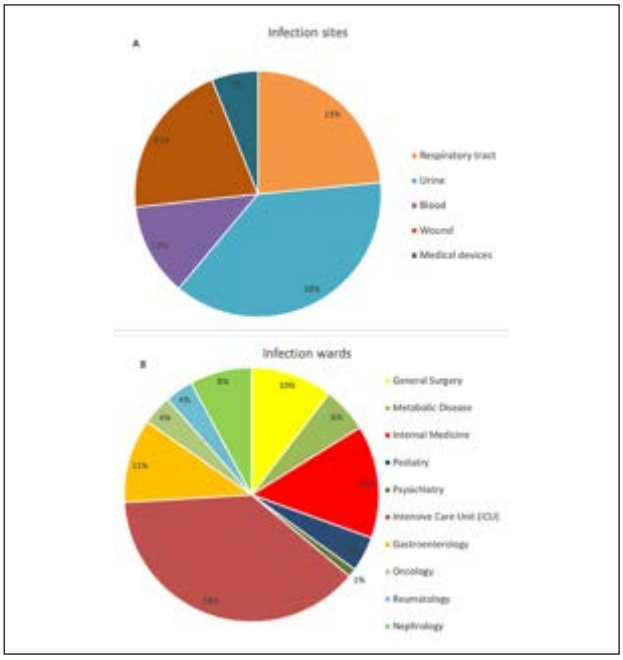


Figure 1

significant difference. The average age was 58 years old, whereas the most representative age group was the one with patients over 60 years old (59.6%) followed by 41-60 (25%), 21-40 (5.7%) and <20 (9.7%).

Table 1 - *Susceptibility and resistance rates of different antibiotics over five years at University Hospital of Campania "Luigi Vanvitelli".*

Antibiotics n (%)		*S*	*R*
Penicillins	Ampicillin	32 (3.3)	956 (96.7)
	Amoxicillin/ Clavulanic Acid	418 (42.3)	570 (57.7)
	Piperacillin	393 (39.8)	595 (60.2)
	Piperacillin/ Tazobactam	481 (48.7)	507 (51.3)
Cephalosporins	Ceftazidime	468 (47.3)	520 (52.7)
	Cefotaxime	474 (48.0)	514 (52.0)
	Cefepime	517 (52.4)	471 (47.6)
	Cefuroxime	424 (43.0)	564 (57.0)
	Ceftazidime/ Avibactam[a]	496 (90.5)	55 (9.5)
	Ceftolozane/ Tazobactam[a]	490 (88.9)	56 (10.2)
Fluoroquinolones	Ciprofloxacin	490 (49.6)	498 (50.4)
	Levofloxacin	492 (49.8)	496 (50.2)
Aminoglycosids	Gentamicin	636 (64.4)	352 (35.6)
	Amikacin	644 (65.2)	344 (34.8)
Carbapenems	Ertapenem	586 (59.4)	402 (40.6)
	Imipenem	633 (64.1)	355 (35.9)
	Meropenem	656 (66.4)	332 (33.6)
Miscellaneous agents	Trimetoprim/ Sulfametoxazolo	570 (57.7)	418 (43.3)
	Fosfomycin	744 (75.4)	244 (24.6)
Tetracycline	Tigecycline	510 (51.7)	478 (48.3)

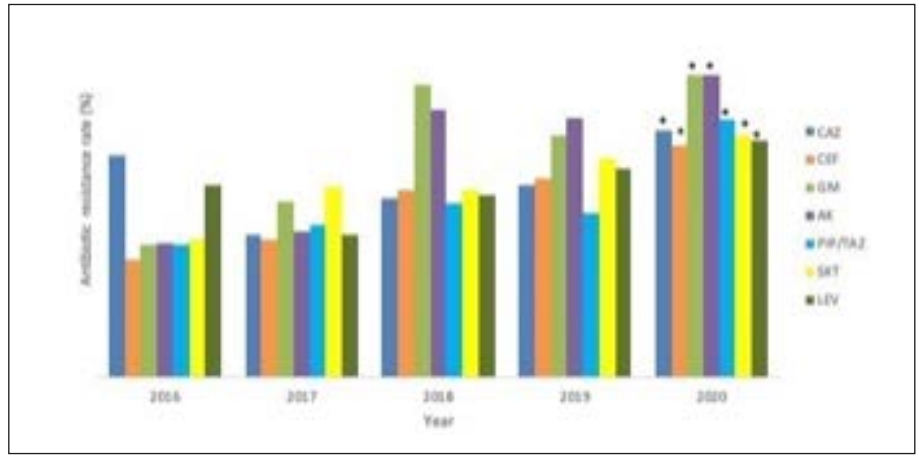
[a]Data from only the last three years relative to the introduction in clinical practice at our hospital.

Figure 1 shows the distribution of *K. pneumoniae* clinical isolates from different sample sources (1A) and infection wards distribution (1B). The highest rates of isolation were obtained from urinary samples (38%) followed by respiratory samples (23%) and wound district (21%). Nevertheless, the rate of isolation in blood remained considerably elevated (12%). *K. pneumoniae* can cause both community and hospital-acquired infections associated with high mortality and morbidity rates. As shown in *Figure 1B*, *K. pneumoniae* isolates were isolated in the Intensive Care Unit (ICU) (39.0%) followed by Internal Medicine (14.8%) and General Surgery (10.6%).

As shown in *Table 1*, *K. pneumoniae* isolates were susceptible to fosfomycin (75.4%), gentamicin (64.4%), and amikacin (65.2%). Sensitivity percentages also appear to be encouraging for meropenem and imipenem, at 66.4% and 64.1%, respectively. Ertapenem does not show statistically significant susceptibility reduction rates. A substantial proportion of isolates showed reduced susceptibility to ampicillin (96.7%), piperacillin (60.2%), and cephalosporins like ceftazidime (52.7%) and cefotaxime (52.0%). 90.5% of isolates remained susceptible to ceftazidime/avibactam, although reduced susceptibility was observed for ceftolozane/tazobactam (88.9%). In term of variation in trends of antimicrobials administered in clinical practice, *Figure 2* shows a significant increase ($p<0.05$) of the most representative antimicrobial agents such as ceftazidime, cefepime, levofloxacin, and trimethoprim/sulfamethoxazole. Resistance rates for Aminoglycoside and penicillins such as like piperacillin/tazobactam decreased in 2019, but both increased significantly in 2020. The figure also shows the increased resistance rates for cefepime and ceftazidime, with a small decrease of fluoroquinolones rates in 2017 and 2018.

Analyzing the carbapenems resistance trend over the 5-year study period (2016-2020), meropenem, imipenem, and ertapenem showed a significant increase in the resistance rate ($p<0.05$) of *K. pneumoniae* iso-

Figure 2



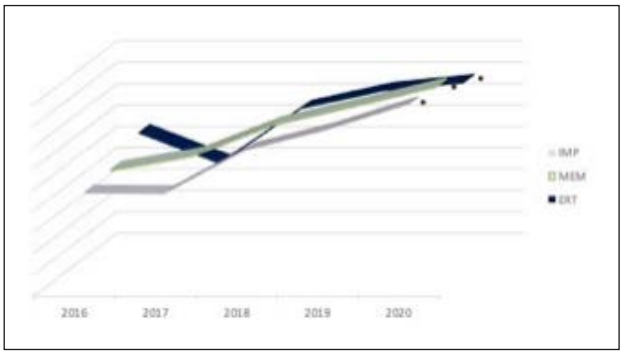


Figure 3

lates: from around 45% in 2016 to over 80% in 2020 (*Figure 3*).

The resistant rates of carbapenem antibiotic class are related to the increase of *K. pneumoniae* carbapenemase producers (CPE) over time since 2016. The evolution of *CPE* varied from 7.2% in 2016 to 37.7% in 2017 and 29.0% in 2019. In this study on 988 *K. pneumoniae* clinical isolates, 647 (65.5%) were Multi Sensible *K. pneumoniae* (MS-*KP*), 273 (27.5%) had ESBL-producing profile (ESBL-*KP*), and only 69 (7.0%) were carbapenemase producing (CPE). We analyzed the gender and district distribution prevalence of extended-spectrum-β-lactamase-producing *K. pneumoniae* (ESBL-*KP*) and CPE isolates. The district distribution of ESBL-*KP* revealed high incidence in urine, respiratory tract and blood (28.2%, 24.5%, and 15.0%, respectively). We also found 22.3% ESBL-*KP* resistance profiles in wound and ulcer districts and 9.8% in the others. The incidences of the different districts were not significant. Regarding CPE sample distribution, the highest incidence was in respiratory tract samples (27.5%), urine (20.2%), and wound specimens (23.1%), followed by blood (10.1%), and other districts (18.8%). Regarding the relation between gender and *K. pneumoniae* infection frequency; ESBL-*KP* was more commonly isolated in males (142) than in females (131) ($p>0.05$) while there was no significant difference for CPE infections (34 females and 35 males).

DISCUSSION

K. pneumoniae infections are commonly associated with hospital-acquired urinary tract infections, pneumonia, septicemias, and soft tissue infections (Hu *et al*., 2020; Podschun *et al*., 1998). In order to limit the spread in hospital outbreaks, the aim of this study was to describe the prevalence and epidemiology distribution of *K. pneumoniae* isolated in University Hospital of Campania "Luigi Vanvitelli." The high rates of carbapenem class resistance over the study period emphasize its emerging role in the spread of resistant phenotypes strains, such as extended-spectrum-β-lactamase (ESBL) producers and carbapenemase-producing *K. pneumoniae* (CPE) isolates. As a known potential drug-resistant pathogen, *K. pneumoniae* has received increasing attention in clinical infections (Guo *et al*., 2016). In our study, a total of 988 *K. pneumoniae* were isolated from different clinical samples. The study population was 53.3% female; the most representative age group was >60 years (59.6 %). We found, as did the Navon-Venezia study (Navon-Venezia *et al*., 2017), that isolation rates varied among the *K. pneumoniae* strains in different sample sources, with the highest rates of isolation in urinary samples (38%), respiratory (23%), and wound swabs (21%). As in several studies (Maki *et al*., 2008; Palmeiro *et al*., 2019), the highest number of *K. pneumoniae* isolates came from the ICU wards, followed by internal medicine, medical surgery, and nephrology. The antibiotics susceptibility pattern varied for the different drugs (Tian *et al*., 2019). More than 50% of the isolates were resistant to ampicillin, amoxicillin/clavulanic acid, ceftazidime, levofloxacin, ciprofloxacin, and cefepime. *K. pneumoniae* isolates showed resistance that varied from 20% to 40% for carbapenems, gentamicin, amikacin, trimethoprim/sulfamethoxazole, and tigecycline. In our epidemiology setting, fosfomycin, ceftazidime/avibactam, and ceftolozane/tazobactam are still therapeutic alternatives because few isolates exhibited resistance to these antimicrobial agents, as described in Deshpande's study (Despande *et al*., 2006). Data related to ceftazidime/avibactam and ceftolozane/tazobactam were reported only for the last three years since their introduction into clinical practice at our hospital (Lavano *et al.*, 2020) and showed a 90.5% susceptibility rate. Analyzing the carbapenems resistance trend over the 5-year study period (2016-2020), meropenem, imipenem, and ertapenem showed a significantly increased resistance rate ($p<0.05$) of *K. pneumoniae* isolates, from around 45% in 2016 to over 80% in 2020. These data conform to an increasing rate of carbapenemase producers (CPE) in our hospital since 2017 (37.7%), which is consistent with the rise of carbapenem-resistant isolates in the country, as reported in the study by Conte *et al.* (Conte *et al*., 2016). Several studies have reported the rapid spread of *K. pneumoniae* strains across regions and countries; others have focused on outbreaks in single hospitals (Aires-de-Sousa *et al*., 2019; Navon-Venezia *et al*., 2017). In either case, the investigations commonly identify multidrug-resistant (MDR) strains, especially carbapenem-resistant strains (Moradigaravand *et al*., 2017). Data from the European Centre for Disease Prevention (EARS-Net) revealed that, in 2014, 62.3% of Greek *K. pneumoniae* isolates were resistant to carbapenems. An important epidemiological change has also occurred in Spain in recent years, characterized by a rapid increase in the number of cases of carbapenemase-producing

Enterobacteriaceae (CPE), causing both nosocomial outbreaks and single infections (Oteo *et al*., 2014). Considering data from outside of Europe, there were several reports of carbapenemase producing *K. pneumoniae* in hospitalized patients in the northeastern United States (Jure *et al*., 2019). The China Antimicrobial Surveillance Network (CHINET) emphasizes that the prevalence of imipenem-resistant *K. pneumoniae* has increased each year in China, from 3.0% in 2005 to 25.0% in 2018 (Hu *et al*., 2020). Some epidemiological risk factors associated with *K. pneumoniae* carbapenem-resistant infections include gender, specimens, age, hospitalization status, admission to an ICU facility, antimicrobial exposure (particularly carbapenems and fluoroquinolones, hematology patients and patients with immunodeficiency (Effah *et al*., 2020). In our hospital, the highest incidence of CPE isolates was from respiratory tract (27.5%) and urine samples (20.2%), instead of blood culture (10.1%). Dissemination of CPE isolates was restricted to the ICU setting, as in Tian *et al.*, which reported 22.18% of CPE strains, of which more than 50% in the Intensive Care Unit, equaling the levels observed in that epidemic region (Tian *et al*., 2016). The incidence of ESBL-*KP*-producing isolates has been increasing steadily over recent years and represents a serious clinical problem associated with a high mortality rate (Pitou *et al*., 2008) (Tumbarello *et al*., 2006). Our data reported that the overall percentage of ESBL-*KP* isolates was 27.5%, mainly isolated from urine, respiratory tract, and blood samples. District incidence and gender distribution were not significant. In conclusion, our epidemiology study describes the prevalence and distribution of *K. pneumoniae* isolated in the University Hospital of Campania "Luigi Vanvitelli" over 5 years (2016-2020). Our study has some limitations, given that we included isolates from a single hospital. However, is very important to monitor and report the changes in antimicrobial-resistant *K. pneumoniae* isolates in Southern Italy. This data will guide doctors in prescribing the proper antimicrobials in case of resistance gene evolution, in line with the antimicrobial stewardship program currently in use at our hospital. On the other hand, it will provide information on clinical characteristics and epidemiology data on contemporary *K. pneumoniae* evolution to help mitigate the spread of *K. pneumoniae* isolates.

The global emergence and spread of genes of antimicrobial resistance, such as ESBL and carbapenemase genes in *K. pneumoniae* isolates, present a significant danger to public health. Our study describes the evolution of the *K. pneumoniae* susceptibility profile with resistant phenotype strains, such as extended-spectrum-β-lactamase (ESBL) producers and carbapenemase-producing *K. pneumoniae* (CPE) isolates. Data incidence of ESBLs and carbapenem resistance among *K. pneumoniae* could be related with the antimicrobial diagnostic stewardship program and implementation of infection control strategies in the hospital, which were aimed to contain and mitigate the risks of nosocomial infections and outbreaks. Surveillance at admission and screening for patients admitted or transferred from other hospitals or with a history of recent hospitalization/stay in long-term care facilities was implemented in our hospital following national guidelines issued in 2016. This screening highlights an important role for local microbiology laboratories and the crucial support of laboratory information systems in infection control. The rapid global emergence of MDR *K. pneumoniae* strains resistant to almost all β-lactams, including carbapenems, as seen in this study, shows the increasing rate of this organism in our hospital since 2017. Systematic screening at hospital admission, surveillance studies, antimicrobial stewardship programs, and early detection of these isolates are implemented to limit their further spread and avert the endemic levels that have been observed in Southern Italy and in other European countries.

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