UNIVERSITY OF TURIN

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Doctoral School of Medical Physiopathology

Cycle XXXV

Thesis title:

"Ceftazidime-Avibactam for blood stream infections caused by carbapenemase-producing Klebsiella pneumoniae: pharmacoepidemiology and retrospective cohort study at a single tertiary-care center in Italy"

Candidate:

Dr. Nour Shbaklo

Tutor:

Prof. Francesco Giuseppe De Rosa

PhD Coordinator:
Prof. Franco Veglio

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Abstract

Background: Multi-drug resistant (MDR) *Klebsiella pneumoniae* is a common healthcare-associated pathogen causing a variety of severe systemic infections, including bloodstream infections (BSIs). In response to the medical need for new treatment options, several new antibiotics have been developed such as the β-lactamase inhibitor (BLI) combination ceftazidime-avibactam (CAZ-AVI).

Methods: We conducted a retrospective study on KPC-Kp BSIs between 2010 and 2021. The primary objective was to describe trends and change in susceptibility rates in KPC-Kp BSI cases and in antimicrobial use (CAZ-AVI, carbapenems, and colistin), expressed in DDD/1000 patient-days during a prevalence period (August 2019-January 2021). Secondary objectives were to describe risk factors for KPC-BSI and outcomes with CAZ-AVI treatment on 30-day mortality.

Results: We included 524 patients. Older age, higher Charlson score, congestive heart failure, invasive devices and seven-day nephrotoxicity in colistin and aminoglycoside treatments were significantly associated with 30-day mortality. The length of stay in the CAZ-AVI group was significantly lower than the standard of care (SOC) group. CAZ-AVI therapy was shown to be a protective factor for mortality. Mortality was significantly higher in the SOC group compared to the ceftazidime-avibactam group. Carbapenem use significantly decreased during the observed period for antibiotic use.

Conclusions: Invasive procedures, prolonged hospital stays, and colonization increased the risk of KPC-Kp BSI calling for effective source control and appropriate empiric therapy. New drugs, such as CAZ-AVI, are now available for the treatment of such invasive infections, and have significantly contributed to improving patient outcome in this setting. Identifying changes in the resistance profile should be an alarm for healthcare institutions to further focus efforts in stewardship programs and infection control practices.

Introduction

Background

MDR *Klebsiella pneumoniae* is the third most frequently reported healthcare-associated pathogen and causes a variety of severe systemic infections, including bloodstream infections (BSIs). MDR *Klebsiella pneumoniae* has accumulated a wide range of resistance determinants and has evolved into a difficult-to-treat pathogen that poses an increasing healthcare threat with limited treatment options (1). Italy is among the highest consumers of antibiotics in general, and of broad-spectrum agents in particular, in Europe. Italian antimicrobial resistance (AMR) rates for several pathogens are considered hyper-endemic, and the rate of carbapenem-resistance among *K. pneumoniae* invasive isolates is around 30% (2). The 2017 European Center for Disease Prevention and Control (ECDC) country visit to discuss AMR found the high AMR rates in Italy appeared to be accepted and somehow considered unavoidable by all stakeholders, with little sense of urgency, institutional support, professional leadership, accountability, and coordination of activities at all levels (2).

In response to the medical need for new treatment options, several new antibiotics have been developed such as the β-lactamase inhibitor (BLI) combination ceftazidime/avibactam (CAZ-AVI). While ceftazidime has been in clinical use for years, the addition of the novel β-lactamase inhibitor avibactam restores in vitro activity against Klebsiella pneumoniae carbapenemase (KPC)– and OXA-48–producing gram-negative pathogens. CAZ-AVI therefore may be a useful alternative to more toxic antibiotics such as colistin (3).

For blood-stream infections (BSIs) in particular, the role of CAZ-AVI use in infections by MDR *K.pneumoniae* has been investigated only through observational studies, with sample sizes up to 500 patients (4–11). CAZ-AVI was approved by the Italian medicine agency (AIFA) in 2017. Since its introduction, at the A.O.U. Città della Salute e della Scienza, a 1200-bed tertiary-care and teaching hospital of Turin, in Northern Italy, the prescription of CAZ-AVI was restricted to: pre-prescription authorization was required, i.e., physicians require the authorization of an infectious disease consultant to be able to prescribe this agent. Understanding CAZ-AVI uptake and usage patterns at the patient and hospital levels could be useful to determine whether there is a need for increased antimicrobial stewardship (AMS) efforts.

Epidemiology of Klebsiella pneumoniae carbapenemase-producing

In the early 2000s, CP-Kp was first identified in Europe, and its prevalence has since increased (12). Current European epidemiology ranges from sporadic imported cases and hospital outbreaks to interregional spread and endemic CP-Kp in healthcare settings (13). Among carbapenemase producers, KPC-producing *K.pneumoniae* (KPC-Kp) is the most common in Italy (14–17). The global dissemination of KPC-Kp has been linked to the successful spread of a specific genetic line designated clonal group 258 (CG258). The KPC-coding gene, *bla*KPC, is generally found within a Tn*4401* transposon, a mobile genetic element originated from the Tn3 transposon family that aids its dissemination (18). Italy, together with some Balkan countries and Greece, is the only nation in Europe with resistance values to carbapenems above 25%.

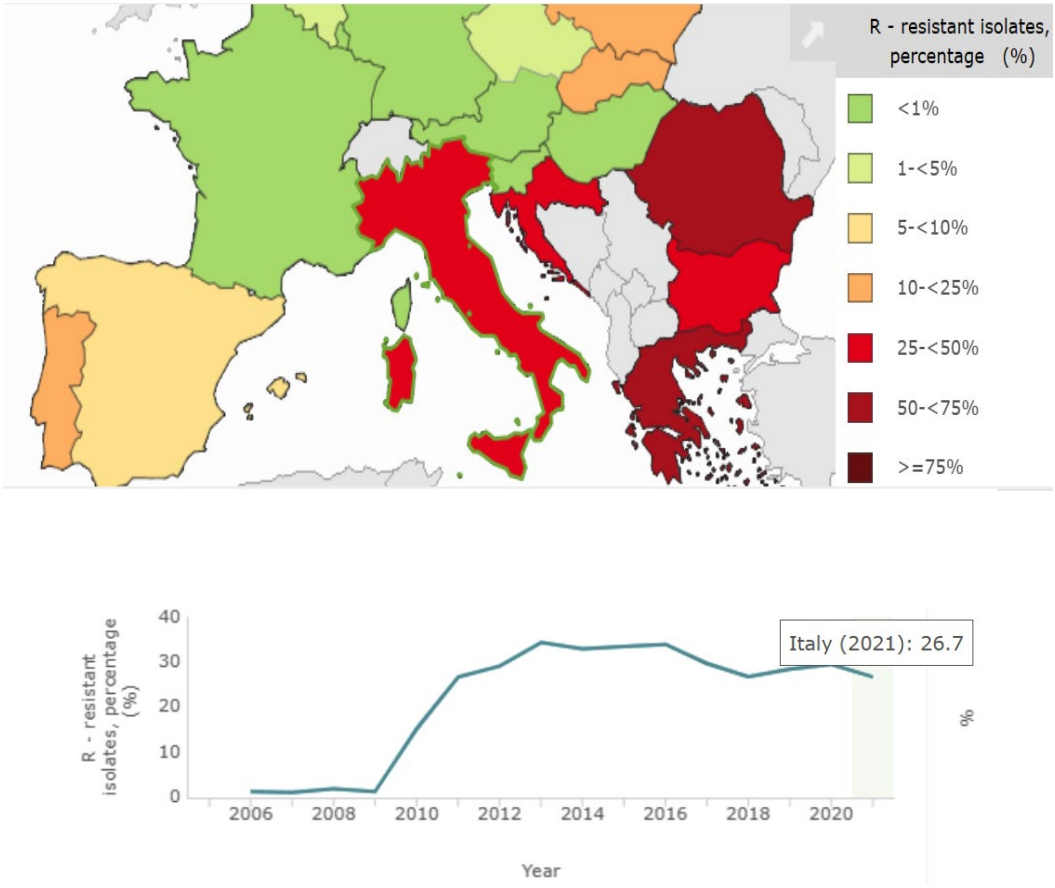
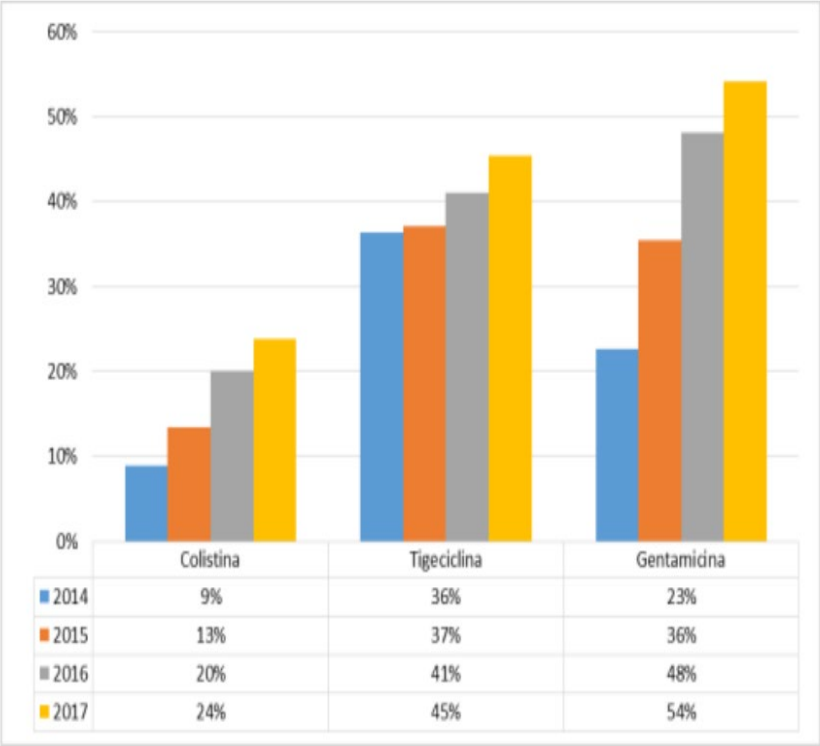


Figure 1: WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 – 2020 data

Regional Surveillance of Klebsiella pneumoniae carbapenemase-producing (SEREMI)

Klebsiella pneumoniae (KP) has been under "special surveillance" among the microorganisms present in the panel of microorganisms for years ALERT. Also in Piedmont KP shows a remarkable resistance to semi-synthetic penicillins associated with a beta-lactamase inhibitor such as amoxicillin/clavulanate and piperacillin/tazobactam (AMC and TZP), a 3rd generation cephalosporins such as cefotaxime and ceftazidime (CTX and CAZ) and fluoroquinolones such as ciprofloxacin (19).



	Colistina	Tigeciclina	Gentamicina
2014	9%	36%	23%
2015	13%	37%	36%
2016	20%	41%	48%
2017	24%	45%	54%

Figure 2: Bacteraemia from *Klebsiella pneumoniae* R/I to meropenem and/or carbapenemase producer. Strains resistant or insensitive to colistin, tigecycline and gentamicin, per year of isolation. Percentage of the total strains isolated in the Piedmont year 2014-2017

The role of CAZ-AVI and its potential resistance

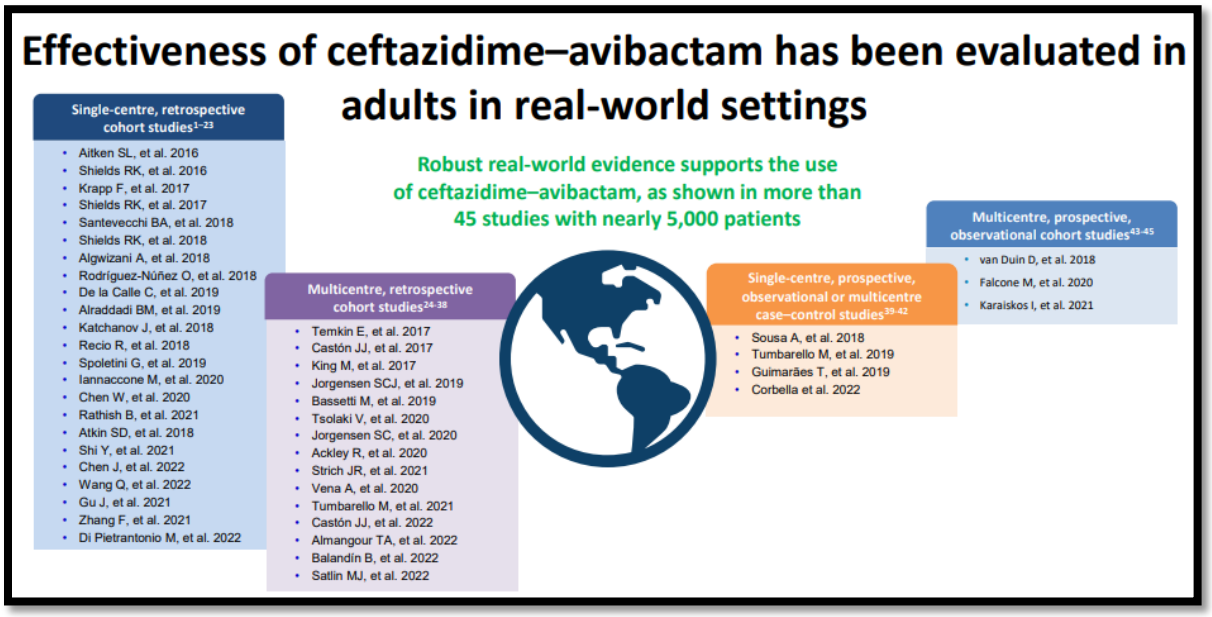


Figure 3: Effectiveness of CAZ-AVI in real-world studies

Ceftazidime-avibactam (CAZ-AVI) is a β-lactam/β-lactamase inhibitor combination available since 2015, in Italy since February 2018. Interestingly, avibactam is structurally distinct from other β-lactamase inhibitors used in clinical practice, lacking a β-lactam core (20). The mechanism of inhibition involves the opening of the avibactam ring, but the reaction is reversible because deacylation results in the regeneration of the compound and not in hydrolysis and turnover (21). Rapidly in these years, CAZ-AVI has become a first-line option against KPC-producing *Enterobacterales*, especially in critical patients with high INCREMENT-CPE score and it has been associated to a protective effect in mortality (22).

The safety and efficacy of CAZ-AVI have been assessed in non-inferiority RCTs, providing evidence that CAZ-AVI is non-inferior to carbapenems for treatment of Gram-negative bacterial infections (urinary tract infections, healthcare-acquired pneumonia, intra-abdominal infections). Results of individual RCTs were pooled into secondary studies, with conflicting results. Indirect *(in vitro)* evidence was used to support the use of CAZ-AVI for several clinical conditions caused

by susceptible microorganisms, including those resistant to the standard of care used in the non-inferiority RCTs (23).

The emergence of resistance to ceftazidime-avibactam most commonly occurs because of mutations in the blaKPC gene translating to amino acid changes in the KPC carbapenemase. Estimates of the emergence of resistance after clinical exposure to ceftazidime-avibactam are approximately 20% (1).

Antimicrobial Stewardship programs

Antimicrobials are very commonly prescribed for treatment in human medicine, but may be used unnecessarily in up to 50% of cases (23). It is important that the effectiveness of existing antimicrobials is preserved for the treatment of infections with CRE. Furthermore, the antimicrobial pipeline is running dry, with a deficit in novel antimicrobial development to address the rise in CRE (24).

AMS are coordinated programs that implement activities to ensure appropriate antimicrobial prescribing. In any healthcare setting, antimicrobial stewardship should be implemented as part of a multimodal and integrated approach, along with the application of infection prevention and control (IPC) measures and the invaluable support of a microbiology laboratory that has the capacity for timely and accurate detection of CRE (25). Antimicrobial stewardship programs should be multidisciplinary, with a core team made up of an infectious disease physician or clinical microbiologist, and a clinical pharmacist with training in infectious diseases (26). In order to develop and implement a local antimicrobial stewardship program, it is important that the advice of specialists with expertise in diagnosis, management and prevention of infection is available to all types of healthcare settings including acute, primary and residential care.

The Manual of Empiric Therapy: Molinette Hospital

As a part of the antimicrobial stewardship program in our facility, a Manual of Empiric Therapy was introduced to improve the appropriateness of empiric therapy in patients admitted to internal medicine and surgical wards (general surgery and urology). Surgical antimicrobial prophylaxis

recommendations were detailed in a separate manual. The antimicrobial therapy manual covered the primary choice antimicrobials for treatment and detailed alternatives for patients with allergy to penicillin. Guidelines were provided for neutropenic and non-neutropenic patients and for various infections. Dosing, route and duration of treatment were specified for each infection (27).

When the manual was introduced, on-site education sessions were provided on different wards by infectious diseases physicians and healthcare workers from other disciplines who were involved in the study. Follow-up meetings were conducted once a month rotating between the different medical and surgical wards, for approximately three months after the introduction (27).

Local antimicrobial susceptibility patterns and in-hospital broad spectrum antimicrobial consumption data were reviewed before preparing the manual. A multidisciplinary team led by infectious diseases specialists and one internal medicine specialist together with microbiologists, infection prevention and control practitioners, pharmacists and hospital management provided the recommendation for the development of the manual, which was developed by means of programmed meetings within the hospital as a part of continuous education in medicine (ECM programs in Italy). No restrictive policy on antimicrobial prescribing was applied.

Later, we had conducted a four-year prospective interventional study (2015–2019) that aimed to assess the effect of manual introduced in June 2017, on both MDR trends and antimicrobial consumption. Outcomes were evaluated in two periods: the pre-intervention period (January 2015–May 2017) and post-intervention period (June 2017–December 2019) (27).

Antimicrobial consumption

In medical wards, we observed a significant decrease in consumption of piperacillin-tazobactam (−33.29, $P < 0.001$). A significant decrease in the trends of consumption was identified for tigecycline and vancomycin ($P < 0.001$), Figure 4. In surgical wards, there was a significant decrease in consumption of fluoroquinolones, tigecycline, and piperacillin-tazobactam (−17.4, −2.6, and −32.0 DDD/1000 PD, respectively). This decrease was maintained in trend for all the antimicrobials but was significant for tigecycline only, Figure 5 (27).

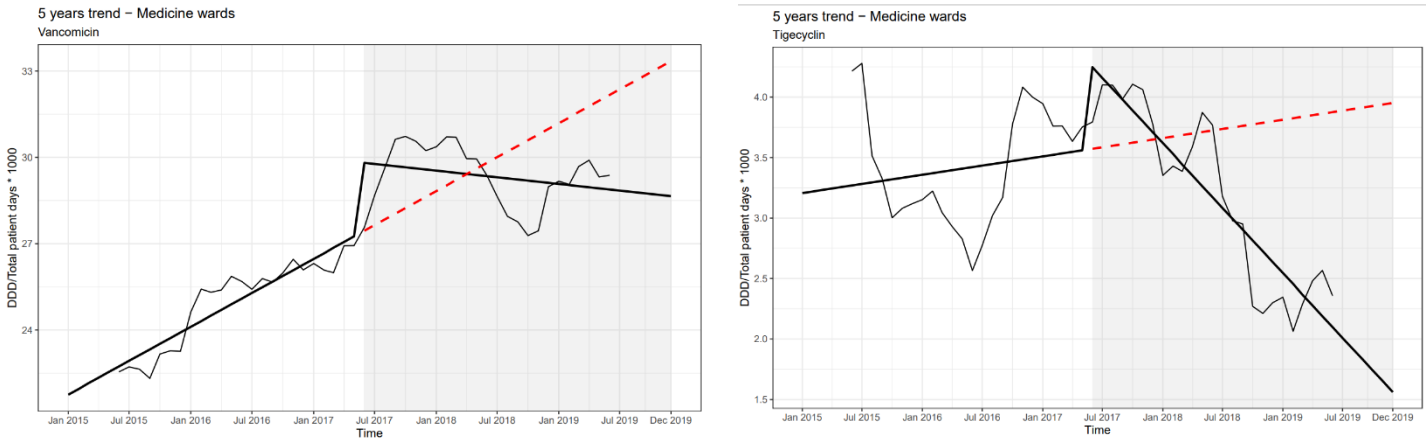


Figure 4: Vancomycin and tigecyclin trends in medicine wards

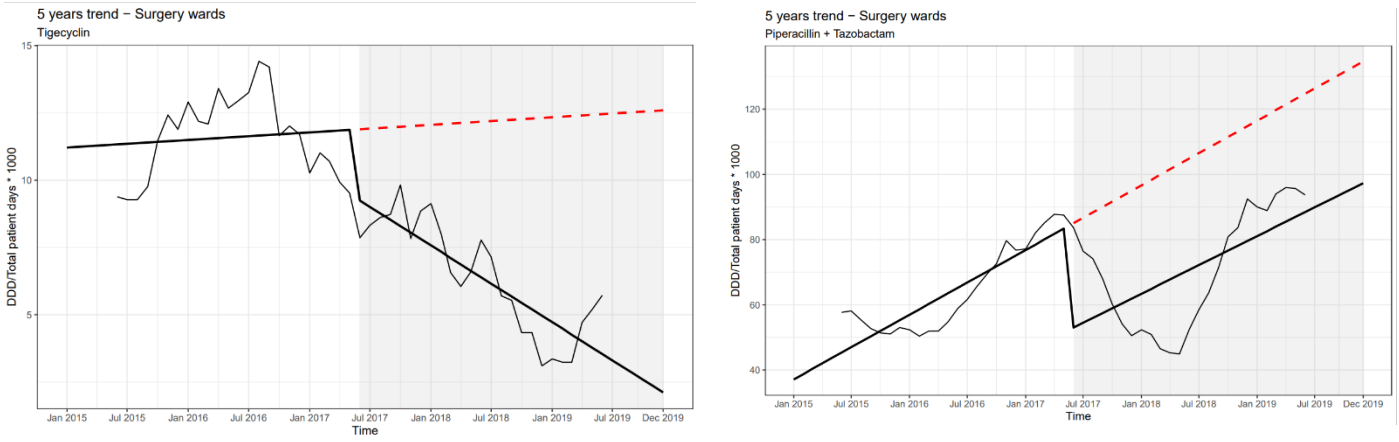


Figure 5: Tigecycline and piperacillin-tazobactam trends in surgical wards

Microbial data

Regarding microbial data, a total of 1449 BSI episodes were reported. In medical wards, there was a significant reduction in MRSA cases after the introduction of the manual (−39.0%, 2.57 episodes/1000 PD, P = 0.032). *C. albicans* cases decreased by −43.7% (0.7 episodes/1000 PD) in the post-intervention period. Similarly, in surgical wards, we observed a decrease in MRSA cases (−45.6%, 0.51 episodes/1000 PD) and ESBL-*E. coli* cases (−17.9%, 2.05 episodes/1000 PD) after

intervention. In addition, we observed a decrease in *C. albicans* cases (−24.7%, 0.81 episodes/1000 PD) and in CDI cases (−9%, 1.1 episodes/1000 PD). For KPC-Kp, the overall cases decreased by 22.5% in medical wards and 74.3% in surgical wards in the post-intervention period.

Our results showed that a persuasive educational approach to antimicrobial stewardship with an empiric antimicrobial therapy manual and continuous education sessions, was effective in reducing antimicrobial use and hospital-acquired infections BSIs (27).

Infection Control of CRE

On admission to the healthcare setting, frontline HCWs should evaluate all patients to see whether they fall into any one of the four risk categories, and whether they have prior microbiological evidence for CRE carriage. Any patient who is a potential carrier should have the following three preliminary supplemental measures implemented: a) pre-emptive isolation in a single room while waiting for results of screening b) active screening for CRE by obtaining swabs from rectal or perirectal areas and any other site that is either actively infected or considered to be colonised c) contact precautions implemented and used by anyone entering the room. If the result of the active screening is positive for CRE, the measures (patient isolation and contact precautions) are continued and additional supplemental measures are added (28).

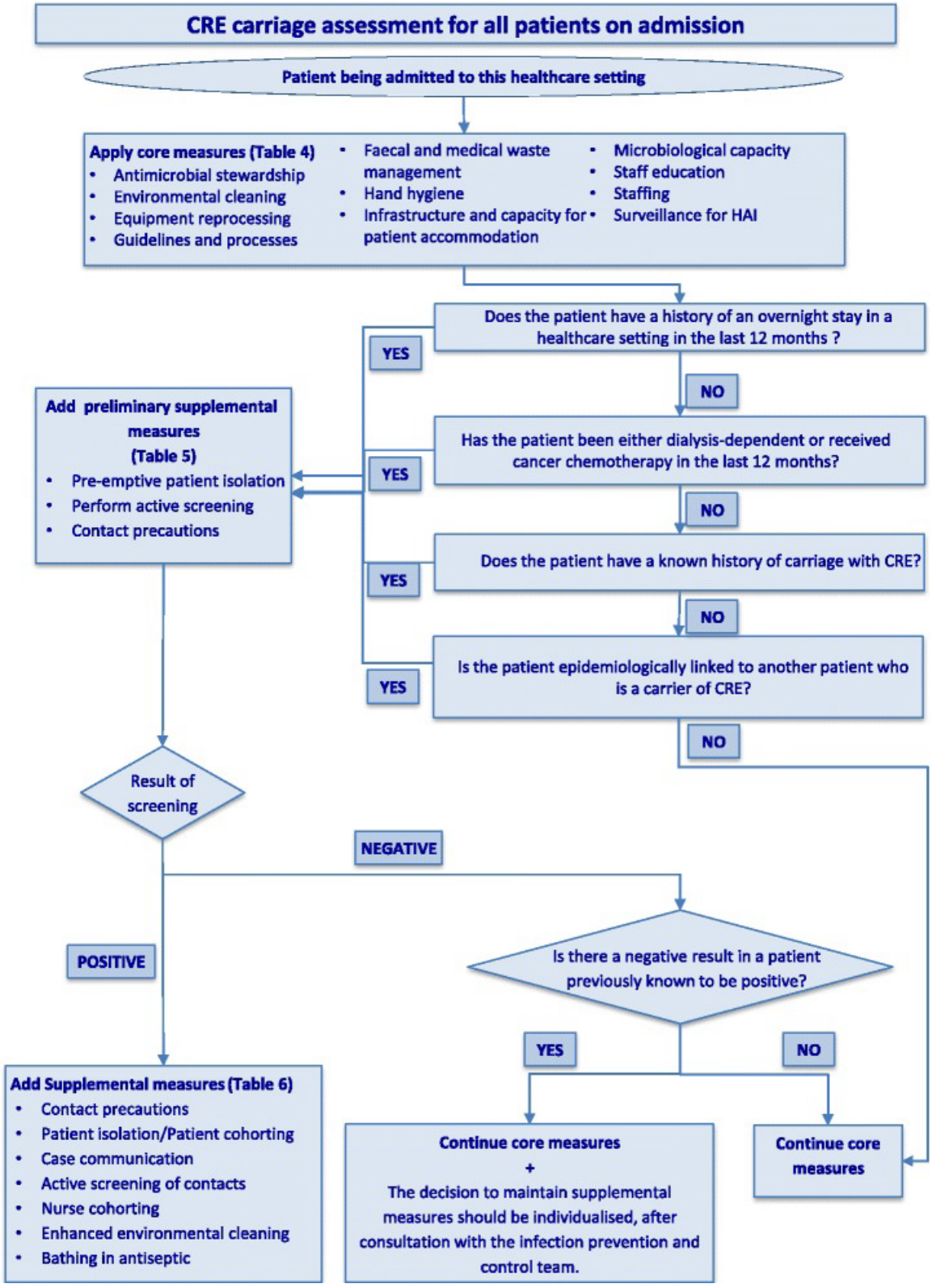


Figure 6: Flowchart for assessment of carriage of carbapenem-resistant Enterobacterales in patients being admitted to healthcare settings.

Table 1: Core infection prevention measures for CRE infections

Intervention (Evidence source)	Comments on measure and implementation
Antimicrobial stewardship (SR)	✓ Healthcare settings should have a formally defined antimicrobial stewardship programme for assuring appropriate antimicrobial use [54] ✓ Healthcare settings should have facility-specific treatment (and prophylaxis) recommendations, based on national guidelines and local microbial susceptibility, to assist with empiric antimicrobial selection [54] ✓ Should be part of a multimodal, integrated programme, along with IPC
Environmental cleaning (SR) Equipment reprocessing (SR)	✓ Responsibilities for environmental cleaning and equipment reprocessing must be well-defined and described in hospital internal procedures ✓ Hospitals should review the processes for environmental cleaning and equipment reprocessing, follow instructions of manufacturers, and consider screening (or auditing) to ensure quality of processes
Faecal and medical waste management (EO)	✓ Adequate toilet facilities should be available for all patients ✓ When patients are incontinent or have diarrhoea, bedpans or commodes may be indicated
Guidelines and processes (EO)	✓ Adherence to evidence-based guidelines, processes and pathways for the prevention of healthcare-associated infections (EO)
Hand hygiene (SR)	✓ There is evidence for the effectiveness of hand hygiene, as part of a multimodal strategy, for the reduction of transmission of MDROs [56–58] ✓ Patients should be encouraged to perform hand hygiene, as suggested by WHO guidelines [58]
Infrastructure and capacity for patient accommodation (EO)	✓ Healthcare managers should ensure that the ward occupancy does not exceed the capacity for which it is designed [72] ✓ Healthcare managers should ensure that infection prevention and control building recommendations are followed
Microbiological capacity (EO)	✓ Healthcare settings should have access to microbiology laboratories with capacity to detect CRE from both clinical and screening specimens ✓ Healthcare settings should have systems in place to ensure that potentially significant results are communicated by the microbiology laboratory in a timely manner to the relevant staff in the healthcare setting ✓ Should be part of a multimodal, integrated programme, along with IPC and antimicrobial stewardship
Staff education (SR)	✓ On-going education and training should be provided to all staff with patient contact, with specific reference to CRE
Staffing (EO)	✓ Staffing, appropriate skill level and workload of frontline healthcare workers must be adapted to acuity of care and the number of pool/agency nurses and physicians minimised [72]
Surveillance (EO)	✓ Routine surveillance of healthcare-associated infections

Methods

Design of the Study

Data on patients admitted to the A.O.U. Città della Salute e della Scienza, a 1200 university hospital in Turin, between 2010 and 2021 were retrospectively collected. The study was approved by the Intercompany Ethics Committee on 13 March 2020, protocol number 0027840.

- The primary objective of this study was to describe trends and change in susceptibility rates in KPC-Kp BSI cases and in antimicrobial use (CAZ-AVI, carbapenems, and colistin), expressed in DDD/1000 patient-days during a prevalence period (August 2019-January 2021).
- The secondary objectives were to describe risk factors for KPC-Kp BSI and outcomes with CAZ-AVI treatment on 30-day mortality.

Inclusion criteria

Inclusion criteria were all KPC-Kp nosocomial bloodstream infections among patients admitted between 2010-2021, defined as at least one couple of blood cultures positive for *Klebsiella pneumoniae* KPC-producing collected after ≥2 days from admission and concomitant Systemic Inflammatory Response Syndrome (SIRS) signs [corporeal temperature <36 °C or >38 °C, pulse rate > 90 beats/minute, respiratory rate >20 breaths/minute, blood cells count < 4000 cells/mm^3 or >12.000 cells/mm^3 or >10% immature neutrophils (band form).

Data collection

Risk factors (including age, comorbidities, length of hospital stay, colonization and clinical characteristics) and outcomes (in terms of recurring BSI, nephrotoxicity and 30-day mortality) were compared among patients treated with CAZ-AVI vs. other agents.

KPC-Kp surveillance in various samples was reported as well as the presence of invasive procedures such as: central venous catheter (CVC), mechanical ventilation, continuous venovenous hemofiltration (CVVH), and extra-corporeal membrane oxygenation (ECMO). Moreover, data on antibiotic treatment was described.

Statistical analysis

Demographic and clinical characteristics of patients were summarized through absolute frequencies and percentages for categorical variables and percentiles (mean and standard deviation) for the continuous variables. Categorical variables were tested against 30-day mortality or CAZ-AVI vs. SOC treatment using chi-square test, continuous variables were tested using Mann-Whitney test. The survival rate in CAZ-AVI vs. SOC was estimated by Kaplan–Meier analysis. The effects of different risk factors on 30-day mortality were tested using Cox models. Trends in antimicrobial consumption (expressed as monthly DDD/1000 PD) were investigated using an ARIMA model. Statistical analysis was run using SAS version 9.4 and SPSS version 28.

Definitions

- *Empirical therapy* was considered as any antibiotic treatment started before blood cultures collection and the communication of their results by the laboratory, administered for at least 48 hours after blood cultures collection.
- *Targeted therapy* was defined as the administration of any active antibiotic against KPC-Kp once the blood culture results were available to the clinicians
- *Combination therapy* was defined as at least two antibiotics administered ≥48 hours.
- *Appropriate therapy* was defined as the administration of at least one active *in vitro* antibiotic for ≤48 h from blood culture collection.
- *Nephrotoxicity* was considered as defined by modified KDIGO guidelines as a 1.5-fold increase in baseline serum creatinine levels within 7 days of treatment initiation.
- *CAZ-AVI* therapy was considered as any therapy with ceftazidime-avibactam administered ≥48 hours, including mono, combination, empiric and targeted therapy.

Results

Trends & susceptibility

There were 524 patients included. Dividing the period in half, antibiotic susceptibility decreased in the latest part. Sensitivity significantly decreased in gentamycin, tigecycline, and cotrimoxazole in the recent years ($p < 0.05$), Table 2. Fosfomycin sensitivity increased after 2018 from 26% to 39%, p=0.012, Figure 7.

Table 2: Change in antibiotic susceptibility after the introduction of CAZ-AVI

Antibiotic	2010-2018 N (%)	2018-2021 N (%)	Total	p-value
Amikacin	149 (37)	35 (33)	184 (40)	0.424
Gentamicin	315 (78)	52 (48.6)	367 (71.8)	**<0.001**
Tobramicin	76 (18.8)	14 (13)	90 (17.6)	0.212
Tigecycline	321 (79.5)	30 (28)	351 (68.7)	<0.001
Fosfomicin	107 (26.5)	42 (39.3)	149 (29.2)	**0.012**
Cotrimoxazole	109 (27)	21 (19.6)	130 (25.4)	**<0.001**
Colistin	260 (64.4)	71 (66)	331 (64.8)	0.061

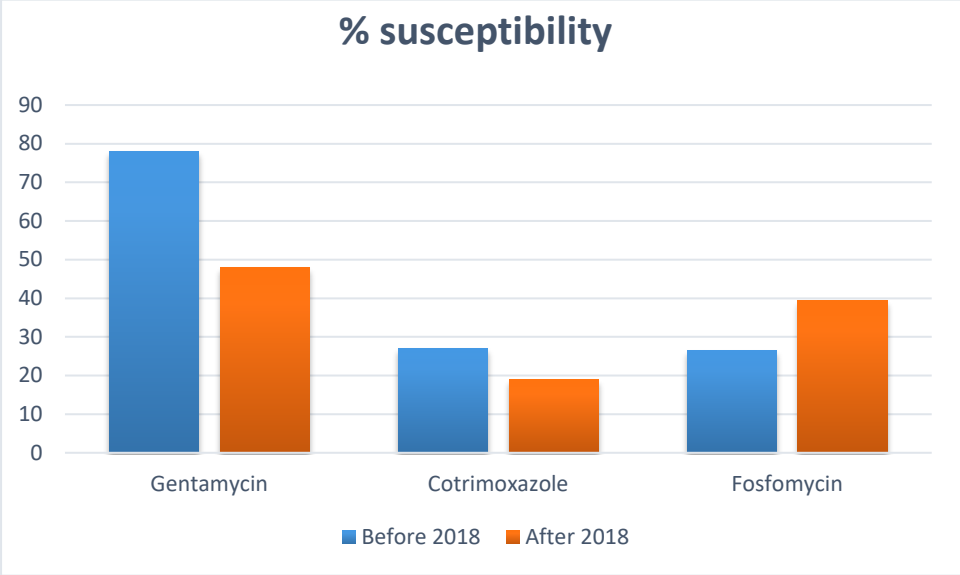


Figure 7: Percentage of susceptibility before and after 2018.

Baseline Characteristics of the Overall Population

We included 524 patients with KPC-kp BSI and reviewed their clinical charts. Overall, 327 patients (62.6%) were males and the mean age of the sample was 62 years with a standard deviation of ± 14 years. Patients admitted to medical ward, surgical ward, and intensive care unit (ICU) were 182 (34.9), 180 (34.5), and 160 (30.7), respectively. The median length of stay was 41 days (IQR 25), and the median time to KPC-Kp BSI onset from admission was 28 days (IQR 30). The mean Charlson comorbidity index was 4 (Table 3).

Congestive heart failure, was present in 130 (25%) patients; 126 patients (24%) had chronic kidney disease, 114 (22%) had chronic lung disease, 108 (21%) had diabetes mellitus, 64 (12%) were solid-organ transplant recipient, 52 (10%) had hematological malignancies, 49 (9%) had liver disease, 52 (10%) had hematological malignancies, 33 (6%) had metastatic malignancies, 23 (4.6%) had severe neutropenia, 2 (0.46%) had HIV infection.

At the time of the BSI onset, a KPC-Kp rectal swab was positive in 276 (55%) patients. The CVC was the most common probable source of KPC-Kp BSI in 118 patients (23%), the respiratory tract in 100 patients (20%), the abdomen in 36 patients (7%), the urinary tract in 40 patients (8%),

whereas in 149 patients (29%) the source of BSI was not identified. Source control was achieved in 30% of the patients.

MDR colonization, beyond MDR *K. pneumoniae*, was found in 33 (6%) patients. Most commonly, colonization with CR-*A.baumannii* was reported in 20 (4%) patients. Polymicrobial BSI was found in 47 (9%) patients. ESBL *E.coli* and VRE BSI were reported in 12 (2.5%) and 9 (2%), respectively. Empiric antibiotic treatment was administered to 368 (71%) patients and it was appropriate in 182 (48%) of them. Targeted treatment was given to 347 (67%) patients.

Significant variables for 30-day mortality

Older age was significantly associated with 30-day mortality with a mean of 65 and 61 years for dead and alive patients (p=0.01), respectively. A significant higher Charlson score was reported in patients who died, 4 vs. 3 for dead and alive patients (p= 0.02), respectively. Congestive heart failure was significantly associated with 30-day mortality, 31% and 22% for dead and alive patients (p=0.01), respectively. The presence of an invasive device significantly increased the risk of 30-day mortality ($p < 0.05$) in: CVC (91% vs. 83%), mechanical ventilation (65% vs. 44%), CVVH (28% vs. 13%) and ECMO (13% vs. 5%) in dead and alive patients, respectively. Source control was significantly higher in patients who survived on day 30 vs. those who didn't 149 (30%) vs. 35 (19%), p= <0.001, respectively. A concomitant BSI with *P.aeruginosa* was significantly higher in dead patients 5 (2.6%) vs 1 (0.3%) in alive patients on day 30 (p=0.029); Table 3. Seven-day nephrotoxicity in colistin and aminoglycoside treatments was significantly associated with mortality (p=0.002), Figure 9.

Table 3: Patient characteristics on 30-day mortality

Variable	Alive on day 30 N= 329 (62.7)	Dead on day 30 N=195 (37.2)	Total N=524 (100)	p-value
I. Demographics				
Gender:				
Male	209 (63.9)	118 (60.5)	327 (62.6)	
Female	118 (36.1)	77 (39.5)	195 (37.4)	0.437
Age	61.4 ± 15.2	64.6 ± 14	62 ± 14	**0.010**
Ward:				0.350
• **Medical ward**	119 (36.4)	63 (32.3)	182 (34.9)	
• **Surgical ward**	115 (35.2)	65 (33.3)	180 (34.5)	
• **Intensive care unit**	93 (28.4)	67 (34.4)	160 (30.7)	
ICU vs. other wards	94 (28.7)	67 (34.4)	161 (30.8)	0.179
Length of stay	53 ± 31	30 ± 20	41 ± 25	**0.005**
II. Clinical course				
Comorbidities:				
• Congestive heart failure	70 (21.5)	60 (30.8)	130 (25)	**0.018**
• Chronic lung disease	63 (19.3)	51 (26.2)	114 (21.9)	0.068
• Liver disease	26 (8.0)	23 (11.8)	49 (9.4)	0.148
• Chronic Kidney Disease	72 (22.0)	54 (27.7)	126 (24.1)	0.143
• Metastatic malignancy	19 (5.8)	14 (7.2)	33 (6.3)	0.534
• Hematologic malignancy	29 (8.9)	23 (11.8)	52 (10.0)	0.280
• Diabetes mellitus	64 (20.4)	44 (23.3)	108 (21.5)	0.443
• Neutropenia	15 (4.8)	8 (4.2)	23 (4.6)	0.777
• SOT	42 (12.8)	22 (11.3)	64 (12.3)	0.588
• HIV	0 (0.0)	2 (1.0)	2 (0.4)	0.139
Surgery during stay:				
• Surgery other than abdominal	96 (30.9)	65 (34.4)	161 (32.2)	0.385
• Abdominal surgery	77 (24.8)	37 (19.6)	114 (22.8)	
Charlson score	3 ± 2.1	4 ± 2.3	4 ± 2	**0.028**
Invasive Procedures:				
• CVC	272 (83.2)	178 (91.3)	450 (86.2)	**0.009**
• Mechanical Ventilation	143 (43.7)	126 (64.6)	269 (51.5)	**<0.001**
• Urinary catheter	244 (46.5)	164 (31.2)	408 (77.8)	**0.013**
• ECMO	16 (4.9)	26 (13.3)	42 (8.1)	**<0.001**

Variable	Alive on day 30 N= 329 (62.7)	Dead on day 30 N=195 (37.2)	Total N=524 (100)	p-value
• Hemodialysis	21 (6.4)	28 (14.4)	49 (9.4)	**0.006**
• CVVH	41 (12.6)	54 (27.7)	95 (18.2)	**<0.001**
Possible source:				**<0.001**
• Respiratory	52 (16.4)	48 (26.1)	100 (20)	
• CVC	82 (25.9)	36 (19.6)	118 (23.6)	
• Urinary catheter	35 (11)	5 (2.7)	40 (8)	
• Intraabdominal	23 (7.3)	13 (7.1)	36 (7.2)	
• Multiple sites	23 (7.3)	13 (7.1)	36 (7.2)	
• Unidentified	85 (26.8)	67 (36.4)	152 (30.2)	
Source control	114 (36)	35 (18.9)	149 (29.7)	**<0.001**
III. Microbiological characteristics:				
Time to KPC BSI from admission	29.8 ± 33	26.4 ± 24	28 ± 30	0.825
KPC-Kp colonization	179 (57)	97 (51.3)	276 (54.9)	0.215
KPC-Kp in samples:				
• Respiratory	114 (34.9)	76 (39.0)	190 (36.4)	0.345
• Urinary	90 (27.4)	35 (17.9)	125 (23.9)	**0.014**
• Drainage	44 (13.5)	23 (11.8)	67 (12.8)	0.583
MDR Coloniztion:	21 (6.4)	12 (6.2)	33 (6.3)	0.903
• *A.baumannii*	11 (3.4)	9 (4.6)	20 (3.8)	0.471
• VRE	7 (2.1)	2 (1.0)	9 (1.7)	0.495
• ESBL	3 (0.9)	2 (1.0)	5 (1.0)	>0.99
Clostridium difficille	9 (2.8)	4 (2.1)	13 (2.5)	0.775
Polymicrobial BSI:	29 (8.9)	18 (9.2)	47 (9)	0.889
• P.aeruginosa	1 (0.3)	5 (2.6)	6 (1.1)	**0.029**
• VRE	5 (1.5)	4 (2.1)	9 (1.7)	0.733
• ESBL	9 (2.8)	3 (1.5)	12 (2.3)	0.549
• MRSA	5 (1.5)	0	5 (1.0)	0.163
• Candida	2 (0.6)	5 (2.6)	7 (1.3)	0.108
Post BSI:				
• MRSA	1(0.3)	0(0.0)	1(0.2)	>0.990
• Candidemia	4(1.2)	3(1.5)	7(1.3)	0.715
• CDI	5(1.5)	2(1.0)	7(1.3)	>0.99
General Combination	2 ± 1	2 ± 1	2 ± 1	0.255
Empiric therapy:	217 (66.6)	151 (77.8)	368 (70.8)	**0.006**
• Empiric therapy appropriate	110 (48.7)	72 (46.5)	182 (47.8)	0.670
• Days Empiric therapy	10 ± 9	10 ± 8	11 ± 10	0.438
• Combination empiric	1 ± 1	2 ± 1	2 ± 1	**0.003**
• Meropenem	106 (50.7)	77 (52.4)	183 (51.4)	0.757
• Amikacin	21 (10)	9 (6.2)	30 (8.4)	0.200

Variable	Alive on day 30 N= 329 (62.7)	Dead on day 30 N=195 (37.2)	Total N=524 (100)	p-value
• Tigecycline	61 (29.2)	56 (38.4)	117 (33)	0.071
• Colistin	40 (19.2)	31 (21.1)	71 (20)	0.666
• Piperacillin tazobactam	66 (31.6)	69 (46)	135 (37.6)	**0.005**
• Bactrim	11 (5.3)	8 (5.5)	19 (5.4)	0.937
• Fosfomycin	12 (5.7)	9 (6)	21 (5.8)	0.900
• Ceftazidime-avibactam	14 (6.5)	6 (4.1)	20 (5.5)	0.320
Targeted therapy:	236 (72.8)	111 (57.8)	347 (67.2)	**<0.001**
• Days Targeted Therapy	17 ± 14	9 ± 7	15 ± 13	**<0.001**
• Combination targeted	2 ± 1	2 ± 1	2 ± 1	0.320
• Meropenem	103 (46.2)	54 (50.9)	157 (47.7)	0.420
• Amikacin	23 (10.5)	8 (7.5)	31 (9.5)	0.402
• Tigecycline	119 (54.1)	74 (69.8)	193 (59.2)	**0.007**
• Colistin	65 (29.1)	47 (43.9)	112 (33.9)	**0.008**
• Gentamycin	103 (45.8)	47 (44.3)	150 (45.3)	0.806
• Ertapenem	29 (13.1)	7 (6.7)	36 (11)	0.082
• Bactrim	26 (11.8)	7 (6.7)	33 (10.1)	0.154
• Fosfomycin	33 (14.6)	14 (13.1)	47 (14.1)	0.710
• Ceftazidime-avibactam	59 (25)	22 (19.3)	81 (23.1)	0.236
CAZ-AVI duration				**0.053**
• **Up to 5 days**	11 (24)	1 (4.8)	12 (18)	
• **More than 5 days**	34 (75.6)	20 (**95**)	54 (81.8)	
Monotherapy	99 (30.7)	51 (27.1)	150 (29.4)	0.387
On-time therapy	197 (61.2)	117 (61.3)	314 (61.2)	0.986
KPC reoccurence	27 (8.2)	2 (1)	29 (5.5)	**<0.001**
7-day nephrotoxicity:				**<0.001**
• Nephrotoxicity	33 (17.7)	49 (39.8)	82 (26.5)	
• Acute renal failure at baseline or death before 7 days	42 (22.6)	36 (29.3)	78 (25.2)	
Time to death	57.7 ± 33	10 ± 8.2	21 ± 26	**<0.001**
In-hospital mortality	50 (15.2)	175 (89.7)	225 (43)	**<0.001**

Significant variables in CAZ-AVI group

Eighty-one patients (15.4%) received CAZ-AVI as an empiric and/or targeted therapy, whether mono or in combination. The length of stay in the CAZ-AVI group was significantly shorter than the SOC group; 44 ± 22 vs. 115 ± 89 days (p= 0.005), respectively. Patients in the CAZ-AVI group were significantly more often colonized with *A.baumannii* than in the SOC group; 13% vs. 2%

(p= <0.001), respectively. CAZ-AVI was used more in solid-organ transplant patients than other antibiotics 23% vs. 3.5%; p <0.001. It was also more significantly used in patients on hemodialysis 18 (19%) and colonized patients 65 (82%); p <0.001. In the univariate analysis, in-hospital mortality was significantly lower in the CAZ-AVI group 30% than in the SOC group 42% (p= 0.03). Similarly, thirty-day mortality was lower in the CAZ-AVI group 27% than in the SOC group 36%; although non-significant (p=0.116), (Table 4).

Table 4: Patient characteristics in any CAZ-AVI therapy vs. SOC

Variable	CAZ-AVI 81 (15.4)	SOC 269 (51.3)	Total 524 (100)	p-value
I. Demographics				
Gender:				0.520
Male	63 (67)	224 (63.5)	287 (64.2)	
Female	31 (33)	129 (36.5)	160 (35.8)	
Age	72 ± 13	58 ± 14	62 ± 14	0.060
Ward:				0.105
• Medical ward	23 (24.5)	125 (35.4)	148 (33.1)	
• Surgical ward	36 (38.3)	126 (35.7)	162 (36.2)	
• Intensive care unit	35 (37.2)	102 (28.9)	137 (30.6)	
ICU vs. other wards	36 (38.3)	102 (28.9)	138 (30.9)	0.079
Length of stay	44 ± 22	115 ± 89	79 ± 55	**0.005**
II. Clinical course				
Comorbidities:				
• Congestive heart failure	25 (26.9)	73 (20.7)	98 (22)	
• Chronic lung disease	26 (28)	68 (19.3)	94 (21.1)	0.200
• Liver disease	11 (25.6)	32 (9.1)	43 (9.6)	0.442
• Chronic Kidney Disease	27 (28.7)	83 (23.5)	110 (24.6)	0.297
• Metastatic malignancy	4 (4.3)	21 (5.9)	25 (5.6)	0.623
• Hematologic malignancy	6 (6.4)	38 (10.8)	44 (9.8)	0.205
• Diabetes mellitus	18 (22.8)	74 (21.1)	92 (21.4)	0.739
• Neutropenia	1 (1.3)	16 (4.6)	17 (4)	0.333
• Solid Organ Transplant	22 (23.2)	36 (3.5)	58 (12.9)	**<0.001**
• HIV	0	2 (0.6)	2 (0.6)	> 0.990
Surgery during hospitalization				0.390
• Surgery not abdominal	19 (25)	115 (32.8)	134 (31.4)	
• Abdominal surgery	20 (26.3)	77 (21.9)	97 (22.7)	
Charlson score	4.7 ± 2	4.5 ± 2	3.6 ± 2	0.884

Variable	CAZ-AVI 81 (15.4)	SOC 269 (51.3)	Total 524 (100)	p-value
Invasive Procedures:				
• CVC	7 (7.4)	53 (15)	60 (13.4)	**0.056**
• Mechanical Ventilation	50 (53.2)	178 (50.4)	228 (51)	0.633
• Urinary catheter	67 (72)	278 (78.8)	345 (77.4)	0.169
• ECMO	8 (8.6)	26 (7.4)	34 (7.6)	0.689
• Hemodialysis	18 (19.1)	20 (5.7)	38 (8.5)	**<0.001**
• CVVH	14 (15.1)	63 (17.8)	77 (17.3)	0.526
Possible source:				0.798
• Respiratory	17 (21.8)	74 (21.1)	91 (21.2)	
• CVC	22 (28.2)	78 (22.8)	100 (23.3)	
• Urinary catheter	8 (10.3)	29 (8.3)	37 (8.6)	
• Intraabdominal	7 (9)	41 (11.7)	48 (31)	
• Multiple sites	5 (6.4)	26 (7.4)	31 (7.2)	
• Unidentified	19 (24.4)	103 (9.3)	122 (28.4)	
Source control	26 (32.9)	105 (29.9)	131 (30.5)	0.785
III. Microbiological characteristics:				
Time to KPC BSI	24 ± 16	27 ± 20	28 ± 30	0.068
KPC-Kp colonization	65 (82.3)	159 (45.3)	224 (52.1)	**<0.001**
KPC in samples:				
• Respiratory	37 (39.4)	118 (33.4)	155 (34.7)	0.283
• Urinary	24 (25.3)	91 (25.8)	115 (25.7)	0.919
• Drainage	8 (8.5)	51 (14.4)	59 (13.2)	0.131
MDR Coloniztion:	12 (12.8)	15 (4.2)	27 (6)	**0.002**
• *A.baumannii*	12 (12.8)	7 (2)	19 (4.3)	**<0.001**
• VRE	1 (1.1)	6 (1.7)	7 (1.6)	> 0.99
CDI pre	5 (5.3)	8 (2.3)	13 (2.9)	0.118
Polymicrobial BSI:	5 (5.3)	36 (10.2)	41 (9.2)	0.145
• *P.aeruginosa*	0	5 (1.4)	5 (1.4)	0.589
• VRE	1 (1.1)	6 (1.7)	7 (1.6)	> 0.99
• ESBL	2 (2.1)	9 (2.5)	11 (2.5)	> 0.99
• MRSA	0	4 (1.1)	4 (1.1)	0.302
• Candida	1 (1.1)	5 (1.4)	6 (1.3)	> 0.99
Post BSI:				
• Candedemia	3 (3.2)	4 (1.1)	7 (1.6)	0.158
General combination	1 ± 1	2 ± 1	2 ± 1	0.538

Variable	CAZ-AVI 81 (15.4)	SOC 269 (51.3)	Total 524 (100)	p-value
Empiric therapy:	52 (55.9)	250 (71)	302 (67.9)	**0.006**
• Empiric therapy appropriate	32 (56.1)	115 (45.5)	147 (47.4)	0.144
• Empiric therapy (days)	7 ± 9	13 ± 10	11 ± 10	0.815
• Combination empiric (drugs)	1 ± 1	2 ± 1	2 ± 1	0.696
Targeted therapy:	84 (92.3)	263 (74.5)	347 (78.2)	**<0.001**
• Days Targeted Therapy	8 ± 4	10 ± 7	15 ± 13	0.187
• Combination targeted	1 ± 1	2 ± 1	2 ± 1	0.439
On-time therapy	63 (70.8)	214 (61)	277 (63)	0.087
Time to death	17 ± 10	25 ± 12	21 ± 26	0.449
In-hospital mortality	28 (29.5)	147 (41.6)	175 (39.1)	**0.031**

Cox Model for 30-day mortality & Kaplan Meier survival analysis

In the overall Cox model for 30-day mortality, the proportional risk was respected for all covariates except for targeted therapy which was adjusted by separating the cases who received targeted treatment and those who didn't. The two separate Cox models were then run. CAZ-AVI therapy was a protective factor for mortality in both models, HR: 0.59 (95% 0.27-1.26); p=0.30. A respiratory source for KPC-Kp BSI reached near significance as a risk factor for mortality, HR: 1.6 (95% CI 1.05-2.68); p= 0.06. KPC-Kp colonization and isolation in urine tended to be as a protective factor against mortality: HR: 0.81 (95% CI 1.48-4.36); p=0.88 and HR: 0.27 (95% CI 0.10-0.75); **p=0.04** (Table 5).

In the Kaplan-Meier survival analysis, mortality was significantly higher in the SOC group compared to the ceftazidime-avibactam group (p=0.0151). The survival rate in SOC and CAZ-AVI was 55% vs. 70% at day 30, respectively, (Figure 8).

Table 5: Overall and adjusted targeted therapy Cox model

Variable	Overall			Targeted Therapy		
	HR	95% HR CI	p-value	HR	95% HR CI	p-value
CAZ-AVI therapy	0.594	0.279-1.262	0.3039	0.513	0.209-1.262	0.2470
Congestive heart failure	1.218	0.732-2.028	0.9169	1.114	0.52-2.388	0.7835
CHARLSON score	1.126	0.99-1.282	0.4574	1.293	1.062-1.574	0.1470
CVC	2.074	0.779-5.522	0.6440	2.333	0.343-15.857	0.9231
Respiratory source	1.679	1.052- 2.682	**0.0649**	1.395	0.785-2.478	**0.0603**
KPC in urine	0.534	1.052-2.682	0.0946	0.278	0.102-0.761	**0.0466**
Empiric therapy	1.573	0.186-1.295	0.3400	1.716	0.848-3.475	0.2709
KPC colonization	0.815	1.487-4.368	0.8870	1.297	0.606-2.776	0.3206

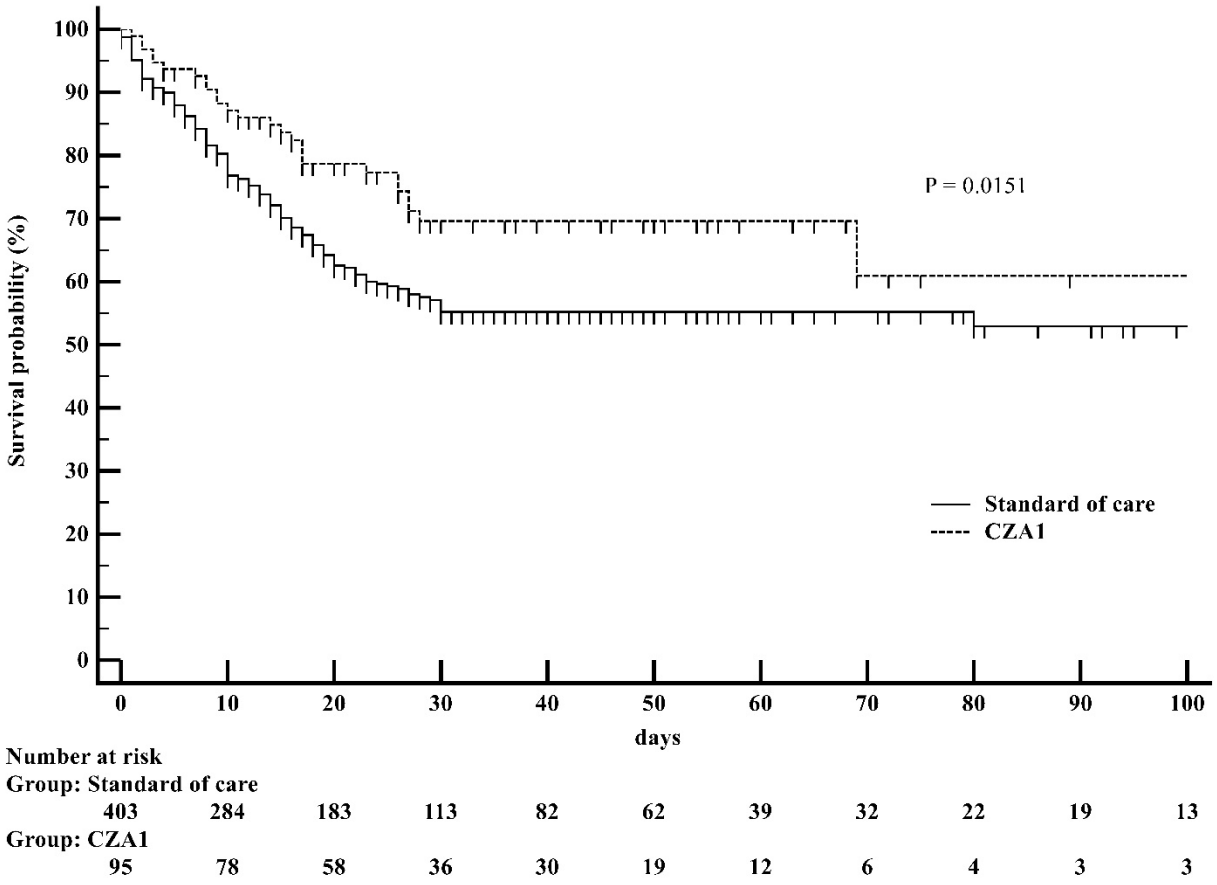


Figure 8 Kaplan-Mier survival analysis in CAZ-AVI vs. SOC

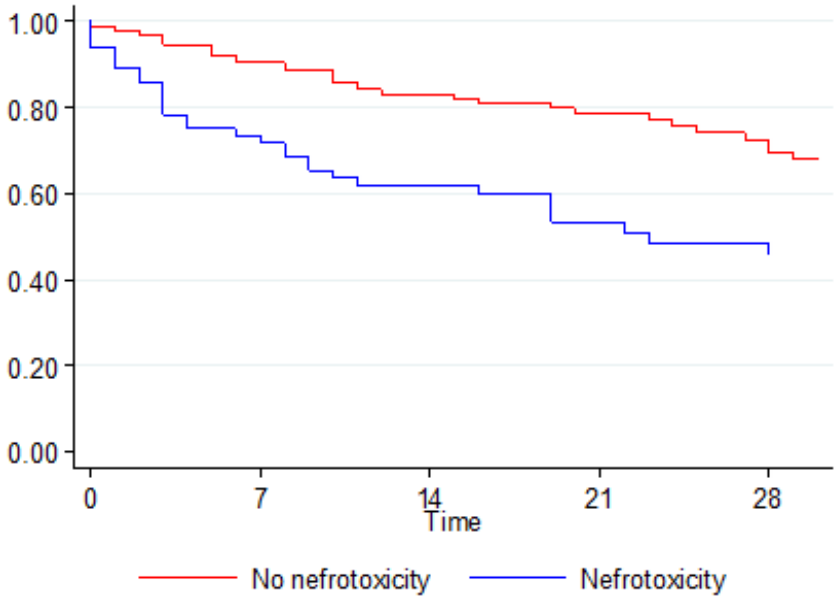


Figure 9: Colistin/AG nefrotoxicity and in-hospital survival (p= 0.002).

Antibiotic Use

Carbapenem use significantly decreased by -53.16 DDD/1,000 patient days/month (p <.001) during the observed period for antibiotic use. Colistin and ceftazidime-avibactam showed a slight increase of 92.2 and 6.3 DDD/1,000 patient-days/month, respectively, (Table 6, Figure 10).

Table 6: Time series analysis for antibiotic use

Antibiotic	Estimate	p-value
Carbapenems	1924.909	**<.001**
• Trend	-53.165	
Ceftazidime-avibactam	88.299	**<.001**
• Trend	6.349	
Colistin	193.632	0.486
• Trend	92.227	

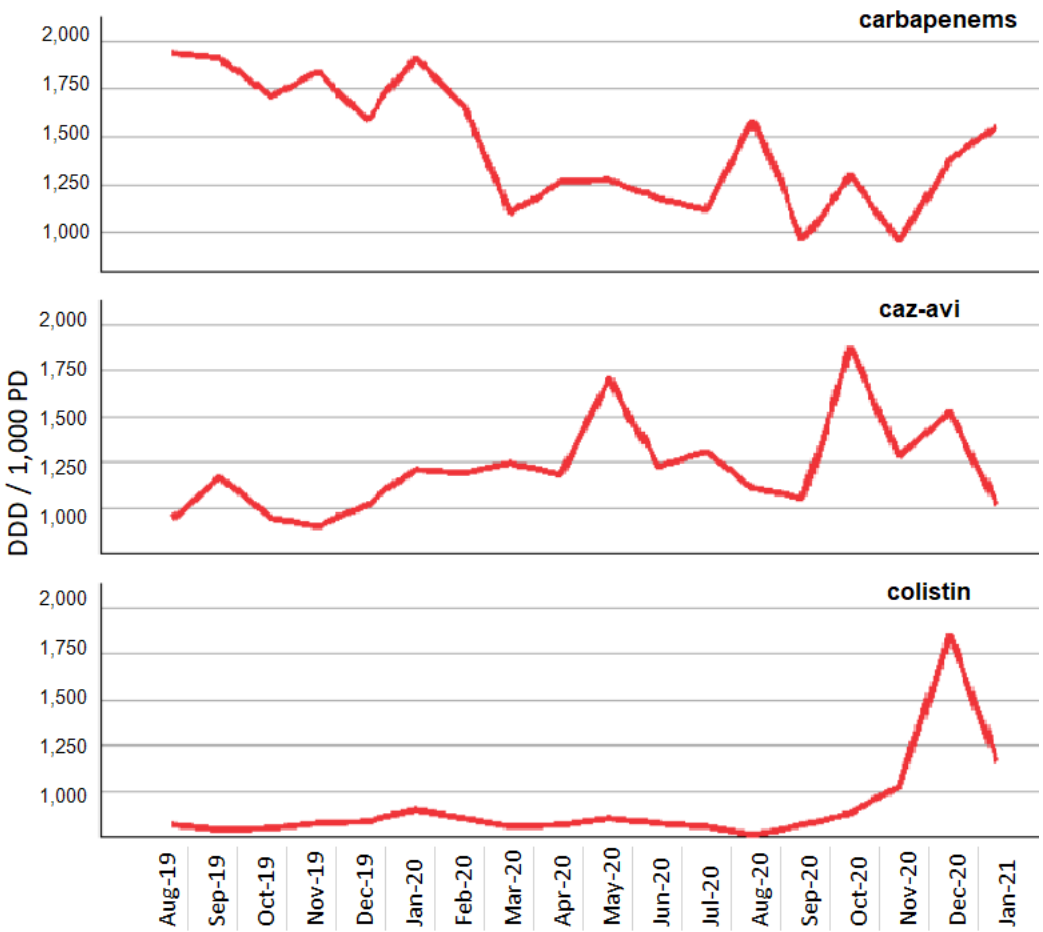


Figure 10 Time series anaylysis for antibiotic consumption (DDD/1,000 patient days)

Discussion

KPC-Kp infections are a major threat among patients admitted to acute care and long term hospitals, with a mortality rate ranging from 20% to 70%. (29–33). Usually, KPC-Kp BSI occur in hospitalized patients with several comorbidities, as also confirmed in our setting in which 63% of all KPC-Kp BSI were observed in patients ≥60 years old.

The significant increase in resistance observed in our isolates is also confirmed by Zhang et al. where they demonstrated an increased resistance of KPC in antibiotics mainly in: carbapenems, pip- tazo, amikacin in a large pool of KPC-Kp isolates between 2017 and 2020 (34). Interestingly, fosfomycin sensitivity was significantly restored after 2018 with an increase in sensitivity.

KPC-Kp colonization has been recognized as a predictor of KPC-Kp infections; nonetheless, it does not seem to be a predictor of mortality itself (35,36). Even in our cohort, 55% of the patients were colonized by KPC-KP, but mortality did not differ between the groups. An explanation for this result could be the early administration of appropriate empirical therapy to colonized patients. In parallel, the rest of the cases (45%) occurred in patients with unknown colonization suggesting the need of clinical suspicion and maintaining standard precautions in a high endemic setting.

An isolation of KPC-Kp in urine was a protective factor against mortality. A reason for this could be: treatment in real-time due to early symptoms of urinary infections. In addition, urinary tract infections are associated with low mortality since source control is feasible and most antibiotics are effective since renally excreted. On the other hand, we observed that a respiratory source for KPC-Kp BSI could be risk factor for mortality. A justification could be the fact that it cannot be controlled or removed like catheters, if it's the source of infection. Thus, such a starting point could result in a complicated progression of the case.

Identifying the source of infection in presentations of sepsis and achieving source control are cornerstones of therapy as highlighted by the Surviving Sepsis Campaign (SSC). This requires not only rapid administration of broad spectrum antibiotics, but also a thorough investigation to determine the source (37). Source control includes performing all physical measures in patients with septic shock to eliminate sources of infection, to control contamination, and to restore the patients' anatomy and function (38). In 2016, the SSC recommended the target time (no more than 6–12 h after the diagnosis of sepsis or septic shock) of the performance of source control was sufficient for most cases. It was a strong recommendation, but the grading system of the evidence level was not specific and the evidence of the effectiveness of performing source control is lacking (39).

In our study, long hospital stay and presence of CVC were risk factors for mortality, as already demonstrated in CVC-related bloodstream infections and similar studies (40–44). The Kaplan mier analysis confirmed that the administration of CAZ-AVI increases the survival rate by 70% on day 30. CAZ-AVI continues to demonstrate its effect against mortality as reported previously (10).

Time series analysis demonstrated a decrease in carbapenem use. A similar decrease was reported previously despite the increase in MDR isolates (45). This could partly be a positive outcome of antimicrobial stewardship programs as well as the introduction of new drugs.

Attention should be drawn to the increase of colistin use in our data that could continue over time. Sparing colistin because of significant nephrotoxicity that we have documented is essential and supports the use of CAZ-AVI as an alternative with higher tolerability. More time is needed to know the definitive effect of CAZ-AVI on the consumption of other antibiotics. Our results outline the importance of early treatment with CAZ-AVI in an endemic setting and in patients with risk factors.

The strength of this study is that it well reflects real-world KPC-Kp BSI cases in a large Italian hospital and includes a wide sample across a decade. Among the limitations there are the single-setting and retrospective nature of the study where incomplete clinical records were faced occasionally. In addition, our data lacked a clinical severity assessment scores such as Sequential Organ Failure Assessment (SOFA), Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) or Pitt Bacteremia Score at KPC-Kp BSI presentation, because of the various time periods, as well as a confounding effect of educational stewardship activities progressively introduced.

Conclusions

In conclusion, we reported here ten years of experience of KPC-Kp infections. The overall resistance rates of MDR *Klebsiella pneumoniae* to antibiotics increased in our setting, giving a significant challenge to control *K. pneumoniae* related infections. Invasive procedures, prolonged hospital stays, and colonization increase the risk of KPC-Kp BSI calling for effective source control and appropriate empiric therapy. New drugs, mainly ceftazidime-avibactam, are available now for the treatment of these infections, and have significantly contributed to improving patient outcome in this setting. Therefore, identifying changes in the resistance profile should be an alarm for healthcare institutions and government agencies to focus efforts on investigation and control, and to support and maintain a stewardship program and infection control practices.

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