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FULL PAPER

Pathogens distribution and antimicrobial resistance pattern of blood stream infections in Southern Italian hospital, 2016-2021 surveillance

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SUMMARY

Bloodstream infections (BSIs) monitoring and antibiotic susceptibility assumes a priority relevance to guide antibiotic treatment strategies and prevention programs. The study aims to identify the most common causative agents of BSIs, seasonal distribution and variation of antimicrobial susceptibility rates during a 6-year period in a in a Level II EAD Southern Italian Hospital. The study was conducted from 2016 to 2021 at Hospital of National Relevance (AORN) Sant'Anna and San Sebastiano, Caserta, Campania Region in Italy. BSIs Gram positive causative pathogens were *S. aureus* and *Enterococci*; Gram negative pathogens were *E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii*. Seasonal distribution showed the main incidence in April-June for Gram positive BSIs pathogens and in July-September months for Gram negative. Antimicrobial susceptibility fluctuations rates from 2016-2018 to 2019-2021 highlighted a significant decrease in *S. aureus* oxacillin resistance rates. *Enterococci* incremented resistance was reported for gentamicin. Gram negative pathogens antimicrobial susceptibility revealed decreased carbapenem-resistance rates for *K. pneumoniae* (-21.5%) and *P. aeruginosa (-19.7%)*. *A. baumannii* colistin resistance had a significant increase in 2019-2021. *K. pneumoniae* and *E. coli* isolates showed decreased trend of extended-spectrum β-lactamase-producing (ESBL) and carbapenem-resistant (CRE) resistance profiles. Our finding reflects the success of our Istitution regarding antimicrobial stewardship program and highlights the need to know the trend of antimicrobial resistance characterization focus on local pathogens' profile. In this way, in conjunction with infection control strategies, il could be possible to constantly reduce the spread of Multi Drug Resistant organisms.

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INTRODUCTION

Bloodstream infections (BSIs) are a major cause of illness and death worldwide. BSIs incidence has increased over time, associated with healthcare costs and extended hospital stay (Rhee *et al.*, 2020). BSIs represent 40% of cases of community-acquired and hospital-acquired sepsis and septic shock and approximately 20% of Intensive Care Units-acquired cases (Timsit *et al.*, 2020). Rising incidences are related to an aging population, increasing prevalence of underlying conditions, and invasive procedures (Spaulding *et al.*, 2019). Despite advances in antimicrobial drug therapy and prevention strategies, BSIs are strictly connected to increases in antimicrobial resistance and multidrug-resistant (MDR) microorganisms (Dhingra *et al.*, 2020). Recent studies have also reported BSI mortality in patients hospitalized with COVID-19 (Cona *et al.*, 2021). Incidence and outcome of BSIs in Italy (Barchitta *et al.*, 2019) were analyzed but most of these reports focus on selected hospitals or hospital units, a specific causative agent, or either healthcare/community-acquired BSIs in select patient populations (Alicino *et al.*, 2015; Bassetti *et al.*, 2020). We collected data from "AORN Sant'Anna and San Sebastiano" hospital and analyzed annual BSIs incidence, causative agents and outcomes over six years. The aim of this study was to evaluate the prevalence of main causative BSIs agents, seasonal distribution, and antimicrobial susceptibility profile focused on MDR strains trend.

Key words:
Bloodstream infections, antimicrobial resistance, extended spectrum β-lactamase-producing, carbapenem-resistant, Multi Drug Resistant.

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MATERIALS AND METHODS

Study design and data collection

From January 2016 to December 2021, we conducted a retrospective surveillance study on BSIs at

AORN Sant'Anna and San Sebastiano hospital, Caserta. The Province of Caserta is located in Campania, a Southern Italian region, with an approximate population of 900,000 inhabitants. It is a Level II EAD Hospital had 613 beds with 23 thousand admissions per year. Distribution of BSIs analysis included 4941 isolates collected from a total of 61,351 blood culture specimens. Patient records were reviewed for demographic and clinical data, including age, sex, hospital ward, isolated organisms, and associated antibiotic susceptibility profiles. Positive blood cultures were defined by growth of one or more microbes from a blood culture combined with clinical evidence of a systemic infection. For each patient, blood culture results were collated from two sets of one aerobic, one anaerobic, and one fungal blood culture bottle obtained from separate peripheral venipuncture and central venous catheter sites according to CDC guidelines. Multiple positive blood cultures with the same pathogen within 96 h were merged into one positive in the analyses. If the pathogen was detected again after 96 h, a new "positive" was counted. Organisms commonly associated with contamination were included in positive blood culture numbers only if isolated from 2 blood culture sets obtained from separate sites. The bottles were brought to the laboratory and incubated for up to 5 days in an automated instrument.

Bacterial identification and antimicrobial susceptibility

Blood cultures were performed using the BACTEC system (Becton Dickinson Diagnostic Instrument Systems, NJ, USA). When the growth index of a bottle was positive, broth aliquots were collected for standard identification studies. Positive blood cultures were further examined using Gram staining, and species identification was performed used matrix-assisted laser desorption/ionization- time of flight mass spectrometry (MALDI-TOF MS, Biomèrieux, Marcy l'Étoile, France), following single colony isolation on blood agar, MacConkey and Sabouraud Glucose agar medium (Becton Dickinson, NJ, USA), and incubated overnight at 37°C. Clinical specimens from patients were routinely submitted to the microbiology laboratory and antimicrobial susceptibility testing results were processed and recorded. Susceptibility tests were tested using VITEK-2 systems (VITEK MS, Biomèrieux, Marcy l'Étoile, France) and Phoenix System (Becton Dickinson, Franklin Lakes, NJ) automated systems. Automated instrumentation (Thermo Scientific™ Sensititre™) for determination of MICs in microdilution was used specifically for ceftazidime/avibactam, ceftolozane/tazobactam, colistin and piperacillin/tazobactam. Further confirmation tests were performed for MDR organisms including NG-Test CARBA 5 tests (NG Biotech, Guipry, France) and Xpert CARBA-R (Cepheid, Sunnyvale, CA, USA) for carbapenemase producer organisms, NG-Test CTX-M (NG Biotech, Guipry, France) for ESßL rapid detection and Vancomycin E-test or Xpert vanA/vanB (Cepheid, Sunnyvale, CA, USA) for vancomycin-resistant enterococcus (VRE). BSIs pathogens testing and identification were carried out according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines along with breakpoint interpretation of the tested antibiotics.

Statistical analysis

Time changes in pathogen distribution by season and in antimicrobial susceptibility were determined by Fisher's exact test using IBM SPSS 22.0 for IOS (SPSS Chicago, IL, USA). P values were calculated using a chi-square test with significance level at ≤0.05.

RESULTS

Study population and BSIs pathogens distribution

From January 2016 to December 2021, 4941 positive blood culture isolates were collected from patients admitted at AORN Sant 'Anna and San Sebastiano hospital. Study population baseline characteristic showed 65.7% male with average age of 63.3 years. A total of 27% of the patients were admitted in the Intensive Care Unit (ICU) followed by Cardiac Surgery Intensive Care Units and Cardiological wards, 11.1%

Table 1 - *BSI causative pathogens at AORN Sant 'Anna e San Sebastiano.*

Pathogen	*Total BSI (%)*
Gram positive, n (%)	3045 (61,6%)
Coagulase-negative *S taphylococci*	1184 (38,9%)
Staphylococcus aureus	726 (23,8%)
Enterococcus sp.	438 (14,4%)
Enterococcus faecalis	327 (10,7%)
Enterococcus faecium	201 (6,6%)
Streptococcus sp.	148 (4,7%)
Others	21 (0,9%)
Gram negative, n (%)	1896 (38.4%)
Klebsiella pneumoniae	472 (24,9%)
Escherichia coli	451 (23,8%)
Acinetobacter baumannii	374 (19,7%)
Pseudomonas aeruginosa	305 (16,1%)
Enterobacter cloacae complex	96 (5,1%)
Proteus mirabilis	90 (4,7%)
Serratia sp.	43 (2,3%)
Stenotrophomonas maltophilia	22 (1,1%)
Providencia sp.	16 (0,8%)
Morganella morganii	12 (0,6%)
Bulkholderia sp.	8 (0,4%)
Others	4 (0,4%)
Citrobacter sp.	3 (0,1%)

and 10.4 % respectively. BSIs pathogens isolates are shown in *Table 1*. Gram positive isolates (61.6%) exceeded Gram negative (38.4%). Coagulase negative *Staphylococci* (CONS) were in high proportion, followed by *S. aureus* (28.8%) and *Enterococci* (14.4%). Gram negatives were 23.8% *E. coli*, 24.9 % *K. pneumonia*, 19.7% *A. baumannii* and 16.1% *P.aeruginosa* strains.

Distribution of pathogens in different age groups.

Figures 1a e 1b show BSI pathogens distribution in different age groups. Gram positives showed a gradual increase in the 11-20 and 61-70 age groups with a peak in age group 71-80 for *Enterococci* and *S. aureus* (26% and 27.5%, respectively). CONS showed a gradual decrease in the 71-80 and 81-90 age groups, while they were more present (10%) in the 0-10 group (*Figure 1a*). Regarding Gram negative isolates, gradual increases with advancing age were reported (11-20 to 71-80 age groups). *A. baumanii*, *P. aeruginosa*, and *K. pneumoniae* showed a linear trend, while fluctuating trends were reported for *E. coli* with increased peaks in the 0-10, 31-50, 61-70, and 81-90 age groups. Figure 1b reports A. *baumannii* isolates in the 51-60 range, *K. pneumoniae* isolates in the 61-70 range and *P. aeruginosa* in the 71-80 range. Finally, *E. coli* isolation rates for the 0-10, 31-40, and 81-90 age groups were higher than other gram-negative bacteria (*Figure 1b*).

BSIs pathogens seasonal distribution

BSIs seasonal distributions are shown in Figures 2a and 2b. *S.aureus* (30%, 27.2%), *Enterococci* (26.7%, 26.6%) and CONS (28.7%, 24.2%) percentages were higher from April to June and from October to December. All Gram-positive isolates showed a similar trend across the seasons (*Figure 2a*). *E. coli* isolation rates were stable, whereas *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* isolates, in the four quarters, were statistically different ($p<0.05$). *P. aeruginosa* and *K. pneumoniae* were more frequently isolated

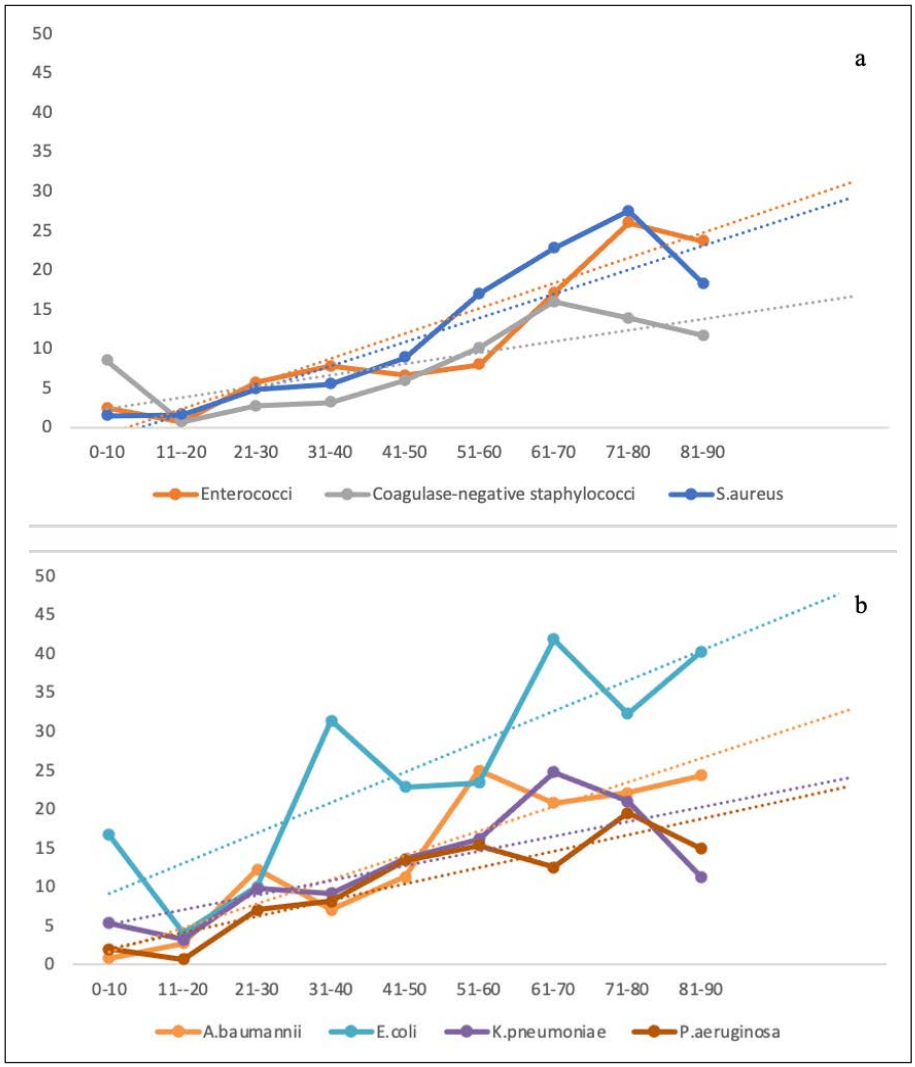

Figure 1 - *Distribution of main gram positive (a) and gram negative (b) BSIs pathogens with age.*

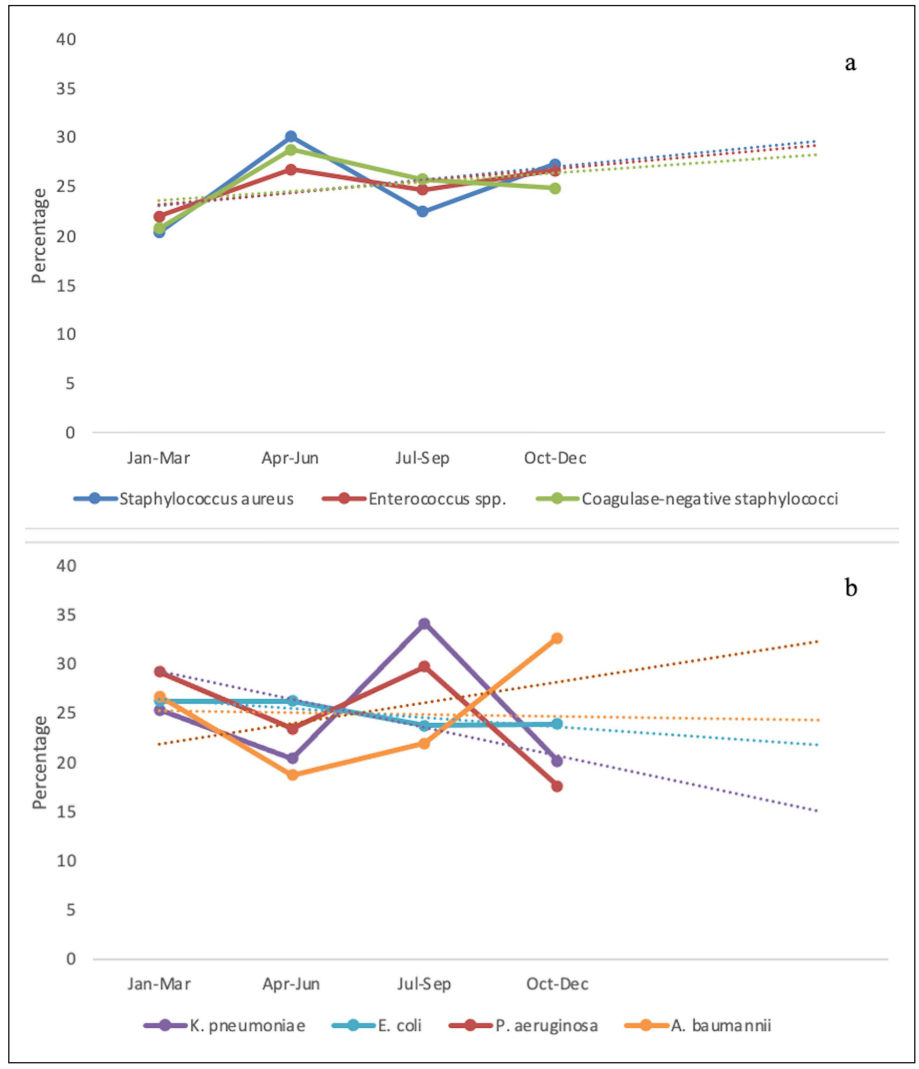

Figure 2 - *Gram positive (a) and Gram negative (b) BSIs pathogens seasonal distribution.*

in the first and third quarter than were *A. baumannii* and *E. coli*. *A. baumannii* were isolated commonly from October to December (*Figure 2b*). The BSI seasonal distribution revealed a reverse distribution of isolates: April-June for Gram positive and July-September for Gram negative.

Antimicrobial susceptibility time changes in pathogens.

We analyzed antimicrobial susceptibility rate fluctuation between 2016-2018 and 2019-2021 (*Table 2*). The main Gram positive and Gram-negative pathogens isolated were reported. *S. aureus* and CONS erythromycin resistance rates increased significantly during the study periods ($p<0.05$). CONS methicillin resistance decreased significantly ($p<0.05$), while *S. aureus* methicillin resistance (MRSA) was slightly reduced. Resistance rates of *E. faecalis* and *E. faecium* to all agents tested did not vary significantly over time, except for gentamicin high concentration, which increased in *E. faecium* from 52.8% in 2016-2018 to 62.2% in 2019-2021 but decreased in *E. faecalis* isolates (-2.9%). Our data also reported *Enterococci* Vancomycin Resistant (VRE) zero percentages during the 2019-2021 period (*Table 3a*). High resistance rates for all the antibiotics tested have been reported in *A. baumannii* strains. Worrying data have been reported for colistin resistance, which increased significantly from 8.7% in 2016-2018 to 18.7% in 2019-2021. Therefore, for *E. coli,* colistin and ciprofloxacin resistance rates decreased significantly ($p<0.05$) compared to the increase in carbapenems resistance percentages. Ciprofloxacin and carbapenem percentages decreased for *K. pneumoniae* and *P. aeruginosa* isolates ($p<0.05$) (*Table 2b*).

Trends of multi-drug resistant (MDR) strains

The frequency of methicillin-resistant *S. aureus* (MRSA), extended spectrum β lactamase (ESBL) *E. coli*, and *K. pneumoniae* and carbapenem-resistant *K. pneumoniae* (CRE) frequency was analyzed over the study period (*Figure 3*). The proportion of MRSA

Table 2 - *Antimicrobial susceptibility rates fluctuations in main pathogens from 2016-2018 to 2019-2021.*

Gram positive a)

Pathogens	Antibiotic agents	Resistance rate (%)			Change (%)	p-value
		Pooled	2016-2018	2019-2021		
S. aureus (n=726)	*ERY*	46,4	41,9	47,9	+6	0,075*
	GM	8,5	8,6	8,5	-0,1	0,756
	TE	8,8	6,2	1,7	-4,5	0,399
	VA	1,1	1,9	0,8	-1,1	0,426
	TEC	2,6	4,5	8,2	+3,7	0,190
	DAP	2,6	3,0	3,9	+0,9	0,867
	OXA	42,7	43,1	38,6	-4,5	0,347
	LNZ	3,3	4,9	5,9	+1	0,653
CoNS (n=1184)	*ERY*	65,8	64,9	76,6	+11,9	0,069*
	GM	56,4	55,5	57,7	+2,2	0,543
	DAP	2,8	2,9	2,4	-0,5	0,971
	VA	0,2	0,2	0,0	-0,2	0,1
	TEC	27,7	23,5	23,9	+0,4	0,896
	TE	24,3	22,3	21,6	-1,0	0,882
	OXA	67,4	75,3	66,3	-9,0	0,096*
	LNZ	3,8	3,9	2,3	-1,6	0,904
E. faecalis (n=337)	*GENH*	44,7	46,3	43,4	-2,9	0,565*
	TEC	0,0	0,0	0,0	–	–
	LNZ	2,2	2,5	2,0	-0,5	0,975
	VA	0,6	1,3	0,0	-1,3	0,904
	AMP	3,4	1,3	5,1	+3,8	0,702
E. faecium (n=201)	*GENH*	57,5	52,8	62,2	+9,4	0,132
	TEC	4,1	8,3	0,0	-8,3	0,234
	LNZ	0,0	0,0	0,0	–	–
	VA	0,0	0,0	0,0	–	–
	AMP	91,8	100	83,8	-16,2	0,045*

Gram negative b)

Pathogens	Antibiotic agents	Resistance rate (%)			Change (%)	p-value
		Pooled	2016-2018	2019-2021		
A. baumannii (n=374)	*AMK*	96,2	97,6	95,6	-2	0,756
	GM	95,1	97,1	93,4	-3,7	0,190
	MEM	96,6	97,8	95,6	-2,2	0,564
	CIP	98,5	99,3	96,2	-3,1	0,390
	SXT	94,2	96,1	95,6	-0,5	0,745
	COL	7,1	8,7	18,7	+10	0,059*
E. coli (n=451)	*AMK*	1,7	1,6	1,9	+0,3	0,823
	GM	18,3	19,8	16,8	-3,0	0,732
	CIP	57,4	62,6	52,2	-10,4	0,039*
	AMC	41,8	40,7	42,9	+2,2	0,782
	MEM	0,6	0,0	0,6	+0,6	0,845
	IMI	0,5	0,5	0,6	+0,1	0,987
	COL	12,8	14,3	0,6	-13,7	0,067*
	CTX	29,6	29,0	29,8	+0,8	0,897
	CAZ	25,8	28,0	23,6	-4,4	0,564
	TZP	16,9	17,0	16,8	-0,2	0,972
P. aeruginosa (n=305)	*AMK*	20,1	26,9	11,3	-15,6	0,058*
	GM	29,1	37,2	21,3	-15,9	0,065*
	CIP	43,3	56,4	41,3	-15,1	0,053*
	AMC	63,8	61,7	60	-1,7	0,319
	MEM	29,1	41,0	21,3	-19,7	0,053*

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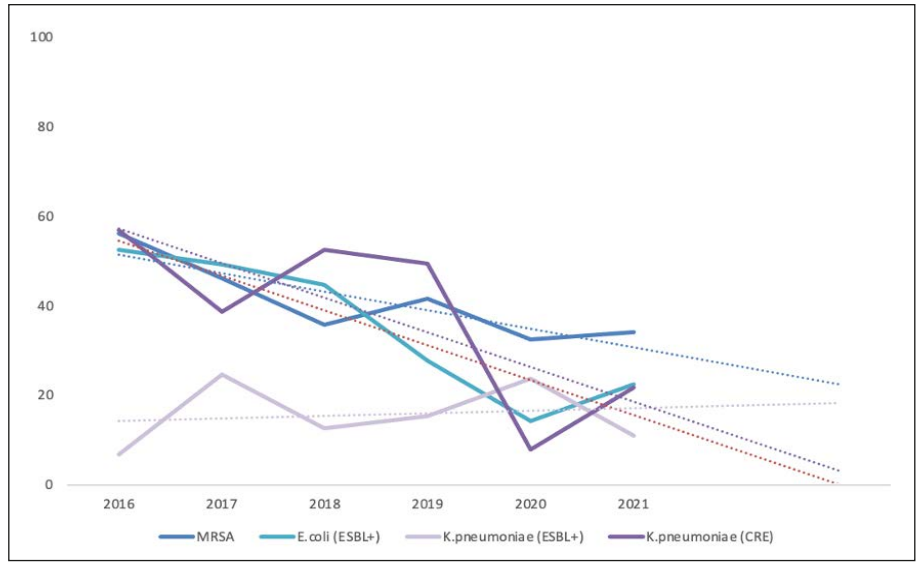
Pathogens	*Antibiotic agents*	*Resistance rate (%)*			*Change (%)*	*p-value*
		Pooled	*2016-2018*	*2019-2021*		
	IMI	41,8	64,1	31,3	-32,8	0,078
	COL	13,4	12,8	5	-7,8	0,449
	FOS	32,2	31,5	33	+1,5	0,423
	FEP	14,8	34,6	27,5	-7,1	0,435
	CAZ	15,7	20,5	26	+5,5	0,301
	C/T†	21,3	–	21,3	–	–
	CZA†	20	–	20	–	–
	TZP	24,6	30,6	15	-15,6	0,057*
K. pneumoniae (n=472)	*AMK*	11,2	13,5	8,5	-5	0,893
	GM	32,1	30,9	33,3	+2,4	0,196
	CIP	61,5	71,5	50,4	-21,1	0,019*
	AMC	75,8	80,7	70,9	-9,8	0,136
	MEM	29,9	40,6	19,1	-21,5	0,020*
	IMI	62,8	47,8	14,9	-32,9	0,031*
	COL	22,8	30,4	5,7	-24,7	0,057*
	FOS	31,9	32,1	29,8	-2,3	0,231
	FEP	49,4	53,6	47,5	-6,1	0,277
	CTX	54,2	55,1	50,4	-4,7	0,978
	CAZ†	55,5	57,4	50,5	-6,9	0,269
	C/T†	27,7	–	27,7	–	–
	CZA	2,1	–	2,1	–	–
	SXT	28,3	28,1	28,4	+0,3	0,989
	TZP	35,0	35,7	35,5	-0,2	1,765

AMK, amikacin; AMP, ampicillin; CAZ, ceftazidime; CIP, ciprofloxacin; FEP, cefepime; CTX, cefotaxime; GM, gentamicin; IMI, imipenem; MEM, meropenem; FOS, fosfomycin; C/T, ceftolozane/tazobactam; CZA, ceftazidime/avibactam; SXT, trimethoprim/sulfamethoxazole; TZP, piperacillin/tazobactam; OXA, oxacillin; VA, vancomycin; LNZ, linezolid; TEC, teicoplanin; ERY, erythromycin; TE, tetracycline; DAP, daptomycin; GENH, gentamicin-high.
*p value <0.05
†Data for 2016-2018 were not reported because this antimicrobial agent was not already used in our hospital practice.

isolates decreased from 56.1% to 34.1%. The *E. coli* ESBL isolates were significantly reduced from 52.4% in 2016 to 14.2% in 2020. The prevalence of *K. pneumoniae* CRE was 5.9% in 2020 compared to 2018 and 2019. Instead, *K. pneumoniae* ESBL strains decreased in 2018, 2019 and 2021 but not at a significant rate. Data on MDR strains isolated from BSIs at our hospital demonstrated low rates from 2019 to 2021 based on implemented antimicrobial stewardship strategies.

Figure 3 - *MDR trend percentages from 2016 to 2021.*



DISCUSSION

Antimicrobial resistant organism surveillance in BSIs is one of the most effective ways to decrease the spread and lessen the effects of resistant bacteria (Wang *et al.*, 2018). The present study revealed the pathogen distribution and susceptibility profile of BSIs during six years in a single center in Southern Italy. A total of 4941 isolated specimens were collected. CONS, *S. aureus* and *Enterococci* were the most common gram-positive BSIs pathogens according to our surveillance data. These results were similar to studies conducted in Finland, which reported *S. aureus* infection at 13% in Hubei province (Tian *et al.*, 2018), but a decrease in BSIs caused by CONS (from 11% to 7%) (Kontula *et al.*, 2021). The US rate of *E. faecalis* and *E. faecium* showed signs of consistent decline after 2016 (Mendes *et al.*, 2018). Our study is consistent with Farah *et al.* (2019), which reported *E. coli* as the most frequent Gram-negative isolate, followed by *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* (Farah *et al.*, 2019). Seasonal trends should be considered for BSIs (Paul *et al.*, 2012). Kolonitsiou *et al.* (2017) reported that Gram-positive bacteria isolation rates were higher than Gram negative in winter months. BSIs incidence increases with temperature (Kolonitsiou *et al.*, 2017). Our data showed Gram-negative prevalence in summer months for *K. pneumoniae* and *P. aeruginosa* and in spring for *E. coli* and *A. baumannii*, in contrast with other studies (Filho *et al.*, 2021). As described in the ECDC report, Italy is one of the countries in which antimicrobial resistance rates and antibiotic consumption in community and hospital settings are increasing (WHO, 2020). Data analysis conducted in our hospital showed similar results for the most frequently detected organisms, but the susceptibility profile varies. Since 2017, the first National Action Plan on Antimicrobial Resistance (Piano Nazionale per il Contrasto dell'Antibiotico Resistenza, PNCAR 2017-2020) has worked to prevent and control antimicrobial resistance at the national level. The Campania Region, has issued an annual report, Regional Antibiotic Resistance Surveillance System (Sistema Regionale di Sorveglianza dell'Antibiotico Resistenza, Si.re.Ar.), that reported the trend towards resistance and antibiotics used in local hospitals (Regione Campania, 2019). Our study analyzed six years of antimicrobial susceptibility rates and resistance fluctuation percentage from 2016 to 2018 and 2019 to 2021. Significantly increased variation in resistance to erythromycin, gentamicin and teicoplanin was reported in *S. aureus* and CONS. Encouraging data about oxacillin resistant rates was shown (-9%, -4.5%) as per the Diekema *et al.* study (2021) (Diekema *et al.*, 2021). *A.baumannii* isolates were resistant to all tested antibiotics, as local epidemiology and the percentage of colistin susceptibility were significantly reduced due to inadequate prescription practices (Habyarimana M. *et al.*, 2021). Carbapenem percentage reduction in *P. aeruginosa* and *K. pneumoniae* not according to Mohd Asri *et al.* (2021) meta-analysis, which reported the pooled prevalence of nosocomial K.pneumoniae at 32.8% (Mohd *et al.*, 2021).

Overall, fluoroquinolones and colistin resistance rates in *E. coli* isolates decreased significantly. Antimicrobial agents abuse in acute care settings can stimulate the development of MDR strains (Guisado-Gil *et al.*, 2020). An observational study analyzed the incidence of carbapenem-resistant *Enterobacteriaceae* colonization and incidence in an Italian ICU. This study reported that CRE incidence increased from 6.7% in 2019 to 50% in 2020. In our hospital, MDR bacterial BSIs incidence for CRE and *Enterobacteriaceae* ESBL positive showed a decreasing trend. Data on the prevalence of carbapenemases belongs only to *K. pneumoniae* isolates among the *Enterobacteriaceae* order. 98% of *Enterobacteriaceae* carbapenemase producing isolated was *K. pneumoniae* carbapenemase (KPC)-producing bacteria. No vancomycin resistant *Enterococcus faecium* (VRE) was reported during the 2019-2021 study period, in contrast with national and international studies (Carvalho *et al.*, 2020; Davtyan *et al.*, 2021). MRSA isolates decreased from 56.1% to 34.1%. The low rate of MDR BSIs isolated in our hospital in the 2019-2021 period highlighted the success of antimicrobial stewardship strategies. Our study collected data from microbiological records; therefore, we did not investigate the clinical records on sequential therapy with other antibiotics. However, our results suggest that the prevalence of antibiotic resistance is changing in metropolitan cities. In this scenario, in agreement with clinicians, we will provide a monthly audit in line with the antimicrobial stewardship program control. This will allow clinicians and infectious diseases specialists to know the epidemiological data from their hospital. The study limitation is data collected from a single hospital in Southern Italy; however, our hospital is the fulcrum in emergency management in a provincial reality. It provides health services in ordinary hospitalization, first aid, day hospital and even outpatient, and has allowed us to include a very heterogeneous group of patients in our analysis. Information from active surveillance systems is needed to better characterize the trend of antimicrobial resistance incidence locally. As well, BSIs antimicrobial resistance surveillance may be the starting point for modifying and developing antimicrobial stewardship interventions and infection control strategies.

Ethical Statement

Ethical approval by the Human Research Ethics Committee was not requested, as our study used lab-

oratory management data and clinical information on patients, collected from databases. This is a retrospective study and is not directly associated with patients.

Conflict of Interest

The authors have no conflicts of interest.

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