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ORIGINAL RESEARCH

Changes in Antimicrobial Resistance and Etiology of Blood Culture Isolates: Results of a Decade (2010–2019) of Surveillance in a Northern Region of Colombia

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On behalf of Germen Antimicrobial Surveillance network

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Background: Bloodstream infections (BSI) are important causes of morbidity and mortality worldwide. Antimicrobial surveillance is essential for identifying emerging resistance and generating empirical treatment guides, the purpose of this study is to analyze trends in antimicrobial susceptibility of BSI from 2010 to 2019 in healthcare institutions from Medellin and nearby towns in Colombia.
Methods: A Whonet database was analyzed from the GERMEN antimicrobial surveillance network; frequency and antibiotic susceptibility trends were calculated on more frequent microorganisms using Mann Kendall and Sen's Slope Estimator Test.
Results: 61,299 isolates were included; the three microorganisms more frequent showed a significant increasing trend through time *E. coli* (Sen's Slope estimator = 0.7 p = <0.01) *S. aureus* (Sen's Slope estimator = 0.60 p = <0.01) and *K. pneumonia* (Sen's Slope estimator = 0.30 p = <0.01). *E. coli* showed a significant increase trend in cefepime and ceftazidime resistance, while *K. pneumoniae* showed a significant increase in resistance to cefepime, ciprofloxacin, and gentamicin. *P. aeruginosa* increases its susceptibility to all analyzed antibiotics and *S. aureus* to oxacillin. No increasing trend was observed for carbapenem resistance.
Conclusion: An upward trends was observed in more frequent microorganisms and resistance to third and fourth-generation cephalosporins for *E. coli* and *K pneumoniae*; in contrast, not increasing trends in antibiotic resistance was observed for *P. aeruginosa* and *S. aureus*. The essential role of AMR-surveillance programs is to point out and identify these trends, which should improve antibiotic resistance control.
Keywords: bacteremia, drug resistance bacterial, antibacterial agents, antimicrobial surveillance

Introduction

Bloodstream infections (BSI) have a broad spectrum of clinical manifestations; they can vary from self-limited and asymptomatic infections to the development of sepsis.[1] BSI and sepsis are among the leading causes of mortality in hospitalized patients, as high as 40% in high-income countries.[2] In Europe, there are approximately 1,200,000 BSI episodes with 157,000 annual deaths, and in the United States, there are 575,000–677,000 BSI episodes per year with 79,000–94,000 deaths from this cause.[3] Although the information is limited, the situation might be similar in low- and middle-income countries.[2]

The epidemiology and etiology of BSI are multifactorial and vary according to geographical location, age group, origin of infection, the conditions of health care, the frequency of central line associated blood stream infections, and the clonal spread of more pathogenic strains causing BSI, among others.[4–7] In addition, there are important variations in corresponding

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antimicrobial susceptibility profiles, with an increase in the prevalence of multi-drug-resistant bacteria, especially among Gram-negative bacteria.[6,7] Based on a recent report, the most common pathogens isolated from BSIs worldwide are *Staphylococcus aureus* (20.7%), followed by *Escherichia coli* (20.5%), *Klebsiella pneumoniae* (7.7%), *Pseudomonas aeruginosa* (5.3%), and *Enterococcus faecalis* (5.2%).[6] Some of these bacteria are included in the list of microorganisms prioritized by the World Health Organization (WHO) to guide research and efforts to develop new antibiotics.[8]

Infections caused by resistant microorganisms are a significant public health problem. In 2019, WHO declared antimicrobial resistance (AMR) as one of the ten main public health problems facing humanity and added two indicators to its 2019–2023 program: BSI caused by *E. coli* resistant to third-generation cephalosporins and methicillin-resistant *Staphylococcus aureus* (MRSA) as well as the trend in the national consumption of antibiotics.[9]

The most recent report from the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) shows a frequency of 36% for *E. coli* resistant to third-generation cephalosporins and 24.9% for methicillin-resistant *Staphylococcus aureus* causing bloodstream infections. It also shows that the highest resistance proportions were in low- and middle-income countries.[10] For example, in Colombia, in hospitalized patients, the National Institute of Health reported up to 35% oxacillin resistance in *S. aureus*, and for *K. pneumoniae* and *E. coli*, resistance to third and fourth-generation cephalosporins was in a range between 24% and 40%.[11]

Surveillance of etiology and antimicrobial susceptibility patterns of microorganisms associated with BSI is an essential tool for the diagnosis, adequate treatment, and control of these infections.[12] AMR surveillance active in local, regional, and national settings plays a crucial role in documenting the spread of resistance, detecting emerging resistant pathogens, and evaluating the effectiveness of control measures.[10,11,13] Considering the increasing of antibiotic resistance in our country[11,14] and the lack of data showing long-term surveillance, we set up a study with the objective to describe the trends in the etiologies of BSI in different age groups and hospital wards, as well as trends in their antimicrobial susceptibility patterns, by analyzing the data collected by GERMEN, a regional network of antimicrobial resistance surveillance that function in northern Colombia based in Medellín the second most populated city and in surrounding municipalities, during a decade, 2010 to 2019.

Materials and Methods

This is a retrospective, observational, and descriptive study of positive blood culture results and antimicrobial susceptibility of isolated microorganisms between 2010 and 2019. The information was obtained from the GERMEN antimicrobial surveillance network database that uses the WHONET 5.6 platform (www.whonet.org). GERMEN is an antimicrobial resistance surveillance network (www.grupogermen.org) composed of 31 medium- and high-complexity hospitals and eight clinical laboratories located in the city of Medellín and surrounding municipalities that represents 70% of hospital beds in the region.

Study setting and population: Medellin metropolitan area and surrounding municipalities have an approximate population of 4.5 million. The data included in the study were from those patients entered into the Whonet database with a first positive blood culture. Repeated isolates, isolates for screening purposes, and isolates that did not have antimicrobial susceptibility results were excluded. All participating institutions were engaged in quality assurance programs, external quality controls, and proficiency testing coordinated by the National Reference Laboratory at Colombian Instituto Nacional de Salud. In addition, the GERMEN network performed quality control of all data received in WHONET format from participating institutions yearly, following recommendations by CLSI.[15]

Isolate identification and Antimicrobial Susceptibility methods: All pathogens were identified and tested for antimicrobial susceptibility in each healthcare institution using automated methods, all of them used Vitek 2 (BioMérieux, Inc. Durham, NC 27712, USA) for identification and susceptibility tests. In addition, 9 of them used Maldi tof for identification purposes (either Maldi tof MS - BioMérieux, Inc. Durham, NC 27712, USA or Maldi tof Bruker Daltonics GmbH & Co. KG). Antimicrobial susceptibility testing was interpreted following the Clinical and Laboratory Standard Institute (CLSI) guidelines.[16]

Species of microorganisms that presented a prevalence of ≥0.5% during the study period were included in the analysis. Species with lower frequencies for descriptive analysis were grouped in the category of "others." Descriptive analyzes of frequencies and percentages of microorganisms by age group and hospital wards were done using the

WHONET 5.6 program. Age groups were classified as follows: neonates (≤28 days), pediatric (≥29 days - ≤14 years), adults (≥15 years - ≤64 years), and older adults (≥65 years). The analysis by ward was performed according to where the patient was at the time of obtaining the blood culture, intensive care unit (ICU), non-ICU hospitalization ward, emergency, and outpatient services.

Using the SPSS statistical package (v.18; SPSS Inc. Chicago, IL), trends in the frequencies of microorganisms and the antimicrobial susceptibility profiles were evaluated using Mann Kendall and Sen's Slope Estimator Test, considering a p-value ≤0 0.05 as significant. This last analysis was done with microorganisms prioritized by the WHO and those with the highest frequencies, particularly: *Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae* and *Serratia marcescens*. According with this list of microorganisms the tested antibiotics analyzed were: vancomycin, oxacillin, ceftazidime, cefepime, imipenem, meropenem gentamicin, ciprofloxacin, piperacilline/tazobactam

Results

From 2010 to 2019, a total of 61,299 isolates were analyzed. The year with the highest number of isolates was 2016, with 6921 (11.3%), and the year with the lowest number was 2012, with 5130 representing 8.4% of the total isolates. An increase in the number of isolates was observed associated with an increase in the number of added institutions in later years, comparing the initial and final years of the study.

Overall, gram-negative bacteria accounted for 43.96% of isolates. In comparison, gram positives were 40.74%, 2.8% were *Candida* spp., and 12.4% were other bacterial species with individual frequencies less than 0.5% out of the total isolates. The most frequently isolated microorganisms was *E. coli* (20.38%), followed by *S. aureus* (14.84%), *S. epidermidis* (11.70%), and *K. pneumoniae* (10.65%). Mann Kendall and Sen's Slope Estimator Test showed a significant upward trend in the frequency of the most isolated bacteria such as *E. coli* (Sen's Slope estimator = 0.7 p = <0.01), *S. aureus* (Sen's Slope estimator = 0.60 p = <0.01), *K. pneumoniae* (Sen's Slope estimator = 0.30 p = <0.01) and *Proteus mirabilis* (Sen's Slope estimator = 0.10 p = <0.01); during the study period while *S. epidermidis* (Sen's Slope estimator = - 0.66 p = <0.01), *S. hominis* (Sen's Slope estimator = - 0.55 p = <0.01) and *P. aeruginosa* (Sen's Slope estimator = - 0.10 p = <0.05) had a significant tendency to decrease in frequency during the same period. The frequencies observed for the other microorganisms during the 10-year period did not show trends with significant variations (Table 1 and Figure 1).

According to age groups, 4,010 isolates were obtained from the neonatal group, 7,499 from the pediatric population, 23,556 from adults, and 21,911 isolates from older adults. For the neonate's group, the most frequently isolated microorganisms was *S. epidermidis* (32.4%), followed by *E. coli* (8.9%), *S. aureus* (7.5%), Group B-streptococcus (4.2%), *Candida* spp. (2,0%) and *S. pneumoniae* (0.5%). For the pediatric age group, the most frequent microorganism found was *S. epidermidis* (20.0%), followed by *S. aureus* (14.7%), *S. hominis* (10.1%), *E. coli* (7,0%), and *K. pneumoniae* (6.0%). For adults, the most frequent microorganisms were *E. coli* (21.0%), *S. aureus* (16.9%), and *K. pneumoniae* (12.3%), while for older adults, the frequencies were *E. coli* (26.9%), *S. aureus* (14.0%) and *K. pneumoniae* (11.9%) (Table 2). *E. coli, P. aeruginosa* and *P. mirabilis* were more frequently isolated in older adults than in the rest of the groups. *S. aureus* was more frequently isolated from adults than pediatric patients, older adults, and neonates. *S. hominis* and *S. pneumoniae* were more frequent in the pediatric population, and S. *epidermidis*, coagulase negative staphylococci, *E. faecalis*, group B streptococci, and *S. marcescens* were more frequent in the neonatal group (Table 2).

The analysis showed 13,491 microorganisms causing BSI isolated from patients in the intensive care unit (ICU), the most frequent bacteria were *S. epidermidis* (17.0%) followed by *K. pneumoniae* (12.5%) and *S. aureus* (11.0%). Meanwhile, 23,990 isolates were obtained from non-ICU hospitalization wards, and 22,390 isolates were obtained from patients in the emergency room. *E. coli* was the main microorganism in both places, followed by *S. aureus* and *K. pneumoniae*. Overall, the most frequent microorganisms isolated from the different services were *E. coli* (20.4%) and *S. aureus* (15.4%) (Table 3).

The trend analysis of antimicrobial susceptibility did not show significant changes for gram-positive cocci (Table 4, Figure 2). However, antibiotic susceptibility in gram-negative bacteria showed significant changes over time. Susceptibility to third-generation (ceftazidime) and fourth-generation (cefepime) cephalosporins in *E. coli* showed a significant downward trend in the studied period, going from 87.8% of isolates susceptible to ceftazidime and 87.7% to cefepime in 2010 to 76% for both antibiotics in 2019 (Sen's Slope estimator = −1.22 p = <0.01 and Sen's Slope estimator = −1.26 p = <0.01 respectively).

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Table 1 Trends in the Frequencies of Microorganisms in BSI from Health Institutions in Medellin Area, 2010–2019 GERMEN Antimicrobial Resistance Surveillance Network

Microorganisms	Years n (%)										p	Sen's Slope Estimator	Total
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	–	–	–
E. coli	900 (17.3)	1012 (17.6)	1017 (19.8)	1065 (18.0)	1282 (19.8)	1415 (20.7)	1456 (21.0)	1378 (21.3)	1441 (23.6)	1527 (23.6)	<0.01	0.70	12,493
S. aureus	664 (12.8)	714 (12.4)	683 (13.3)	868 (14.7)	869 (13.4)	1034 (15.1)	1101 (15.9)	1052 (17.1)	1045 (17.1)	1066 (16.5)	<0.01	0.60	9096
S. epidermidis	783 (15.0)	801 (14.0)	677 (13.2)	716 (12.1)	804 (12.4)	772 (11.3)	785 (11.3)	691 (9.6)	585 (9.6)	561 (8.7)	<0.01	−0.66	7175
K. pneumoniae	485 (9.3)	484 (8.4)	506 (9.9)	613 (10.4)	693 (10.7)	817 (11.9)	738 (10.7)	747 (11.6)	691 (11.3)	756 (11.7)	<0.01	0.30	6530
S. hominis	250 (4.8)	409 (7.1)	330 (6.4)	337 (5.7)	348 (5.4)	308 (4.5)	271 (3.9)	193 (3.0)	180 (3.0)	174 (2.7)	<0.01	−0.55	2800
P. aeruginosa	233 (4.5)	235 (4.0)	209 (4.1)	205 (3.5)	276 (4.3)	290 (4.2)	267 (3.9)	205 (3.2)	200 (3.2)	230 (3.6)	0.05	−0.10	2350
Candida spp	124 (2.4)	156 (2.7)	155 (3.0)	208 (3.5)	206 (3.2)	175 (2.6)	174 (2.6)	174 (2.7)	142 (2.3)	189 (2.4)	>0.05	−0.05	1703
E. faecalis	147 (2.8)	141 (2.5)	136 (2.7)	139 (2.4)	172 (2.3)	172 (2.6)	166 (2.4)	193 (3.0)	166 (2.7)	172 (2.7)	>0.05	0.01	1604
E. cloacae	109 (2.0)	125 (2.2)	104 (2.0)	162 (2.7)	173 (2.3)	150 (2.2)	169 (2.4)	184 (2.9)	135 (2.2)	147 (2.3)	>0.05	0.03	1458
S. marcescens	81 (1.6)	189 (3.3)	151 (2.9)	146 (2.5)	175 (2.3)	147 (2.2)	151 (2.2)	145 (2.2)	138 (2.3)	114 (1.8)	>0.05	−0.10	1437
S. pneumoniae	147 (2.8)	148 (2.6)	108 (2.1)	109 (1.8)	135 (2.1)	124 (1.8)	132 (1.9)	148 (2.3)	137 (2.3)	138 (2.1)	>0.05	−0.05	1326
Coagulase negative *Staphylococcus*	240 (4.6)	123 (2.1)	50 (1.0)	167 (2.8)	72 (1.1)	94 (1.4)	102 (1.5)	89 (1.4)	79 (1.3)	94 (1.5)	>0.05	−0.10	1110
S. haemolyticus	69 (1.3)	109 (1.9)	72 (1.4)	107 (1.8)	145 (2.2)	90 (1.3)	90 (1.3)	87 (1.4)	66 (1.0)	80 (1.3)	>0.05	−0.04	915
***Salmonella* sp.**	65 (1.3)	46 (0.8)	76 (1.5)	69 (1.2)	67 (1.0)	109 (1.6)	127 (1.8)	104 (1.7)	81 (1.3)	75 (1.2)	>0.05	0.04	819
P. mirabilis	42 (0.8)	52 (0.9)	53 (1.0)	62 (1.1)	81 (1.3)	74 (1.1)	97 (1.4)	90 (1.4)	79 (1.3)	107 (1.7)	<0.01	0.10	737
K. oxytoca	47 (0.9)	81 (1.4)	40 (0.8)	56 (1.0)	76 (1.2)	88 (1.2)	79 (1.1)	72 (1.1)	48 (0.8)	81 (1.3)	>0.05	0.02	668
S. capitis	26 (0.5)	56 (1.0)	62 (1.2)	61 (1.0)	67 (1.0)	55 (0.8)	61 (0.9)	57 (0.9)	58 (1.0)	66 (1.0)	>0.05	0.01	569
A. baumanii	65 (1.3)	85 (1.5)	48 (1.0)	67 (1.1)	43 (0.7)	40 (0.6)	40 (0.6)	42 (0.7)	46 (0.8)	49 (0.8)	>0.05	−0.06	525
Group B *Streptococcus*	29 (0.6)	27 (0.5)	28 (0.6)	42 (0.7)	31 (0.5)	54 (0.8)	37 (0.5)	46 (0.7)	51 (0.8)	30 (0.5)	>0.05	0.01	375
Other	703 (13.6)	762 (13.2)	625 (12.2)	722 (12.2)	771 (12.9)	835 (12.2)	878 (12.7)	767 (11.9)	731 (12.0)	815 (12.6)	>0.05	−0.10	7609
Total	5209 (100)	5755 (100)	5130 (100)	5921 (100)	6486 (100)	6843 (100)	6921 (100)	6464 (100)	6099 (100)	6571 (100)	–	–	61,299

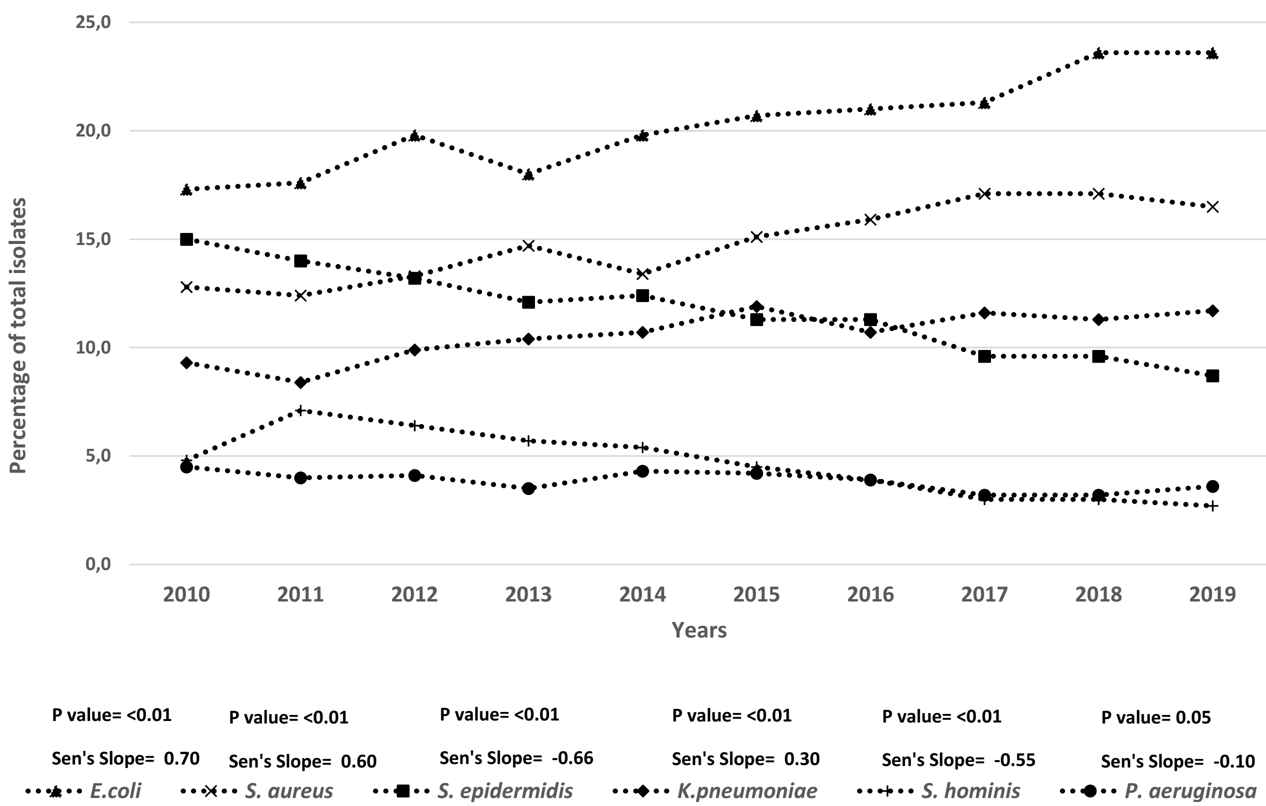

Figure 1 Trends in more frequent microorganisms isolated from BSI in health institutions of Medellin area, 2010–2019 GERMEN antimicrobial resistance surveillance network. P values show the significance of the trend and Sen's slope estimator shows upward or downward trends.

In *K. pneumoniae* the percentage of susceptible strains decreased significantly for cefepime going from 75.8% in 2010 to 74% in 2019 (Sen's Slope estimator = −0.78 p = <0.05), for gentamicin going from 90.3% in 2010 to 83% in 2019 (Sen´s Slope estimator = −0.85 p = <0.05) as well as for ciprofloxacin, going from 88.2% to 81% between 2010 and 2019 (Sen's Slope estimator = −1,23 p = <0.01). The susceptibility to carbapenems for this microorganism trends decreased, although it was not significant (Sen's Slope estimator = −0,05 p> 0.05 for imipenem and Sen's Slope estimator = −0,07 p> 0.05 for meropenem) (Table 4).

A significant increase in susceptible isolates percentage was observed for *P. aeruginosa* in each antibiotic evaluated throughout the study period. *S. marcescens* showed a significant increase in the susceptibility to ceftazidime from 72.9% to 84.7% (Sen's Slope estimator = 2.13 p < 0.05) (Table 4, Figure 2).

Discussion

In the present study, 61,299 isolates from BSI registered in the database of GERMEN antimicrobial surveillance network for ten years (2010–2019) were analyzed. During this period, the most frequently isolated microorganisms were *E. coli* (20.4%), *S. aureus* (14.8%), *S. epidermidis* (11.7%) and *K. pneumoniae* (10.6%). Among all isolates, *E. coli* and *S. aureus* accounted for 35%, a finding like the 40% reported by a global wide SENTRY study.[6] Compared with the stratification by regions reported by the same study, the higher frequency found in our study for *E. coli* (20.4%) over *S. aureus* (14.8%) is like that found in Europe in the period 2013 to 2016 (27% and 16.4% respectively) and Latin America (18.3% and 16.4% respectively). In a recent study in 16 hospitals in China that spanned a decade, 40% of blood culture isolates were *E. coli, K. pneumoniae*, and *S. aureus*.[17]

Considering the six most frequent species of microorganisms isolated, *E. coli, S. aureus, S. epidermidis, K. pneumoniae, S. hominis* and *P. aeruginosa*, the gram-negative bacilli represented 34.8% and gram-positive cocci 31.1%, with a significant tendency to increase in the decade analyzed for *E. coli, S. aureus* and *K. pneumoniae*. Two studies conducted in the USA on bloodstream infections in hospitals have also shown significant changes in the pattern of

Table 2 Distribution of Microorganisms by Age Group in BSI from Health Institutions in Medellín Area, 2010–2019 GERMEN Antimicrobial Resistance Surveillance Network

Microorganisms	n (%) Neonates	n (%) Pediatrics	n (%) Adults	n (%) Older Adults
S. epidermidis	1299 (32.4)	1498 (20.0)	1918 (8.1)	1819 (8.3)
E. coli	356 (8.9)	524 (7.0)	4956 (21.0)	5896 (26.9)
S. aureus	301 (7.5)	1103 (14.7)	3983 (16.9)	3057 (14.0)
S. hominis	293 (7.3)	760 (10.1)	639 (2.7)	825 (3.8)
K. pneumoniae	217 (5.4)	448 (6.0)	2887 (12.3)	2603 (11.9)
coagulase negative *Staphylococcus*	183 (4.6)	198 (2.6)	312 (1.3)	314 (1.4)
E. faecalis	172 (4.3)	214 (2.9)	524 (2.2)	584 (2.7)
grupo B *Streptococcus*	170 (4.2)	23 (0.3)	122 (0.5)	115 (0.5)
S. marcescens	127 (3.2)	188 (2.5)	575 (2.4)	454 (2.1)
E. cloacae	90 (2.2)	159 (2.1)	623 (2.6)	492 (2.2)
S. haemolyticus	86 (2.1)	73 (1.0)	353 (1.5)	312 (1.4)
Candida spp	83 (2.1)	289 (3.9)	673 (2.9)	518 (2.4)
K. oxytoca	51 (1.3)	73 (1.0)	229 (0.1)	268 (1.2)
P. aeruginosa	52 (1.3)	154 (2.0)	982 (4.2)	1001 (4.6)
S. capitis	42 (1.0)	108 (1.4)	161 (0.7)	216 (1.0)
A. baumannii	40 (1.0)	88 (1.2)	211 (0.9)	129 (0.6)
S. pneumoniae	21 (0.5)	266 (3.5)	546 (2.3)	409 (1.9)
Salmonella sp.	12 (0.3)	118 (1.6)	416 (1.8)	230 (1.0)
P. mirabilis	6 (0.1)	21 (0.3)	309 (1.3)	360 (1.6)
Other	492 (12.3)	1194 (15.9)	3137 (13.3)	2309 (10.5)
Total	4010 (100.0)	7499 (100.0)	23.556 (100.0)	21,911 (100.0)

isolated microorganisms over time. The first published in 2004 with data from 1995 to 2002[18] in which gram-positive cocci were predominant, with 64% (Staphylococcus coagulase negative, *S. aureus*) and the second published in 2019 with data from 2015 to 2017[19] that showed almost two decades later the predominance of gram-negatives *E. coli* and *K. pneumoniae*, altogether with *S. aureus*.

When comparing age groups, there were differences with respect to the species isolated, *S. epidermidis* and coagulase-negative staphylococci were more predominant in neonates and pediatric patients (44.3% and 32.1% respectively). Whereas gram-negative bacilli were more frequent in adults and older adults (32.3% and 38.8% respectively). Other studies showed wide differences in the frequency of microorganism causing BSI between countries and regions, probably related to local epidemiological conditions and healthcare practices in pediatric populations[6,20,21] and adults and older adults' populations.[6] Variations in the frequency of microorganisms isolated from blood cultures have been also associated with geographical and economic factors; a study carried out in 23 hospitals around the world showed gram negative bacilli as the most frequently isolated microorganisms from blood in centers close to the equator and with a lesser relationship between gross domestic product and health expenditures.[7]

In the present study, the microorganisms isolated most frequently from blood cultures in ICUs were in their order, *S. epidermidis, K. pneumoniae, S. aureus* and *E. coli*. One of the differences found between ICU and non-ICU wards was

Table 3 Distribution of Microorganisms Obtained from BSI According to Hospital Wards in Medellín Area, 2010–2019 GERMEN Antimicrobial Resistance Surveillance Network

Microorganisms	n (%) ICU	n (%) no ICU	n (%) Emergency Room
E. coli	1445 (10.7)	4217 (17.5)	6611 (29.5)
S. aureus	1488 (11.0)	4156 (17.3)	3603 (16.0)
K. pneumoniae	1694 (12.5)	2800 (11.6)	2034 (9.0)
S. epidermidis	2293 (17.0)	2716 (11.3)	1849 (8.2)
P. aeruginosa	691 (5.1)	1024 (4.2)	600 (2.6)
S. hominis	607 (4.5)	992 (4.14)	1071 (4.7)
E. faecalis	509 (3.7)	652 (2.72)	412 (1.8)
S. marcescens	586 (4.3)	572 (2.3)	246 (1.1)
S. pneumoniae	128 (0.9)	270 (1.1)	845 (3.7)
P. mirabilis	114 (0.8)	282 (1.1)	333 (1.4)
Coagulase negative *Staphylococcus*	207 (1.5)	507 (2.1)	270 (1.21)
Salmonella sp.	81 (0.6)	285 (1.1)	(1.9)
A. baumanii	156 (1.1)	259 (1.0)	85 (0.3)
E. cloacae	423 (3.1)	663 (2.7)	310 (1.3)
Candida spp	362 (2.6)	669 (2.7)	144 (0.6)
S. haemolyticus	885 (1.7)	408 (1.7)	231 (1.0)
K. oxytoca	172 (1.2)	265 (1.1)	211 (0.9)
S. capitis	125 (0.9)	175 (0.7)	236 (1.0)
Group B *Streptococcus*	90 (0.6)	115 (0.4)	165 (0.7)
Other	3161 (23.4)	4964 (20.6)	3903 (17.4)
Total	13,491 (100.0)	23,990 (100.0)	22,390 (100.0)

the frequency of *S. epidermidis*, which in the case of ICU were influenced by the higher proportion of isolates found in neonates and pediatric populations. *S. epidermidis* and coagulase negative staphylococci are not always clinically relevant and are usually considered contaminants; Nevertheless, data from various studies, have demonstrated its etiological role in 10% to 30% of bacteremia.[22,23] In a population surveillance study such as ours, it is not possible to determine the clinical significance of *S. epidermidis* and coagulase negative staphylococci, since one of the criteria for inclusion in the analysis was only one isolate per patient. However, in ICU, non-ICU, and emergency services, the predominant pathogens found were *S. aureus, E. coli*, and *K. pneumoniae*, which are usually significant etiologies when isolated from blood cultures.[24]

During the study period, no significant changes were observed in trends of susceptibility to most of antibiotics active against gram-positive cocci. In addition, some studies have shown a decrease in the proportion of resistant phenotypes in these microorganisms. A SENTRY study analyzed the trend of methicillin-resistant *S. aureus* (MRSA) for 20 years (1997–2016) in several regions of the world, finding a decreasing trend in its frequency in all regions[25]. Other studies have documented significant changes with decreased resistance of *S. aureus* to oxacillin and *Enterococcus* spp. to vancomycin.[26]

Table 4 Trends of Susceptibility to Marker Antibiotics in More Frequent Microorganisms in BSI from Hospital Institutions in the Medellín Area, 2010–2019 GERMEN Antimicrobial Resistance Surveillance Network

Microorganisms	Antibiotic	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	p	Sen's Slope Estimator
E. faecalis	**Vancomycin**												
	% susceptibility	96	99	98	99	99	100	100	100	99	98	>0.05	0.17
	Total	130	126	132	137	168	169	163	188	150	171	–	–
E. faecium	% susceptibility	60	52	73	73	84	76	95	85	67	68	>0.05	2.0
	Total	20	19	15	19	39	21	23	21	28	25	–	–
S. aureus	**Oxacillin**												
	% susceptibility	69	73	69	72	75	74	76	73	72	71	>0.05	2.0
	Total	633	714	680	865	855	1006	1069	1030	1015	1055	–	–
E. coli	**Ceftazidime**												
	% susceptibility	87.8	87.9	84	80.9	82	83.4	80.5	80.0	78.0	76.0	<0.01	−1.22
	Total	769	860	972	1019	1270	1391	1446	1368	1395	1439	–	–
	Cefepime												
	% susceptibility	87.7	89	84.1	81	82.3	83.2	80.7	80.0	78.0	76.0	<0.01	−1.26
	Total	859	985	1006	1047	1269	1394	1440	1367	1393	1516	–	–
	Imipenem												
	% susceptibility	97.7	99.3	99.6	99.6	99.3	99.6	99.7	99.0	99.0	99.0	>0.05	0.01
	Total	848	991	1004	939	1126	1222	1288	1150	1187	1319	–	–
	Meropenem												
	% susceptibility	97.6	99.7	99.5	99.4	99.3	99.6	99.5	99.0	99.0	99.0	>0.05	−0.07
	Total	760	889	1008	1050	1272	1400	1448	1372	1394	1520	–	–
	Gentamicin												
	% susceptibility	86.8	82.8	79.3	77.3	77	78.7	79.2	79.0	79.0	82.0	>0.05	−0.10
	Total	863	992	1007	1049	1273	1347	1448	1370	1399	1521	–	–
	Ciprofloxacin												
	% susceptibility	70.6	68.9	68.2	64.3	63	66.1	69.8	67.0	65.0	65.0	>0.05	−0.51
	Total	865	994	1009	1050	1271	1401	1449	1372	1401	1522	–	–
K. pneumoniae	**Ceftazidime**												
	% susceptibility	75.5	77.3	79.1	75.9	74.4	70.1	74.7	72.0	72.0	75.0	>0.05	−0.52
	Total	409	415	479	588	684	807	723	736	663	715	–	–
	Cefepime												
	% susceptibility	75.8	79.4	80.2	77	75.1	69.8	75.1	73.0	72.0	74.0	<0.05	−0.78
	Total	471	474	500	596	683	807	719	734	662	751	–	–
	Imipenem												
	% susceptibility	93.8	93.2	93.2	91.4	93.6	93.1	93.6	93.0	93.0	92.0	>0.05	−0.05

(*Continued*)

Table 4 (Continued).

Microorganisms	Antibiotic	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	p	Sen's Slope Estimator
	Total	468	472	499	548	595	694	658	623	560	651	–	–
	Meropenem												
	% susceptibility	93.9	95	94	92.1	92.8	93.3	94.1	93.0	94.0	93.0	>0.05	−0.07
	Total	410	435	501	598	683	808	726	735	664	753	–	–
	Gentamicin												
	% susceptibility	90.3	89.7	88.6	87.2	87.3	81.5	84.4	82.0	87.0	83.0	<0.05	−0.85
	Total	473	474	502	600	685	767	726	737	664	754	–	–
	Ciprofloxacin												
	% susceptibility	88.2	89.1	86.4	86.2	81.3	81.7	82	77.0	79.0	81.0	<0.01	−1.23
	Total	473	470	500	601	685	807	728	735	664	753	–	–
P. aeruginosa	**Ceftazidime**												
	% susceptibility	81	83	75	77	82	88	88	84	93	91	<0.01	1.50
	Total	202	208	202	201	272	284	261	200	192	216	–	–
	Cefepime												
	% susceptibility	76	81	78	82	85	89	89	87	94	89	<0.01	1.80
	Total	224	226	207	202	273	287	261	200	190	226	–	–
	Imipenem												
	% susceptibility	73	76	77	78	79	85	88	85	85	91	<0.01	1.71
	Total	224	225	206	186	242	256	235	184	176	215	–	–
	Meropenem												
	% susceptibility	77	77	82	80	78	86	87	86	88	91	<0.01	1.50
	Total	225	227	207	199	274	285	265	203	194	224	–	–
	Gentamicin												
	% susceptibility	75	77	80	87	88	92	91	88	90	90	<0.01	1.67
	Total	225	226	207	202	274	268	262	202	192	225	–	–
	Ciprofloxacin												
	% susceptibility	75	78	76	83	88	89	89	88	90	90	<0.01	1.71
	Total	228	226	207	201	276	286	263	204	194	226	–	–
	Piperacilline/tazobactam												
	% susceptibility	70	73	70	73	75	83	85	81	83	84	<0.01	2.0
	Total	226	223	196	200	264	280	258	200	192	225	–	–

(*Continued*)

Table 4 (Continued).

Microorganisms	Antibiotic	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	p	Sen's Slope Estimator
E. cloacae	**Ceftazidime**												
	% susceptibility	58.5	83.7	68.8	72.5	77.9	82.9	82.2	83.6	81.5	78	>0.05	1.80
	Total	94	98	96	153	172	146	169	183	135	141	–	–
	Cefepime												
	% susceptibility	75.5	88.1	85.6	87.4	92.5	91.3	88.8	89.1	91.1	82.9	>0.05	0.47
	Total	102	118	104	159	173	148	169	184	135	146	–	–
	Imipenem												
	% susceptibility	88.7	92.6	86.4	84.8	89	88.5	92.9	87.9	88.3	89.2	>0.05	0.06
	Total	100	122	103	138	146	122	155	165	120	130	–	–
	Meropenem												
	% susceptibility	92.7	95.6	92.3	89.3	92.4	91.9	94	90.8	94.1	90.4	>0.05	−0.20
	Total	96	113	104	159	172	148	168	184	135	146	–	–
S. marcescens	**Ceftazidime**												
	% susceptibility	72.9	58.9	83.6	79.3	90.8	88.8	91.9	93.7	91.1	84.7	<0.05	2.13
	Total	70	158	146	140	174	143	148	143	135	111	–	–
	Cefepime												
	% susceptibility	87.4	75.7	90	80.2	87.9	86.8	87.8	88.3	86.8	82.5	>0.05	0.01
	Total	79	185	149	142	174	144	148	145	136	114	–	–
	Imipenem												
	% susceptibility	90	77,4	83,3	81	91,3	81.2	93.2	78	69.6	62.5	>0.05	−1.86
	Total	80	182	150	126	149	48	44	59	46	40	–	–
	Meropenem												
	% susceptibility	96	90.2	94	89.4	94.2	93.8	95.3	94.4	91.1	87.7	>0.05	−0.31
	Total	75	174	150	142	173	145	148	144	135	114	–	–

The most significant trend observed in the decade analyzed was the increase in resistance to several antibiotics in *E. coli* and *K. pneumoniae*, two of the most frequent microorganisms isolated in blood cultures. In *E. coli* increased resistance to ceftazidime and cefepime were observed, while *K. pneumoniae* exhibited an increase in the resistance to cefepime, gentamicin and ciprofloxacin. The increased resistance in Enterobacteriaceae to third and fourth-generation cephalosporins found in our study coincides with data from other surveillance studies[5,6,24,26] and data reported in Latin America.[13,27] This increase is probably associated to the presence of CTX-M beta-lactamases which has been reported as endemic worldwide,[28] in South America[29] and in Colombia.[14]

Our data did not show a significant increase in resistance to carbapenems in Enterobacteriaceae and *P. aeruginosa* in the decade analyzed. However, in Latin America, the presence of isolates resistant to carbapenems that carry genes coding for carbapenemases have been reported with increasing frequency[30] indicating their potential for dissemination and a further expansion in the region.

This study has the limitation of reflecting the situation of the etiology and antibiotic susceptibility in BSI isolates from a specific, although the second, more densely populated region in the country. Another limitation of this study was that

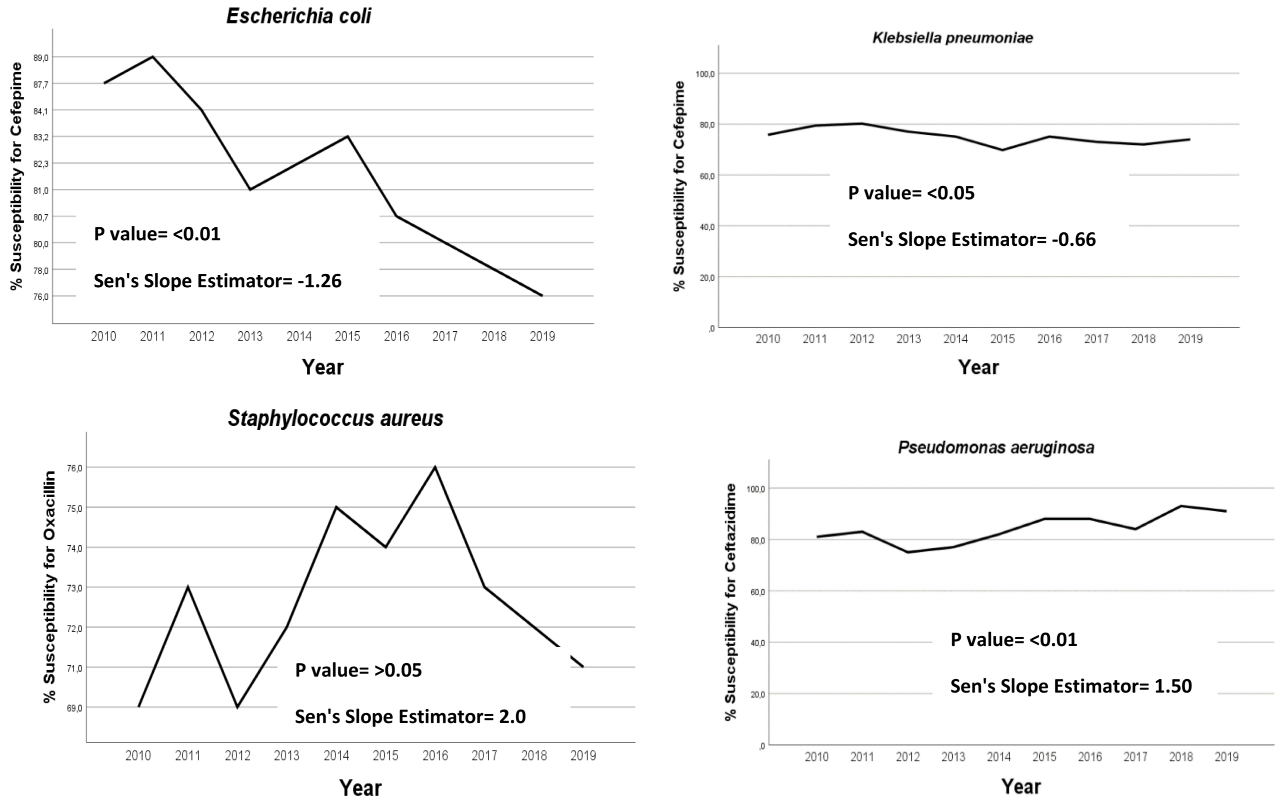

Figure 2 Trends of susceptibility to marker antibiotics in more frequent microorganisms causing BSI from hospital institutions in the Medellín area, 2010–2019 GERMEN antimicrobial resistance surveillance network. P values show the significance of the trend and Sen's slope estimator shows upward or downward trends.

not reference method for susceptibility was used, although all participant institutions perform quality control procedures for the methodologies used. In addition, all processed data were subject to quality control procedures before analysis. Furthermore, our data differ from data published for the country in *K. pneumoniae* which shows a significant and increasing resistance trend for carbapenem resistance from 2014 to 2016.[31] These differences highlight the importance of regional antibiotic resistance surveillance programs data that uncover situations not observed in consolidated and general data, contributing to understanding regional antibiotic resistance dynamics and supporting more specific measures for its control.

Conclusion

Our study shows a significant upward trend for *S. aureus, E. coli*, and *K. pneumoniae* isolated from BSI. Furthermore, the significant increase in resistance to third and fourth-generation cephalosporins in *E. coli* and *K. pneumoniae*, suggest the presence and endemicity of extended-spectrum beta-lactamases in our region. This situation is forcing a more frequent use of carbapenems to treat these infections and, therefore, a future lookout for an increase in the frequency of carbapenemase-producing isolates. The essential role of AMR-surveillance programs is to point out and identify these trends, which should contribute together with solid infection control and antimicrobial stewardship programs to improve the control of antibiotic resistance.

Ethics Statement

Ethical approval was given by the "Comite de Etica en Investigación en Salud" (approval reference number: 20012020) from School of Health Sciences, Universidad Pontificia Bolivariana, Medellin, Colombia.

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