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. pneumoniae (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...
antimicrobial susceptibility profiles, with an increase in the prevalence of multi-drug-resistant bacteria, especially among Gram-negative bacteria. 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%). 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.

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.

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. 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%.

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. 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. Considering the increasing of antibiotic resistance in our country 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. GERMEN is an antimicrobial resistance surveillance network 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.

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 Daltons GmbH & Co. KG). Antimicrobial susceptibility testing was interpreted following the Clinical and Laboratory Standard Institute (CLSI) guidelines.

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 ≤ 0.05 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).
| 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)| 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)| 6646 (100)| 6099 (100)| 6571 (100)| −      | −      | 61,299 |
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 = −0.05 p < 0.05 for imipenem and Sen’s Slope estimator = −0.07 p < 0.05 for meropenem) (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
isolated microorganisms over time. The first published in 2004 with data from 1995 to 2002, 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 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 and adults and older adults’ populations. 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.

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 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) |
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.\(^{26}\)

| 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. baumannii*                          | 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)      |
| 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  | 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 | 87.8 | 87.9 | 84   | 80.9 | 82   | 83.4 | 80.5 | 80.0 | 78.0 | 76   | <0.01 | −1.22 |                       |
| % susceptibility |     | 769  | 860  | 972  | 1019 | 1270 | 1391 | 1446 | 1368 | 1395 | 1439 |     |                       |
| Cefepime      |           |     | 87.7 | 89   | 84.1 | 81   | 82.3 | 83.2 | 80.7 | 80.0 | 78.0 | <0.01 | −1.26 |                       |
| % susceptibility |     | 859  | 985  | 1006 | 1047 | 1269 | 1394 | 1440 | 1367 | 1393 | 1516 |     |                       |
| Imipenem      |           |     | 97.7 | 99.3 | 99.6 | 99.6 | 99.3 | 99.6 | 99.0 | 99.0 | 99.0 | >0.05 | 0.01  |                       |
| % susceptibility |     | 848  | 991  | 1004 | 939  | 1126 | 1222 | 1288 | 1150 | 1187 | 1319 |     |                       |
| Meropenem      |           |     | 97.6 | 99.7 | 99.5 | 99.4 | 99.3 | 99.6 | 99.5 | 99.0 | 99.0 | >0.05 | −0.07 |                       |
| % susceptibility |     | 760  | 889  | 1008 | 1050 | 1272 | 1400 | 1448 | 1372 | 1394 | 1520 |     |                       |
| Gentamicin      |           |     | 86.8 | 82.8 | 79.3 | 77   | 77   | 78.7 | 79.2 | 79.0 | 82.0 | >0.05 | −0.10 |                       |
| % susceptibility |     | 863  | 992  | 1007 | 1049 | 1273 | 1347 | 1448 | 1370 | 1399 | 1521 |     |                       |
| Ciprofloxacin      |           |     | 70.6 | 68.9 | 68.2 | 64.3 | 63   | 66.1 | 69.8 | 67.0 | 65.0 | >0.05 | −0.51 |                       |
| % susceptibility |     | 865  | 994  | 1009 | 1050 | 1271 | 1401 | 1449 | 1372 | 1401 | 1522 |     |                       |
| K. pneumoniae | Ceftazidime | 75.5 | 77.3 | 79.1 | 75.9 | 74.4 | 70.1 | 74.7 | 72.0 | 72.0 | 75.0 | >0.05 | −0.52 |                       |
| % susceptibility |     | 409  | 415  | 479  | 588  | 684  | 807  | 723  | 736  | 663  | 715  |     |                       |
| Cefepime      |           |     | 75.8 | 79.4 | 80.2 | 77   | 75.1 | 69.8 | 75.1 | 73.0 | 72.0 | 74.0 | <0.05 | −0.78 |                       |
| % susceptibility |     | 471  | 474  | 500  | 596  | 683  | 807  | 719  | 734  | 662  | 751  |     |                       |
| Imipenem      |           |     | 93.8 | 93.2 | 93.2 | 91.4 | 93.6 | 93.1 | 93.6 | 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  | 474  | 502  | 600  | 685  | 807  | 728  | 737  | 664  | 753  |         | –                     |
| **P. aeruginosa** |          |      |      |      |      |      |      |      |      |      |      |         | –                     |
| **Cefazidine** |            |      |      |      |      |      |      |      |      |      |      |         | –                     |
| % 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)
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 and data reported in Latin America. This increase is probably associated to the presence of CTX-M beta-lactamases which has been reported as endemic worldwide, in South America and in Colombia. 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 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

| 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 | –   | –         |
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. 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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