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Trends in antimicrobial susceptibility patterns in healthcare-associated methicillin-resistant *Staphylococcus aureus* from bloodstream infections: A joinpoint regression analysis

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To the Editor—*Staphylococcus aureus* ranks third among pathogens causing healthcare-associated bloodstream infections in Brazil, and >60% of reported isolates are methicillin resistant (ie, MRSA).[1] The rise of healthcare-associated MRSA in Brazil occurred in the 1990s, mostly due to the extensive spread of the Brazilian epidemic clone (BEC).[2] BEC harbored the staphylococcal chromosome cassette (SCC) *mec* type III and were typically resistant to several antimicrobials, such as trimethoprim/sulfametoxazole (TMP/SMX), quinolones, and clindamycin. For a long time (before the national registration of linezolid and daptomycin), glycopeptides remained as the sole therapeutic option for healthcare-associated MRSA (HA-MRSA) in Brazil.[3]

Recent studies report that BEC has been substituted for clones harboring SCC*mec* type II, with remarkable increasing susceptibility to TMP/SMX and modest increases in susceptibility to ciprofloxacin and clindamycin.[4,5] Sporadic findings have indicated that TMX/SMX-susceptible, SCC*mec* type IV–harboring MRSA clones, which probably originated in the community, have spread within Brazilian hospitals.[6,7] Susceptibility to TMP/SMX, ciprofloxacin, and clindamycin has been proposed as a proxy marker of the so-called community-associated MRSA (CA-MRSA) invading hospitals.[8]

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Time series analysis, especially joinpoint regression techniques, which detect changes in time trends, have been rather infrequently applied to analyze long-term trends in antimicrobial resistance within healthcare settings. With that in mind, we conducted a time series analysis of HA-MRSA bloodstream infections (BSIs) in a teaching hospital from inner Brazil. The Botucatu Medical School teaching hospital has 500 beds and is a tertiary-care referral facility for an area with 500,000 inhabitants. Briefly, we analyzed monthly proportions of resistance to TMP/SMX, clindamycin, and ciprofloxacin among CA-MRSA BSIs from 2005 through 2019. During that 15 years, 2,291 nonduplicate episodes of CA-MRSA BSI were detected. We used Joinpoint version 4.9 software (National Cancer Institute, Calverton, MD) to identify changes in the time trends of those resistance patterns. We used a linear approach, and a minimum interval of 6 months between joinpoints was selected.

Our results are summarized in Figure 1. The overall resistance rates were as follows: TMP/SMX, 26.6%; clindamycin, 77.6%; and ciprofloxacin, 73.5%. We found 3 joinpoints for TMP/SMX resistance; the most relevant was followed by an abrupt decrease from 80.2% to 41.0% beginning in August 2007. The trend changed to a slower decrease until June 2016 (to 37.5%), with a small increase thereafter. Both clindamycin (1 joinpoint in July 2014) and ciprofloxacin (2 joinpoints in February and September 2011, respectively) presented initial decreases followed by slow increase in resistance. Notably, joinpoints in trends were not simultaneous for different antimicrobials.

This picture is more compatible with the substitution of SCC*mec* type III–harboring BEC for SCC*mec* II–harboring clones, which has been reported to maintain high levels of resistance to

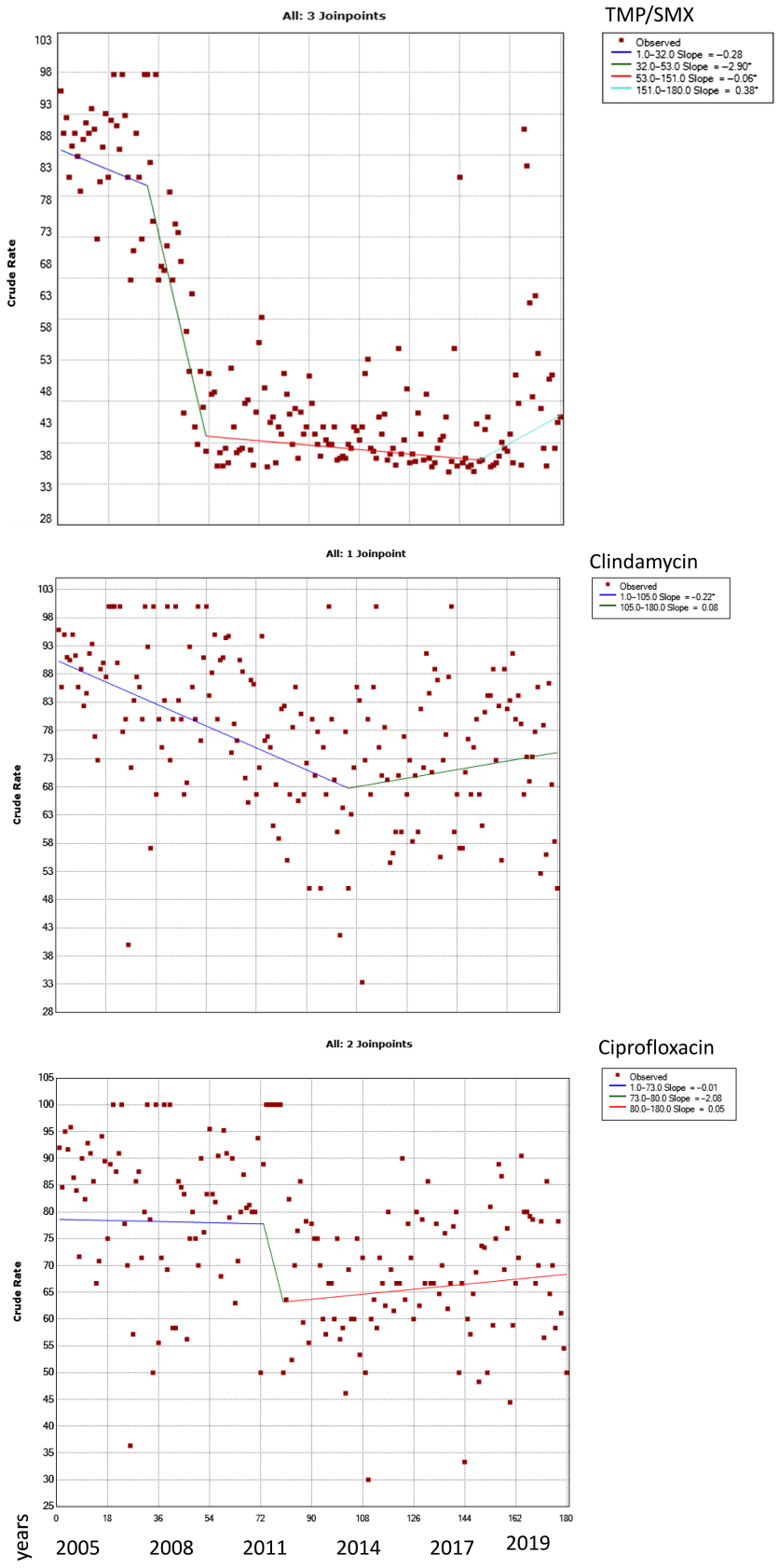

Fig. 1. Joinpoint regression graphics for resistance of healthcare-associated bloodstream infections caused by methicillin-resistant *Staphylococcus aureus*. Trends (monthly % changes) are indicated in the box in the right side of the graphics. Note. TMP/SMX, trimethoprim/sulfametoxazole.

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clindamycin and ciprofloxacin[4] than of invasion by community-associated, multidrug-susceptible SCC*mec* IV–harboring MRSA.[6] Even though our inference is limited by lack of strain and SCCmec typing, the findings are consistent with our recent identification of SCC*mec* type II in MRSA-colonizing nares and oropharynges of acute-care and long-term admissions of psychiatric patients.[9] We also analyzed a time series of 15 years using a robust statistical model to detect sudden changes in trends.

In a classic article, Deurenberg and Stobberingh[10] describe the blurring of distinctions between CA- and HA-MRSA and argue for a pure molecular definition, based on SCC*mec* typing. Because strain typing is not widely available, especially in low-to-middle income countries, careful long-term follow-up of resistant profiles may provide a reasonable proxy for detecting ecological changes in MRSA infections. Those trends also have therapeutic relevance. Although TMP/SMX is not a reasonable choice for treating MRSA BSI, other less-severe infections (eg, skin infections or phlebitis) acquired during hospital admissions may benefit from that antimicrobial. Further studies combining long-term analysis of time series with molecular typing may provide insights on the past, present, and future of healthcare-associated infectious caused by MRSA.

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Retrospective analysis of multidrug-resistant clinical and environmental isolates for the presence of the colistin-resistance gene *mcr-1*

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To the Editor—Carbapenem-resistant Enterobacterales (CRE) are a public health threat due to increased mortality, cost, and transmissibility of these infections. Although colistin is rarely considered as a last-resort antibiotic to treat CRE infections, increasing reports of plasmid-mediated colistin-resistant CRE isolates worldwide[1] are concerning. Resistance to colistin is conferred by *mcr* genes and was first linked to the *mcr-1* gene.[2] Since the initial *mcr-1* report from 2005, researchers have screened isolate collections for *mcr-1* and have found plasmid-mediated colistin resistant strains in animal and human populations.[2] At the time of this study, 4 clinical isolates containing the *mcr-1* gene were identified in the United States,[3] which has since increased to 55 isolates in at least 21 states.[4] The overall prevalence, distribution, and impact of *mcr-1* remain unclear.

In North Carolina, more than half of hospitals have reported CRE infections,[5] yet resistance to colistin has not been systematically examined. Given the active agriculture industry within the state, the potential to identify *mcr-1* among clinical and

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