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Concise Communication

Trimethoprim-sulfamethoxazole resistance patterns among *Staphylococcus aureus* in the United States, 2012–2018

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Abstract

We reviewed trimethoprim-sulfamethoxazole antibiotic susceptibility testing data among *Staphylococcus aureus* using 3 national inpatient databases. In all 3 databases, we observed an increases in the percentage of methicillin-resistant *Staphylococcus aureus* that were not susceptible to trimethoprim-sulfamethoxazole. Providers should select antibiotic regimens based on local resistance patterns and should report changes to the public health department.

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Trimethoprim-sulfamethoxazole (TMP-SMX) is commonly used for the empiric treatment of skin and soft-tissue infections (SSTIs) and other noninvasive infections in areas where methicillin-resistant *Staphylococcus aureus* (MRSA) is common.[1] National surveillance for MRSA is conducted primarily for invasive infections. MRSA infections decreased among hospitalized patients from 2012 to 2017; however, less is known about noninvasive infections in outpatient settings.[2] Among ambulatory care visits for SSTIs in the United States during 2011–2016, an estimated 7.5 million prescriptions for TMP-SMX were given, representing 17.4% of all antibiotics prescribed during these visits.[3] Recently, there have been several reports of resistance to TMP-SMX among MRSA in non-US settings and in a pediatric population at a single US center.[4–6] Here, we describe TMP-SMX resistance patterns among *S. aureus* in the United States using 3 national databases.

Methods

Electronic health record (EHR) databases

We used the Cerner Health Facts EMR[7] and the Premier Healthcare Database[8] to identify *S. aureus* infections among inpatients discharged from participating acute-care hospitals (ACHs) from January 1, 2012, to December 31, 2017. These methods have been described previously.[9] An incident case was defined as isolation of MRSA or methicillin-susceptible *S. aureus* (MSSA) from any source (except nasal, rectal, or perirectal samples) that underwent antimicrobial susceptibility testing (AST) for TMP-SMX and was obtained from a patient with no previous isolate yielding the same resistance phenotype in the 14 days prior. Isolates from nasal, rectal, and perirectal sources were excluded to capture clinical infections rather than colonization. Cases were considered community onset (CO) if the culture was obtained prior to day 4 of hospitalization and hospital onset (HO) if the culture was obtained on or after day 4 of hospitalization. Sterile sites included blood, bone, cerebrospinal fluid, lymph nodes, peritoneal fluid, pleural fluid, and synovial fluid; nonsterile sites included respiratory, urine, and wounds.

Participating hospital characteristics were compared to characteristics of all US hospitals in the American Hospital Survey using an iterative proportional fitting procedure to generate nationally representative weighted estimates based on bed size, US census division, urban or rural designation, and teaching status.[9] We calculated the pooled mean percentages of MRSA and MSSA isolates that were not susceptible to TMP-SMX by year using the weighted estimates. Multivariable logistic regression models were used to assess temporal trends in percentage not susceptible to TMP-SMX for MRSA and MSSA. Among MRSA, percentage not susceptible to TMP-SMX were evaluated by US census region using weighted estimates.

National Healthcare Safety Network (NHSN)

We reviewed AST data among *S. aureus* isolates associated with surgical site infections (SSIs), central-line–associated bloodstream infections (CLABSIs), and catheter-associated urinary tract infections (CAUTIs) from ACHs reported to NHSN in 2012 and 2018. Standard definitions and exclusion criteria were applied.[10] We compared the pooled mean percentage of isolates not susceptible to TMP-SMX in 2012 and 2018 among hospitals that reported

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Table 1. Trend Analysis of Percentage of Methicillin-resistant *Staphylococcus aureus* (MRSA) Incident Cases Not Susceptible to Trimethoprim-Sulfamethoxazole Among Acute-Care Hospital Inpatients in the United States—Cerner Health Facts and the Premier Healthcare Electronic Health Records Databases, Weighted Estimates, 2012–2017[a]

Year	2012 Not Susceptible, No. (%)	2013 Not Susceptible, No. (%)	2014 Not Susceptible, No. (%)	2015 Not Susceptible, No. (%)	2016 Not Susceptible, No. (%)	2017 Not Susceptible, No. (%)	Adjusted Annual Change[b] % Change (95% CI)	Adjusted Cumulative 5-year Change[b] % Change (95% CI)
Total	13,816 (3.5)	13,698 (3.6)	17,129 (4.7)	20,666 (5.7)	24,443 (7.1)	23,780 (7.9)	+17.6 (13.4–21.8)	+124.5 (87.7–168.6)
Epidemiologic classification								
Hospital onset[c]	2,760 (4.2)	2,799 (4.7)	2,873 (5.2)	3,581 (6.8)	3,765 (7.9)	3,643 (8.5)	+12.8 (6.9–19.0)	+82.4 (39.7–138.3)
Community onset[d]	11,057 (3.4)	10,899 (3.3)	14,256 (4.5)	17,085 (5.6)	20,678 (7.0)	20,137 (7.8)	+19.3 (15.1–23.6)	+141.2 (101.8–188.4)
Specimen source								
Sterile site[e]	2,970 (3.9)	3,108 (4.2)	4,278 (6.1)	5,461 (7.4)	6,120 (8.6)	5,316 (8.4)	+11.7 (6.4–17.3)	+74.1 (36.6–121.8)
Nonsterile site[f]	10,847 (3.4)	10,591 (3.4)	12,850 (4.3)	15,205 (5.3)	18,323 (6.7)	18,464 (7.8)	+19.1 (14.4–24.0)	+139.3 (95.5–193.0)
Census region[g]								
Northeast	1,156 (2.4)	1,649 (3.3)	1,475 (3.6)	1,957 (4.7)	2,188 (6.1)	2,591 (7.9)	+27.2 (18.2–36.8)	+232.3 (130.8–378.5)
Midwest	7,184 (4.2)	7,021 (4.2)	7,682 (4.9)	9,362 (6.0)	11,262 (7.4)	10,424 (7.8)	+12.8 (7.9–17.9)	+82.8 (46.6–127.9)
South	3,054 (2.9)	2,558 (2.6)	4,794 (4.6)	5,435 (5.6)	6,477 (6.9)	5,782 (6.8)	+19.8 (12.0–28.2)	+147.1 (76.3–246.2)
West	2,423 (3.5)	2,470 (3.5)	3,178 (4.8)	3,912 (6.1)	4,517 (7.3)	4,983 (10.2)	+24.0 (11.2–38.2)	+193.0 (70.2–404.6)

Note. CI, confidence interval.
[a]Data represent weighted estimates generated by comparing participating hospital characteristics to characteristics of all US hospitals in the American Hospital Survey using an iterative proportional fitting procedure. Total cases for each year may differ slightly from sum of subgroups in the same year due to rounding of weighted estimates. Culture results were obtained for patients admitted to participating acute-care hospitals; these may include cultures from inpatients that were collected in outpatient settings if obtained in the 3 days prior to admission or the 3 days after discharge and the results were available in their inpatient medical record.
[b]Multivariable logistic regression models were used to generate the adjusted annual percentage change and adjusted cumulative 5-year change during the study period.
[c]Cases were defined as hospital onset if the culture was obtained on or after day 4 of hospitalization.
[d]Cases were defined as community onset if the culture was obtained immediately before or within 3 days of hospitalization.
[e]Sterile sites included blood, bone, cerebrospinal fluid, lymph nodes, peritoneal fluid, pleural fluid, and synovial fluid.
[f]Nonsterile sites included respiratory, urine, wounds, and other nonsterile sites.
[g]Based on US Census Regions available at https://www.census.gov/geographies/reference-maps/2010/geo/2010-census-regions-and-divisions-of-the-united-states.html.

consistent healthcare-associated infection (HAI) data in both years using the Pearson χ^2 or the Fisher exact test. Among MRSA isolates, we compared the percentage not susceptible to TMP-SMX by HAI type and state. States with ≥20 MRSA isolates with AST reported in 2012 and 2018 were included in the state-level analysis.

Analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Electronic health record databases

From 2012 to 2017, 232,460 MRSA incident cultures and 227,900 MSSA incident cultures were identified. Based on weighted estimates, from 2012 to 2017, 98.3% of all MRSA cultures underwent AST for TMP-SMX, giving an estimate of 2,155,794 cases; among these, 5.3% were not susceptible to TMP-SMX. Within the same period, a projected 98.5% (2,154,582 cases) of MSSA cultures received AST for TMP-SMX, and 1.4% of cases were not susceptible to TMP-SMX.

Model results

During this period, the estimated proportion of cases that were not susceptible to TMP-SMX increased 124.5% among MRSA cases (adjusted 5-year change; 95% confidence interval [CI], 87.7%–168.6%) (Table 1), with a 51.3% increase among MSSA cases (adjusted 5-year change; 95% CI, 19.2%–92.1%) (Appendix Fig. 1 online).

Among MRSA cases, the trend in percentage not susceptible to TMP-SMX increased among sterile site, nonsterile site, hospital-onset, and community-onset categories. The greatest increases were observed among CO-MRSA cases from nonsterile sites (adjusted 5-year change, +158.2%; 95% CI, 111.1%–215.8%).

The trend in percentage not susceptible to TMP-SMX among MRSA cases increased across all 4 census regions. The greatest

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Table 2. Percentage of Isolates Not Susceptible to Trimethoprim-Sulfamethoxazole Among Methicillin-resistant *Staphylococcus aureus* (MRSA) Associated with Surgical Site Infections (SSIs), Central-Line–Associated Bloodstream Infections (CLABSIs), and Catheter-Associated Urinary Tract Infections (CAUTIs)—National Healthcare Safety Network, 2012 and 2018

Type	Continuously Reporting Facilities[a]	2012 No. Not Susceptible/ No. Tested (% Not Susceptible)	2018 No. Not Susceptible/ No. Tested (% Not Susceptible)	2018 vs 2012[b], Absolute % Difference (95% CI)
Overall	3,135	129/3,550 (3.6)	146/2,642 (5.5)	1.9 (0.8–3.0)[c]
CAUTI	2,638	12/186 (6.5)	5/75 (6.7)	0.2 (−6.4 to 6.9)
CLABSI	2,671	32/637 (5.0)	17/318 (5.3)	0.3 (−2.7–3.3)
SSI	2,753	85/2,727 (3.1)	124/2,249 (5.5)	2.4 (1.2–3.5)[c]

Note. CI, confidence interval; CAUTI, catheter-associated urinary tract infections; CLABSI, central-line–associated bloodstream infections; SSI, surgical site infections.
[a]Continuous reporting facilities were defined as follows: (1) for CLABSIs, hospitals that reported at least 1 month of in-plan CLABSI data, in both 2012 and 2018, for the same location; (2) for CAUTIs, hospitals that reported at least 1 month of in-plan CAUTI data, in both 2012 and 2018, for the same location; and (3) for SSIs, hospitals that reported at least 1 month of in-plan SSI data, in both 2012 and 2018, for the same procedure code.
[b]95% confidence intervals for the difference between years were calculated using the Wald statistic.
[c]Statistically significant difference.

increase was in the Northeast (adjusted 5-year change, +232.3; 95% CI, 130.8%–378.5%); however, the West had the highest overall percentage that were not susceptible (10.2%) by 2017.

National Healthcare Safety Network

Overall, 7,243 MRSA and 8,998 MSSA isolates from HAIs were reported in 2012 and 2018 combined. More than 80% of isolates underwent AST for TMP-SMX each year. Nationally, the percentage not susceptible to TMP-SMX among MRSA isolates was 3.6% in 2012 and 5.5% in 2018 (difference, +1.9%; 95% CI, 0.8%–3.0%), but it was unchanged among MSSA isolates during the same period (1.0% in 2012 vs 1.1% in 2018; difference, +0.1%; 95% CI, −0.4% to 0.6%). Among MRSA HAIs, a statistically significant change was only observed among SSIs (3.1% in 2012 vs 5.5% in 2018; difference, +2.4%; 95% CI, 1.2%–3.5%) (Table 2). Overall, 27 states met inclusion criteria (see Appendix online); 4 (14.8%) showed statistically significant increases in the percentage of MRSA isolates that were not susceptible to TMP-SMX in 2018 compared to 2012: New Jersey (2.4% in 2012 vs 23.2% in 2018; difference, 20.8%; 95% CI, 9.3%–32.3%), Maryland (0.0% in 2012 vs 11.1% in 2018; difference, 11.1%; 95% CI, 0.8%–21.4%), Florida (9.0% in 2012 vs 19.6% in 2018; difference, 10.6%; 95% CI, 1.9%–19.3%), Pennsylvania (1.5% in 2012 vs 6.8% in 2018; difference, 5.3%; 95% CI, 2.2%–8.5%).

Discussion

Among 3 different national databases, we found a slight increase in the percentage of MRSA not susceptible to TMP-SMX between 2012 and 2017/2018; changes in MSSA were less evident. Changes in percentage not susceptible varied geographically, and in some areas, observed increases in percentage of MRSA isolates that were not susceptible to TMP-SMX reached levels that could affect its use as empiric or first-line therapy for suspected MRSA infection.

Increases in percentage not susceptible to TMP-SMX among MRSA isolates varied by epidemiologic classification and HAI type. Community-onset cases from nonsterile sites had the highest increases in percentage nonsusceptible. These cases are more likely to represent noninvasive infections such as SSTIs, for which TMP-SMX is a frequently prescribed empiric treatment in outpatient settings. National increases among HAIs were largely driven by SSIs; this finding could reflect differences in strains more likely to cause SSTIs or differences in exposures among patients with SSIs, compared to those with CLABSIs and CAUTIs.

Our study had several limitations. First, we did not assess resistance patterns in outpatient settings where TMP-SMX is commonly prescribed. Although a substantial portion of community-onset cases may be community acquired, it is not possible to differentiate those that occurred in persons with recent healthcare exposures versus those that were acquired in the community. Second, we used specimen sources as a proxy to identify clinical cultures in the EHR databases, but we were unable to determine whether these represented true infection or colonization. Finally, although TMP-SMX is commonly used to treat SSTIs, for CAUTIs, CLABSIs, and other invasive infections, TMP-SMX resistance among MRSA is less clinically relevant.

Increasing TMP-SMX resistance among MRSA has the potential to limit its effectiveness as a current empiric and first-line therapy and bears careful monitoring. Healthcare providers should ensure that TMP-SMX remains active against MRSA in their area using current antibiograms, select appropriate antibiotic regimens based on local resistance patterns, and monitor patients for treatment failure.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.9

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