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Continued Increase of Erythromycin Nonsusceptibility and Clindamycin Nonsusceptibility Among Invasive Group A Streptococci Driven by Genomic Clusters, United States, 2018–2019

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Abstract

We analyzed 9630 invasive GAS surveillance isolates in the USA. From 2015–2017 to 2018–2019, significant increases in erythromycin-nonsusceptibility (18% vs 25%) and clindamycin-nonsusceptibility (17% vs 24%) occurred, driven by rapid expansions of genomic subclones. Prevention and control of clustered infections appear key to containing antimicrobial resistance.

Keywords

group A *Streptococcus*; invasive disease; antimicrobial resistance; genomic cluster

Penicillin and amoxicillin are first-line treatments for group A *Streptococcus* (GAS) infections as clinical GAS isolates remain universally susceptible to β-lactam antibiotics [1].

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Macrolides (such as azithromycin and clarithromycin) are additional alternatives for treating noninvasive GAS infections, especially among individuals with penicillin allergies [1]. GAS susceptibility and resistance to macrolides can be predicted by testing the first-generation macrolide, erythromycin [2]. The lincosamide antibiotic clindamycin, combined with high-dose penicillin, is the recommended treatment for severe invasive GAS (iGAS) infections [3]. From 2006 to 2017, there has been an increase in the proportion of iGAS infections in the United States caused by strains that are erythromycin nonsusceptible (EryNS) and clindamycin nonsusceptible (CliNS) [4, 5], suggesting underlying changes in the circulating GAS strains.

Macrolide and lincosamide antibiotics inhibit bacterial protein synthesis by binding to the ribosomal peptidyl transferase center. Acquisition of *erm* family genes (eg, *ermB*, *ermTR*, and *ermT*) confers GAS resistance to both macrolides and clindamycin (including inducible resistance). Acquisition of the *mef* and *msrD* family genes confers resistance to erythromycin but not clindamycin [6]. Rare resistance mechanisms include spontaneous mutations in 23S rRNA or ribosomal proteins L4 and L22 target sites [7]. Recently, whole-genome sequencing (WGS) technologies have been applied to detect resistance genes and predict antimicrobial minimum inhibitory concentrations (MICs) [8]. WGS-based analysis can also identify genomically closely related isolate clusters (genomic clusters), indicating close connection in a transmission network. An isolate can be defined as clustered if its genomic sequence is nearly identical to that of another isolate [9–11]. For both GAS and *Streptococcus pneumoniae*, genomic clusters of invasive infection were associated with persons experiencing homelessness (PEH) and persons who inject drugs (PWID) [9–12].

Here, we use WGS to characterize iGAS isolates identified from Active Bacterial Core surveillance (ABCs) to update GAS macrolide and clindamycin resistance trends as well as to identify the underlying determinants.

METHODS

We identified iGAS cases through ABCs, a laboratory- and population-based surveillance for severe bacterial infections currently implemented in 10 US states [13]. The ABCs case definition for iGAS disease was illness with isolation of GAS from a normally sterile site or isolation of GAS from a wound culture and accompanied by necrotizing fasciitis or streptococcal toxic shock syndrome. WGS of iGAS isolates was performed at the CDC *Streptococcus* Laboratory as previously described [14]. We excluded isolates with whole-genome assemblies that contained <1.5 M total bases or >150 contigs from subsequent analysis as a sequencing quality control measure. EryNS and CliNS were defined according to the Clinical and Laboratory Standards Institute MIC breakpoints [2].

Pair-wise single-nucleotide polymorphism (SNP) distances among all iGAS isolates belonging to the same *emm* type were calculated using the MUMmer package as previously described [10]. An isolate was defined as clustered if it differed from another isolate by ≤10 SNPs per 1.5 Mb of the 2 aligned genomes. A core-genome phylogenetic tree was constructed using Parsnp software [15] and annotated using the ggtree R package.

Proportions of EryNS or CliNS iGAS isolates were calculated. Equal group proportions were assessed using the Fisher exact test. The χ^2 test for trend in proportions (trend test) was used to evaluate proportion trends over time. All *P* values were 2-sided, and a *P* value <.05 was considered statistically significant. All analyses were performed using R software version 3.4.3.

ABCs case reporting and isolate collection were considered to be public health surveillance activities that were exempt from institutional review by the Centers for Disease Control and Prevention. Informed consent was not required.

RESULTS

A total of 4369 iGAS isolates identified in 2018–2019 and 5261 isolates identified in 2015–2017 were included in this study, accounting for approximately 85% of all iGAS infection cases reported to the ABCs during the 5-year period. Compared with years 2015–2017, the proportion of EryNS isolates increased significantly from 18.1% (953 of 5261) to 25.0% (1091 of 4369) in 2018–2019 (*P* < .001; Figure 1A). A similar increase was observed for the proportion of CliNS isolates (17.0% vs 24.2%; *P* < .001; Figure 1A). Virtually all CliNS isolates were EryNS due to shared resistance mechanisms. Among all of the 2044 EryNS isolates in 2015–2019, 2034 (99.5%) had 1 of the 4 major macrolide/lincosamide resistance mechanisms (*erm*B, *erm*T, *erm*TR, or *mef* genes). From 2015 to 2019, *ermB*$^+$, *ermT*$^+$, and *ermTR*$^+$ isolates, which were both EryNS and CliNS, each showed a significant increase in proportion among all iGAS isolates (*P* = .01, *P* < .0001, and, *P* < .0001, respectively; Figure 1B). In contrast, the proportion of *mef*$^+$ isolates, which were EryNS but clindamycin susceptible, did not show a significant change in the same period (*P* > .05; Figure 1B). The *ermT*$^+$ isolates increased sharply in 2017–2018, mainly due to the fast expansion of *emm*92, which was a predominantly *ermT*$^+$ strain.

The cluster analysis of 2015–2019 iGAS isolates (n = 9630) identified 5576 (59.9%) clustered isolates. The proportion of clustered isolates among EryNS isolates (63.6%, 1301 of 2045) was slightly but significantly higher than that among susceptible isolates (58.9%, 4465 of 7585; *P* < .0001). To determine the contribution of clustered isolates to the increased resistance among iGAS, we examined the proportions of EryNS isolates that were either clustered or nonclustered among all iGAS isolates (Figure 1C). The proportion of clustered EryNS isolates increased significantly from 10.5% (553 of 5261) in 2015–2017 to 17.1% (747 of 4369) in 2018–2019 (*P* < 0.0001; Figure 1C). In contrast, the proportion of nonclustered EryNS isolates remained comparable between the 2 periods (7.6% vs 7.8%; *P* = .65; Figure 1C). Consistently, the trend test for proportion of clustered EryNS isolates from 2015 to 2019 showed a significant increase (*P* < .0001), while no significant trend was found for proportion of nonclustered EryNS isolates (*P* = .60). For CliNS isolates in 2015–2019, a similar pattern of expansion in the clustered, but not the nonclustered, CliNS isolates was also observed (Figure 1D). In 2018–2019, patients who were PEH or PWID (n = 496) were significantly associated with clusters (odds ratio [OR] = 3.1, *P* < .001), EryNS (OR = 1.4, *P* < .001), and CliNS (OR = 1.5, *P* < 0.001), consistent with results in previous years.

In 2018–2019, 65% EryNS isolates (711 of 1091) belonged to the 6 *emm* types that already had >50% EryNS isolates within the *emm* type in 2015–2017, including *emm* types 92, 11, 83, 169, 58, and 94. A notable exception was observed in *emm49*. In 2015–2017, all *emm49* isolates (368 of 368) were susceptible to both erythromycin and clindamycin (Supplementary Table 1). However, the proportion of EryNS and CliNS isolates within *emm49* increased to 8.3% (12 of 144) in 2018 and further increased to 31.7% (32 of 101) in 2019 due to the emergence of *ermTR*$^+$ (n = 43) and *ermB*$^+$ (n = 1) isolates (Supplementary Figure 1A). Phylogenetic analysis of all *emm49* isolates indicated that 38 of the 44 EryNS and CliNS isolates belonged to a single *ermTR*$^+$ sublineage detected exclusively in Maryland during 2018–2019 (designated $M49_{MD}$; Supplementary Figure 1B). Within the $M49_{MD}$ sublineage, median pairwise distance among the 38 isolates was 3 SNPs (range, 0–7), suggesting a single genomically closely related cluster that emerged recently. In Maryland, the $M49_{MD}$ sublineage was first identified in August 2018, with 37 additional invasive infections by the same subclone occurring within the next 15 months. By the fourth quarter of 2019, $M49_{MD}$ had become the dominant *emm49* sublineage in Maryland, accounting for 71% (10 of 14) of *emm49* iGAS isolates identified in that state.

DISCUSSION

In this study, we found that combined macrolide and clindamycin resistance among iGAS isolates remained substantial in 2018–2019 after a continued increase since 2017. The high prevalence of resistance appeared to result from both expansion of predominantly resistant *emm* types (eg, *emm* types 92, 11, and 83) and emergence of new resistant sublineages among previously susceptible *emm* types (eg, *emm49*). Importantly, nearly all increases of EryNS and CliNS could be accounted for by genomic clusters of resistant isolates, suggesting a prominent role of temporally and genomically related iGAS infections in facilitating the spread of antimicrobial resistance. Genomic clusters were more frequently observed in certain populations including PWH and PWID [10, 11]. These disadvantaged populations also showed a higher risk of EryNS and CliNS infections [4]. Thus, targeted control of clustered iGAS infections, particularly among disadvantaged populations, could help in containing antimicrobial resistance.

The study results also highlight the impact of the fast evolutionary potential of GAS. In this case, the acquisition of *ermTR* genes resulted in the emergence of an EryNS and CliNS *emm49* sublineage that differed from the susceptible *emm49* ancestor by only a few core-genome SNPs. The acquisition event might have increased the fitness advantage of this GAS lineage in the presence of antibiotics, which could in turn facilitate the evolution of further potentially advantageous mutations by allowing continued bacterial replication in antibiotic-treated host individuals. On a more immediate note, the study findings suggest that caution is warranted when using macrolides and clindamycin to treat GAS infections in the United States, given the continued increase of EryNS and CliNS among clinical isolates.

The study had several limitations. The focus on invasive GAS alone provides limited information on the resistance trend in noninvasive infections that could have significant community impacts with respect to antimicrobial selection and to sequelae of incompletely treated streptococcal pharyngitis. The retrospective nature of the study could also limit

the data available for variables such as clinical outcomes for those with resistant isolates. Future studies are needed to evaluate interventions that interrupt the development of resistant clusters and to inform guidance development regarding treatment of streptococcal infections in penicillin-allergic patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

The sequencing reads files of the study isolates were submitted to the National Center for Biotechnology Information Sequence Read Archive under BioProject PRJNA395240. For this study, we used the *Streptococcus pyogenes* multilocus sequence typing website (https://pubmlst.org/organisms/streptococcus-pyogenes/) located at the University of Oxford.

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References

1. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis 2012; 55:e86–102. [PubMed: 22965026]
2. CLSI (Clinical and Laboratory Standards Institute). Performance Standards for Antimicrobial Susceptibility Testing, 31st ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute, 2021.
3. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014; 59:e10–52. [PubMed: 24973422]
4. Fay K, Onukwube J, Chochua S, et al. Patterns of antibiotic nonsusceptibility among invasive group A Streptococcus infections—United States, 2006–2017. Clin Infect Dis 2021; 73:1957–64. [PubMed: 34170310]
5. Li Y, Rivers J, Mathis S, et al. Genomic surveillance of Streptococcus pyogenes strains causing invasive disease, United States, 2016–2017. Front Microbiol 2020; 11:1547. [PubMed: 32849323]
6. Iannelli F, Santoro F, Santagati M, et al. Type M resistance to macrolides is due to a two-gene efflux transport system of the ATP-binding cassette (ABC) superfamily. Front Microbiol 2018; 9:1670. [PubMed: 30108557]
7. Weisblum B Erythromycin resistance by ribosome modification. Antimicrob Agents Chemother 1995; 39:577–85. [PubMed: 7793855]
8. Boolchandani M, D'Souza AW, Dantas G. Sequencing-based methods and resources to study antimicrobial resistance. Nat Rev Genet 2019; 20:356–70. [PubMed: 30886350]
9. Bubba L, Bundle N, Kapatai G, et al. Genomic sequencing of a national emm66 group A streptococci (GAS) outbreak among people who inject drugs and the homeless community in England and Wales, January 2016-May 2017. J Infect 2019; 79:435–43. [PubMed: 31419474]
10. Li Y, Dominguez S, Nanduri SA, et al. Genomic characterization of group A streptococci causing pharyngitis and invasive disease in Colorado, USA, June 2016–April 2017. J Infect Dis 2022; 225:1841–51. [PubMed: 34788828]
11. Metcalf BJ, Chochua S, Walker H, et al. Invasive pneumococcal strain distributions and isolate clusters associated with persons experiencing homelessness during 2018. Clin Infect Dis 2021; 72:e948–56. [PubMed: 33150366]

12. Beall B, Walker H, Tran T, et al. Upsurge of conjugate vaccine serotype 4 invasive pneumococcal disease clusters among adults experiencing homelessness in California, Colorado, and New Mexico. J Infect Dis 2021; 223:1241–9. [PubMed: 32798216]

13. Active Bacterial Core Surveillance. Available at: https://www.cdc.gov/abcs/index.html. Accessed 17 June 2022.

14. Chochua S, Metcalf BJ, Li Z, et al. Population and whole genome sequence based characterization of invasive group A streptococci recovered in the United States during 2015. mBio 2017; 8:e01422–17. [PubMed: 28928212]

15. Treangen TJ, Ondov BD, Koren S, Phillippy AM. The Harvest suite for rapid core-genome alignment and visualization of thousands of intraspecific microbial genomes. Genome Biol 2014; 15:524. [PubMed: 25410596]

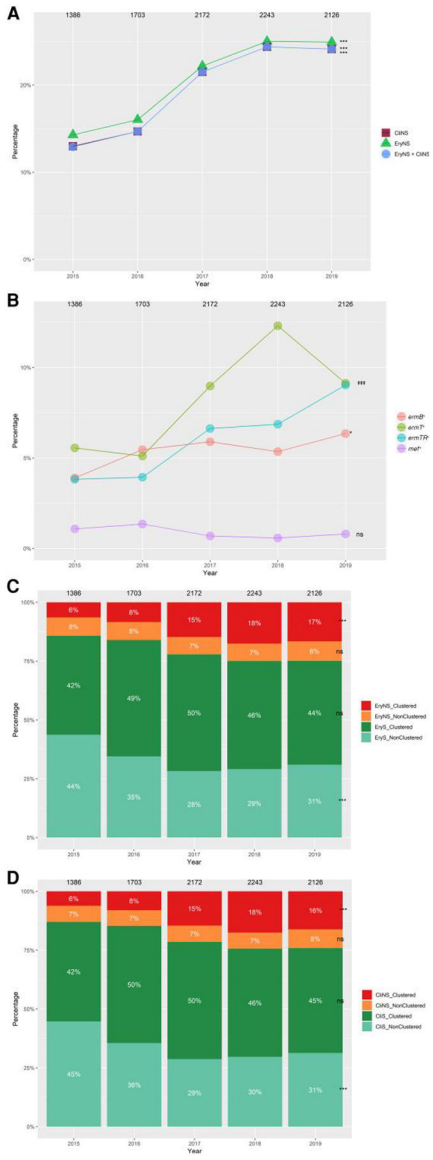

Figure 1.

Increase of erythromycin nonsusceptibility and clindamycin nonsusceptibility among invasive group A streptococci, United States, 2018–2019. *A,* Proportions of isolates that were EryNS, CliNS, or coresistant to both (EryNS + CliNS). The total number of isolates used for proportion calculations is shown for each year. *B,* Proportions of isolates that were positive for resistant gene targets *ermB*, *ermT*, *ermTR*, or *mef*. *C,* Proportions of isolates that were EryNS and clustered (EryNS_Clustered), EryNS and nonclustered (EryNS_Non-Clustered), EryS and clustered (EryS_Clustered), and EryNS and nonclustered (EryNS_NonClustered). See text for details. *D,* Similar to (*C*) except reporting the proportions for clindamycin. ***, $P < .001$ for trend test; *, $P < .05$; ns, $P > .05$. Abbreviations: CliNS, clindamycin nonsusceptible; EryNS, erythromycin nonsusceptible.