



Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc



Brief report

Epidemiological changes in invasive *Streptococcus pyogenes* infection during the UK alert period: A molecular comparative analysis from a tertiary Spanish hospital in 2023



Alfredo Maldonado-Barrueco^a, Iván Bloise^a, Emilio Cendejas-Bueno^{a,b}, Francisco López-Rodrigo^a, Julio García-Rodríguez^{a,b}, Fernando Lázaro-Perona^{a,*}

^a Clinical Microbiology and Parasitology Department, Hospital Universitario La Paz, Madrid, Spain

^b CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain

ARTICLE INFO

Article history:

Received 27 July 2023

Accepted 14 September 2023

Keywords:

Streptococcus pyogenes

GAS, group A *Streptococcus*

Bloodstream infection

Whole-genome sequencing

Emm

ABSTRACT

Objectives: To study the genomic epidemiology of *Streptococcus pyogenes* causing bloodstream infections (GAS-BSI) in a Spanish tertiary hospital during the United Kingdom invasive *S. pyogenes* outbreak alert.

Methods: Retrospective epidemiological analysis of GAS-BSI during the January–May 2017–2023 period. WGS was performed using Ion torrent GeneStudio™ S5 system for *emm* typing and identification of superantigen genes in *S. pyogenes* isolated during the 2022–2023 UK outbreak alert.

Results: During 2023, there were more cases of GAS-BSI compared to the same period of previous year with a non-significant increase in children. Fourteen isolates were sequenced. The *emm1* (6/14, 42.9%) and *emm12* (2/14, 14.3%) types predominated; 5 of 6 (75%) *emm1* isolates were from the M1_{UK} clone. The most detected superantigen genes were *speG* (12/14, 85.7%), *speC* (10/14, 71.4%), *speJ* (7/14, 50%), and *speA* (5/15, 33.3%). *speA* and *speJ* were predominant in M1_{UK} clone.

Conclusions: Our genomic epidemiology in 2023 is similar to the reported data from the UK outbreak alert in the same period and different from previous national *S. pyogenes* surveillance reports.

© 2023 Sociedad Española de

Enfermedades Infecciosas y Microbiología Clínica. Published by Elsevier España, S.L.U. All rights reserved.

Cambios epidemiológicos en la infección invasiva por *Streptococcus pyogenes* durante el periodo de alerta en Reino Unido: análisis molecular comparativo de un hospital terciario español en 2023

RESUMEN

Objetivos: Estudiar la epidemiología genómica de aislados de *Streptococcus pyogenes* causantes de bacteriemia (GAS-BSI) en un hospital de tercer nivel español durante la alerta por incremento de infecciones invasivas por *S. pyogenes* en el Reino Unido.

Métodos: Análisis epidemiológico retrospectivo de GAS-BSI durante el periodo enero-mayo 2017–2023. Se realizó una secuenciación de genoma completo con el sistema Ion torrent GeneStudio™ S5 de los aislados obtenidos durante la alerta de brote del Reino Unido 2022–2023 para tipificación *emm* e identificación de genes de superantígenos.

Resultados: Durante el periodo enero-mayo de 2023 hubo más casos de GAS-BSI que en el mismo periodo de años anteriores con un aumento no significativo en niños. Se secuenciaron 14 aislados. Predominaron los tipos *emm1* (6/14, 42,9%) y *emm12* (2/14, 14,3%); 5 de 6 (75%) aislados *emm1* eran del clon M1_{UK}. Los genes de superantígenos más detectados fueron *speG* (12/14, 85,7%), *speC* (10/14, 71,4%), *speJ* (7/14, 50%) y *speA* (5/15, 33,3%). Los genes *speA* y *speJ* predominaron en el clon M1_{UK}.

Palabras clave:

Streptococcus pyogenes

Estreptococo del grupo A

Bacteriemia

Secuenciación del genoma completo

Emm

* Corresponding author.

E-mail address: fernandolazaroperona@gmail.com (F. Lázaro-Perona).

Conclusiones: Nuestra epidemiología genómica de *Streptococcus pyogenes* causantes de bacteriemia en 2023 es similar a los datos comunicados por el Reino Unido durante el mismo periodo y diferente de los informes nacionales previos de vigilancia.

© 2023 Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

On December 2nd, 2022, the Health Security Agency from London (United Kingdom, UK) alerted of an increase of *Streptococcus pyogenes* (Group A *Streptococcus*, GAS) invasive infections.¹ Characterization of the GAS isolates showed that the recently described M1_{UK} clone and *emm12* were predominant during the outbreak. The emergence of the *S. pyogenes* clone during the UK alert period has raised concerns about the potential spread and impact of these strains,² especially when the M1_{UK} clone has been reported in other countries.^{2,3}

In the pre COVID-19 pandemic period, the National Center for Microbiology of Spain (National Institute Carlos III) reported the first nationwide microbiological, epidemiological and characterization study of invasive GAS disease between 2007 and 2019 being the *emm1*, *emm89*, and *emm3* the most prevalent *emm* types in our country.⁴

Meanwhile, in Madrid (Spain), it has been recently reported an increase of the GAS infections in children compared with the first two pandemic COVID-19 years (2020–2021)⁵ and a non-significant increase of *S. pyogenes* bloodstream infections (GAS-BSI) in children population.⁶

The aim of this study was to investigate possible changes on the genomic epidemiology and incidence of invasive GAS at our tertiary care center, focusing on bloodstream infections, during the UK alert period (2023).

Methods

We recovered all GAS isolated from blood cultures between January and May 2023. Blood cultures were incubated using the VirtuoTM system (BioMérieux®, Marcy l'Etoile, France) and identified according to the protocol described by García-Clemente et al.⁷

Demographic, clinical, and analytical data of patients with GAS-BSI was retrospectively collected from the hospital medical records.

S. pyogenes DNA extraction was carried out using the DNeasy® blood & Tissue kit (Qiagen GmbH, Hilden, Germany) and sequenced in the Ion GeneStudio S5 system (Thermo Fisher Scientific, Massachusetts, EEUU) using the NEBNext® Fast DNA Library Prep Set for Ion TorrentTM (New England Biolabs, Ipswich MA, USA). Genome assembly was performed using spades v3.14.1 (<https://github.com/ablab/spades>) and *emm* typing using the emmtyper tool v0.2.0 (<https://github.com/MDU-PHL/emmtyper>)

Analysis of virulence genes was performed using abricate v1.0.1 (<https://github.com/tseemann/abricate>) and the Virulence Factor DataBase (<https://www2.cdc.gov/vaccines/biotech/strepblast.asp>). Determination of the M1_{UK/global} clone analysis through SNP analysis using the Geneious prime 2023.0.2.⁸ software. Sequencing data of all isolates are available at the European Nucleotide Archive (ENA) under the Project PRJEB64433.

Antimicrobial susceptibility was performed using the microdilution method with MicroScan WalkawayTM (Beckman Coulter®, Indianapolis, IN, USA) system using the MSTRP+ 6 panel. The MIC values were interpreted following EUCAST breakpoints, version 12.0 (http://www.eucast.org/clinical_breakpoints/).

Table 1
Number of *S. pyogenes* bloodstream infections (GAS-BSI) by population age and per years (January–May, 2017–2023).

Year	Patients (January–May)	Pediatric patients (%)	Median age IQR
2017	3	0	53 [41–61]
2018	6	1 (17%)	54 [42–64]
2019	7	4 (57.2%)	29 [2–68]
2020	4	3 (75%)	22 [3–53]
2021	0	N/A	N/A
2022	1	1 (100%)	1 (N/A)
2023	14	3 (21.4%)	50 [33–73]

Results

We diagnosed 35 cases of GAS-BSI during the months of January–May of the years 2017–2023. Between 2017 and 2022, there were 21 cases with a median number of 3.5 [IQR = 2.5–4.5] per year, while the number of cases during the same period in 2023 reached 14 (Table 1). During the 2017–2022 period, there were 9 out of 21 GAS-BSI cases in pediatric population (42.9%) with a mean age of 4 years while in the 2023 period and only 3 out of 14 cases occurred in children (21.43%) with a mean age of 7 years. In relation to the focus of GAS-BSI bloodstream infections in 2023, ten out of the 14 patients (71.4%) had a cutaneous focus, three of 14 (21.4%) had a respiratory portal of entry and one patient (7.2%) had an abdominal focus. Twelve of the 14 patients (85.71%) were pregnant women or had a previous pathology such as transplantation, diabetes, COPD or cancer.

According to the WGS analysis of 2023 GAS-BSI isolates, we reported eight *emm* types: *emm1*, *emm12*, *emm4*, *emm5*, *emm11*, *emm22*, *emm28*, and *emm109* being the most frequent the *emm1* (6/14, 42.9%), and *emm12* (2/14, 14.3%) (Fig. 1). Among the six GAS *emm1*, five out of the six *emm1* types (83.3%) presented the 27 SNPs associated with the M1_{UK} clone. The fourteen GAS-BSI isolates were susceptible to beta-lactams, macrolides, clindamycin and fluoroquinolones.

We analyzed the presence of 11 superantigen genes for each GAS-BSI isolated sequenced by WGS including *smeZ*, *speA*, *speC*, *speG*, *speH*, *speI*, *speJ*, *speK*, *speL*, *speM* and *ssa* genes. The mainly superantigen genes found were the streptococcal mitogenic exotoxin Z (*smeZ*) (14/14, 100%), followed by *speG* (12/14, 85.7%), *speC* (10/14, 71.4%), and *speJ* (7/14, 50%) genes. All five *emm1* M1_{UK} clones had *speA* and *speJ* superantigen genes. However, the only M1_{global} clone had *speJ* but not *speA* superantigen genes.

Discussion

The emergence of the M1_{UK} clone and *emm12* strains in the United Kingdom raised concerns about their potential spread and impact, especially when such increase of cases has been also reported in other countries such as France, the Netherlands, Finland, Sweden or USA.^{9–12}

In the same way, our findings indicate an increase in the number of GAS-BSI in our setting during January–May 2023 compared to the same period in previous years but, contrary to other countries reports, at the expense of the increase in the number of cases in adults. As there have been no changes in the attended population or blood culture extraction protocols in children, the cause of this

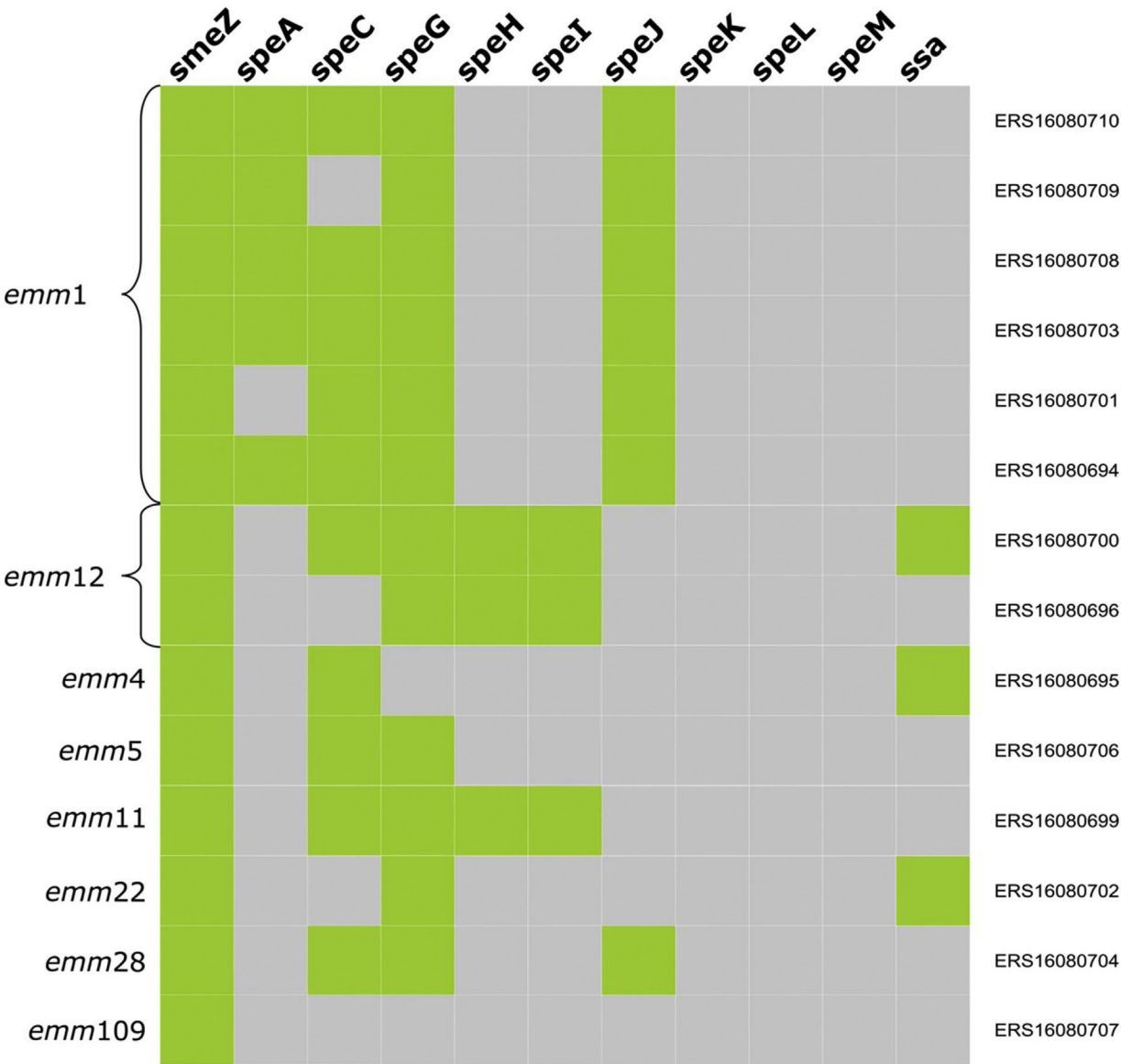


Fig. 1. *emm* types and superantigen genes of *S. pyogenes* bacteremia during January–May 2023. The figure shows the presence (green) or absence (gray) of virulence genes among the *S. pyogenes* *emm* types. The ENA accession to the isolate reads is located on the right column.

discrepancy is yet unknown and will be studied in the future. However, it is important to highlight that in the two years prior to the increase in GAS-BSI cases, marked by the SARS-CoV-2 pandemic, the number of cases were exceptionally low, so it is plausible a relationship between the two events. In addition, our current genomic epidemiology of GAS-BSI seems dominated by the M1_{UK} clone followed by the *emm12*, similar to the data reported in the UK during the GAS alert 2022–2023. This should bring the attention as the M1_{UK} clone detected in Madrid produces both the *speA* and *speJ* superantigens that might be related to higher invasiveness of these strains.^{13,14}

Our main limitation is that we have not characterized the *S. pyogenes* strains isolated from blood cultures in our setting in the 2017–2022 period. Nonetheless, this limitation is compensated by the extensive national and local data published in previous years.⁴ Moreover, we did not include in our study other invasive GAS samples (pleural fluid, CSF, pneumonia, necrotizing fasciitis) as they were scarce and more heterogeneous.

In conclusion, this study provides preliminary insights into the genomic epidemiology and incidence of GAS-BSI during the UK alert period in 2023. The observed increase in GAS-BSI cases overall, but not in children, suggests differences in the affected population in our environment. The predominance of the M1_{UK} clone and the presence of specific superantigen genes among the isolates highlight the need for continued surveillance and further investigation into the molecular characteristics and clinical implications of circulating GAS strains.

Ethics approval

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The data used are from clinical samples that were necessary for the clinical diagnosis of the patients. The epidemiological *S. pyogenes* study was not included in the clinical report of the patients.

Acknowledgements

We would like to thank Pablo Prieto Casado for his support with the sequencing tasks.

Funding

Not funding.

Conflict of interests

None declared.

References

1. Group A streptococcal infections: report on seasonal activity in England, 2022–2023. GOV.UK. <https://www.gov.uk/government/publications/group-a-streptococcal-infections-activity-during-the-2022-to-2023-season/group-a-streptococcal-infections-report-on-seasonal-activity-in-england-2022-to-2023> [consulted 4.7.23].
2. Alcolea-Medina A, Snell LB, Alder C, Charalampous T, Williams TGS, Tan MKI, et al. The ongoing *Streptococcus pyogenes* (Group A *Streptococcus*) outbreak in London, United Kingdom, in December 2022: a molecular epidemiology study. *Clin Microbiol Infect*. 2023;29:887–90.
3. Davies MR, Keller N, Brouwer S, Jespersen MG, Cork AJ, Hayes AJ, et al. Detection of *Streptococcus pyogenes* M1UK in Australia and characterization of the mutation driving enhanced expression of superantigen SpeA. *Nat Commun*. 2023;14:1051.
4. Villalón P, Sáez-Nieto JA, Rubio-López V, Medina-Pascual MJ, Garrido N, Carrasco G, et al. Invasive *Streptococcus pyogenes* disease in Spain: a microbiological and epidemiological study covering the period 2007–2019. *Eur J Clin Microbiol Infect Dis*. 2021;40:2295–303.
5. De Ceano-Vivas M, Molina Gutiérrez MÁ, Mellado-Sola I, García Sánchez P, Grandioso D, Calvo C, et al. *Streptococcus pyogenes* infections in Spanish children before and after the COVID pandemic. Coming back to the previous incidence. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2023;30(S2529– 993X(23)00187–9) (Online ahead of print).
6. Cobo-Vázquez E, Aguilera-Alonso D, Carbayo T, Figueroa-Ospina LM, Sanz-Santaufemia F, Baquero-Artigao F, et al. Epidemiology and clinical features of *Streptococcus pyogenes* bloodstream infections in children in Madrid, Spain. *Eur J Pediatr*. 2023;182:3057–62.
7. García Clemente P, Romero-Gómez MP, García-Rodríguez J, Cendejas-Bueno E. Optimized identification of microorganisms directly from positive blood cultures by MALDI-TOF to improve antimicrobial treatment. *Rev Esp Quimioter*. 2022;35:362–9.
8. Lynskey NN, Jauneikaite E, Li HK, Zhi X, Turner CE, Mosavie M, et al. Emergence of dominant toxigenic M1T1 *Streptococcus pyogenes* clone during increased scarlet fever activity in England: a population-based molecular epidemiological study. *Lancet Infect Dis*. 2019;19:1209–18.
9. Unexpected increase in invasive Group A streptococcal infections in children after respiratory viruses outbreak in France: a 15-year time-series analysis. *Open Forum Infect Dis*. 2023;10:ofad188.
10. Kailankangas V, Vilhonen J, Gröndahl-Yli-Hannuksela K, Rantakokko-Jalava K, Seiskari T, Auranen K, et al. Presence of *Streptococcus pyogenes* in the throat in invasive group A streptococcal disease: a prospective two-year study in two health districts, Finland. *Infect Dis (Lond)*. 2023;55:405–14.
11. Johannesen TB, Munkstrup C, Edslev SM, Baig S, Nielsen S, Funk T, et al. Increase in invasive group A streptococcal infections and emergence of novel, rapidly expanding sub-lineage of the virulent *Streptococcus pyogenes* M1 clone, Denmark, 2023. *Euro Surveill*. 2023;28:2300291.
12. Dunne EM, Hutton S, Peterson E, Blackstock AJ, Hahn CG, Turner K, et al. Increasing incidence of invasive group A *Streptococcus* disease, Idaho, USA, 2008–2019. *Emerg Infect Dis*. 2022;28:1785–95.
13. González-Abad MJ, Sanz MA. Invasive *Streptococcus pyogenes* infections (2011–2018): EMM-type and clinical presentation. *An Pediatr (Engl Ed)*. 2020;92:351–8.
14. Lintges M, Van Der Linden M, Hilgers R, Arlt S, Al-Lahham A, Reinert RR, et al. Superantigen genes are more important than the *emm* type for the invasiveness of Group A *Streptococcus* infection. *J Infect Dis*. 2010;202:20–8.