ORIGINAL ARTICLE

Changes in the epidemiology and prognosis of *Streptococcus pyogenes* necrotizing fasciitis after COVID-19: Insights from a university hospital

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ABSTRACT

Background and aim: Following the COVID-19 pandemic, numerous countries have reported a significant increase in invasive *Streptococcus pyogenes* infections. Our aim was to analyze the epidemiology, clinical characteristics, morbidity, and prognosis of patients with *S. pyogenes*-associated necrotizing fasciitis in the post-COVID-19 era.

Methods: This retrospective study was conducted at a university hospital and included all consecutive adult patients (≥18 years) diagnosed with *S. pyogenes*-associated necrotizing fasciitis between 2012 and 2023. Two study periods were compared: pre-COVID-19 (2012–2019) and post-COVID-19 (2020–2023). The primary objective was to determine incidence (admissions per 100,000 inhabitants). Secondary outcomes included in-hospital mortality, length of hospital stay and intensive care unit admissions between the periods.

Results: A total of 34 cases were included: 17 in the pre-COVID-19 period and 17 in the post-COVID-19 period, with an incidence of 0.42/100,000 vs. 1.13/100,000 inhabitants-year, respectively (P<0.01). Compared to the pre-COVID-19 period, patients in the post-COVID-19 period had lower Charlson comorbidity index score (median 2 vs. 5, P=0.04), and required fewer fasciotomies (median 1 vs. 3, P=0.01). In-hospital mortality was

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17.6% in both periods, while the length of hospital stay was shorter in the post-COVID-19 period (median 15 vs. 29 days, *P*=0.04).

Conclusions: Our findings reveal an increased incidence of *S. pyogenes*-associated necrotizing fasciitis following the COVID-19 pandemic, predominantly affecting younger patients with lower comorbidity and showing a trend toward better clinical outcomes. Further studies are needed to better understand the underlying factors driving these changes. (www.actabiomedica.it)

Key words: *Streptococcus pyogenes*, necrotizing fasciitis, COVID-19, group A streptococcus, fasciotomy

Introduction

Necrotizing fasciitis (NF) is a life-threatening condition that requires urgent and multidisciplinary management. The incidence of NF is estimated to be 0.4 cases per 100,000 population each year, and it occurs more frequently in patients with several comorbidities including immunosuppression conditions (1-3). *Streptococcus pyogenes* (SP) is one of the most frequent etiologies of NF, and cases are often preceded by upper respiratory tract infections. Therefore, SP could reach the damaged tissue directly through the skin or by hematogenous dissemination (1). At the end of 2022 an outbreak of invasive infections caused by SP was declared in the United Kingdom (UK), affecting children primarily and resulting in over 800 cases of invasive SP infections (4). This led to an increase in intensive care unit (ICU) admissions and deaths in comparison to the pre-COVID-19 years (4,5). Similar to the UK outbreak, other countries such as France, Ireland, the Netherlands, Holland, Sweden and Spain have also reported an increase in the incidence of invasive SP infections (6-10). The cause of this epidemic has not yet been clarified. Some authors suggest that the prolonged use of masks and the social distancing measures imposed during the COVID-19 pandemic may have resulted in a decreased immune response to SP (4,8,11-13). There have also been studies supporting that long-term protection against SP is a consequence of an immune response due to repeated exposure to the bacteria (14,15). In addition to the COVID-19 measures, the epidemic of the UK outbreak, as well as other countries, was explained by the emergence of a new M1UK strain (16,17). In this context, data about cases of NF due to SP is scarce. We aimed to evaluate the epidemiology, the characteristics and the outcomes of the patients with *S. pyogenes*-associated necrotizing fasciitis (SP-NF).

Patients and methods

Study design, setting and participants

This is a retrospective study performed in a university hospital in Spain. Prospective adult (18 years) patients admitted to the Orthopedics and Traumatology Department with diagnosis of SP-NF episodes from January 2012 to December 2023 were selected and recorded in an electronical database. The inclusion criteria were a) patients with intraoperative confirmation of NF, characterized by the presence of devitalized fascia and/or seropurulent exudate); b) first surgical intervention performed by the Orthopedic Surgery and Traumatology Department at our centre; c) microbiological confirmation of SP infection detected in cultures; d) exclusive involvement of the extremities; e) minimal follow-up of 12 months. The exclusion criteria were a) initial suspicion of fasciitis that was not subsequently surgically confirmed; b) patients first treated by other non-orthopedic surgeons and/or who were transferred from other hospitals; and c) loss of follow-up or less than 12 months. We analysed the clinical characteristics, management (surgical and antimicrobial treatments) and

the evolution of the patients differentiating two periods: pre-COVID-19 period (from 2012 to 2019) and a post-COVID-19 period (from 2020 to 2023). Comorbidities included rheumatic disease, parenteral drug use, vascular disease, diabetes mellitus (DM), liver disease, heart failure, chronic kidney disease and immunosuppression. We determined the Charlson Comorbidity Index (CCI) to standardize the comorbidity distribution between the two groups of study (18). The Laboratory Risk Indicator for Necrotizing Fasciitis Score (LRINEC) was calculated at admission (19). We also recorded if patients presented symptoms of respiratory tract infection in the previous days and the presence of predisposing cutaneous and/or vascular lesions. The microbiological analysis included the results of the SP rapid test (CerTest Strep A, Biotecâ), the presence of concomitant bloodstream infection (SP detected in blood cultures performed at admission), and if patients presented confirmed coinfections with other microorganisms.

Surgical and medical management

All patients underwent at least one surgical intervention that included fasciotomy, lavage and debridement. Depending on clinical and analytical evolution, sequential lavage and debridement were performed. The total number of surgeries performed in each case were also recorded. Antibiotic treatments analysed included the use of beta-lactams as well other anti-toxin treatments such as clindamycin or linezolid.

Outcomes

The primary outcome was the incidence estimated in number of SP-NF admitted episodes per 100,000 population-year. Secondary outcomes were all-cause mortality during the admission, in-hospital stays, need for ICU admission and major amputations.

Statistical analysis

Quantitative variables were expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. Qualitative variables were expressed as frequencies with percentages. The normality of quantitative variables was assessed using the Shapiro-Wilk test. To compare quantitative variables, we used parametric tests such as Student's t-test and ANOVA, and nonparametric tests such as the Mann-Whitney U test or the Kruskal-Wallis test. To compare dichotomous qualitative variables, we used either the Chi-square test or Fisher's exact test. For the multivariate analysis, logistic regression was used when the dependent variable was dichotomous and linear regression was used when the dependent variable was quantitative. Odds ratios (ORs) with 95% confidence intervals (95% CI) in brackets are reported. To evaluate correlation between nonparametric quantitative variables, a Spearman's rank correlation coefficient was used. A *P*-value of less than 0.05 was considered statistically significant. All analysis were performed using the SPSS program v26.0 (IBM Corp., Armonk, NY, IBM Corp).

Ethical issues

Institutional review board and ethics committee (Medicine Research Ethics Committee Hospital General Universitario Gregorio Marañón) approved the project (code number COT24.7) on 8 January 2025. The requirement for informed consent was waived.

Results

During the study period a total of 41 episodes were recorded, of which six episodes were excluded because NF was not confirmed, and another case was also excluded because it was initially managed by non-orthopedic surgeons. Finally, 34 (82.9%) episodes were included in the study. Considering the two periods of study, there were 17 cases in the pre-COVID-19 period and 17 in the post-COVID-19 period, resulting in an incidence of 0.42 cases per 100,000 population-year vs. 1.13 cases per 100,000 population respectively. Incidence in the post-COVID-19 period was 2.67 higher (95% CI 1.36-5.22; *P*<0,01).

Patient characteristics and clinical presentation

Overall, the mean age of the total cohort was 58 ± 22.6 years and 52.9% were females. The most frequent comorbidity was peripherical vasculopathy (47.0%). Table 1 summarizes the clinical characteristics of the

Table 1. Clinical characteristics of the patients included in the study.

Variables	Pre-COVID-19 N=17	Post-COVID-19 N=17	*P*
Age, years mean (SD)	62.4 (19.2)	53.8 (25.4)	0.27
Females, n (%)	10 (58.8)	8 (47.1)	0.40
Smoker, n (%)	9 (52.9)	4 (23.5)	0.07
Alcohol use, n (%)	6 (35.2)	4 (23.5)	0.45
Hepatopathy, n (%)	4 (23.5)	1 (5.8)	0.14
Vasculopathy, n (%)	9 (52.9)	6 (35.2)	0.49
DM[1], n (%)	3 (17.6)	3 (17.6)	1
IDU[2], n (%)	2 (11.6)	1 (5.8)	0.54
CKD[3], n (%)	4 (23.5)	2 (11.6)	0.36
Rheumatological disease, n (%)	4 (23.5)	1 (5.8)	0.14
HF[4], n (%)	4 (23.5)	1 (5.8)	0.14
Immunosuppression, n (%)	3 (17.6)	2 (11.6)	0.62
Charlson Comorbidity Index, median (IQR)	5 (2-6)	2 (1-3)	**0.04**
Affected area, n (%) Upper extremities Lower extremities Back	 5 (29.4) 12 (70.5) 0	 9 (52.9) 7 (41.2) 1 (5.8)	 0.17
Predisposing lesion, n (%) Loss of skin continuity Hematoma None	 16 (94.1) 0 1 (5.8)	 14 (82.3) 2 (11.6) 1 (5.8)	 0.31
LRINEC, median (IQR)	7 (7-8)	7 (7-9)	0.3
URT[5] infection, n (%)	6 (35.2)	9 (52.9)	0.3

Abbreviations: [1]DM = Diabetes Mellitus; [2]IDUs = Intravenous Drug Users; [3]CKD = Chronic Kidney Disease; [4]HF = Heart Failure; [5]URT = Upper Respiratory Tract.

patients included in the two groups of study: there were statistically significant differences in the CCI in the patients included in pre-COVID-19 period vs. post-COVID-19 period (median 5 vs. 2, *P*=0.04). Although the difference was not statistically significant, patients from the pre-COVID-19 period were older than those in the post-COVID-19 group (62.4 ± 19.2 vs. 53 ± 25.4 years; *P*=0.27). There were not statistically significant differences in the rest of the variables analysed.

The most frequent affected area were lower limbs (55.8%). In 28 cases, the most frequent predisposition condition was the loss of skin continuity, while in four patients it was a superinfected hematoma. There were two cases in which no predisposing lesion was found. The median LRINEC score at admission was 7.6 (IQR 7-8) without differences between the pre- vs. post-COVID-19 periods (median 7 vs. 7, p = 0.30). A total of 47.0% of the patients presented symptoms of upper respiratory tract infection in the previous days before the admission.

Diagnostic and therapeutic management

The SP rapid antigen test was performed in 31 (91.2%) of the cases, being positive in 25/31 (80.7%). Blood cultures were obtained in 21 patients (61.7%), of which seven (33.3%) presented concomitant bloodstream infection, without differences between pre- and post-COVID-19 periods (29.4% vs. 11.8%, *P*=0.21). Coinfection with another bacteria was observed in five

cases (14.7%): two cases (11.6%) in the pre-COVID-19 and 3 (17.6%) in the post-COVID-19 periods (*P*=0.62). In all the cases, *Staphylococcus aureus* was isolated in addition to SP. The median time elapsed from the patient's admission to the first surgery was 12 hours (IQR 5-24) in pre-COVID-19 vs. 14 hours (IQR 4-36) in post-COVID-19 period, *P*=0.69. The median time from the admission to surgery was statistically significant longer in cases with a negative SP rapid test in contrast to those with a positive SP test (median 8 h vs. 67 hours, *P*<0.01).

Table 2 resumes the therapeutic management. Patients in the pre-COVID-19 period required a median of three (IQR 2-4) fasciotomies while those in the post-COVID-19 required a median of one (IQR 1-2), *P*=0.01. The multivariate analysis showed that suffering the SP-NF in the pre-COVID-19 period (95% CI 0.034-2.89; *P*=0.04) and a LRINEC score >7 (95% CI 0.26-3.41; *P*=0.02) were the variables associated with a major number of debridements (Table 3). All cases were treated with a combination of beta-lactams: combination with other anti-toxin antibiotics were performed in 31 patients, which was clindamycin in 26 (76.4%) cases and linezolid in 5 (14.7%). There were no statistically significant differences concerning the anti-toxin treatment received between the pre- and post-COVID-19 periods.

Morbidity and mortality

In-hospital mortality was 17.6%, both in pre-COVID-19 and in post-COVID-19 periods, *P*=1.0. Patients with a positive blood culture did not present increased morbidity (*P*=0.75) or mortality (*P*=0.18). Length of hospitalization was 29 days (IQR 17-39) in pre-COVID-19 vs. 15 days (IQR 9-27.5) in post-COVID-19, *P*=0.04. A positive correlation was observed between the number of debridements and length of stay (Rho=0.49; *P*<0.01). The presence of complications was more frequent in the pre-COVID-19 group (64.0% vs 41.0%; *P*=0.16). In the pre-COVID-19 period 58.8% of patients underwent ICU admission vs. 47.1% of the patients in the post-COVID-19 period (*P*=0.49). The median of days of ICU stay were 6.5 (IQR 2.7-11.7) vs. 6 (IQR 1.5-10.5) respectively (*P*=0.62) (Table 4).

Only one patient (2.9%) required limb amputation (upper right extremity) due to permanent soft tissue damage. In the multivariate analysis a LRINEC score >7 (95% CI 1.12-1.27; *P*=0.04) and older patients (95% CI 1.02-1.43; *P*=0.04) were associated with the risk of complications. The pre-COVID-19 period (95% CI 0.53-40.08; *P*=0.09) and time to first surgery (95% CI 0.88-1.11; *P*=0.08) presented a trend toward for a higher frequency of complications (Table 5).

Conclusion

Our results showed a 267% increase in the incidence of SP-NF after the COVID-19 pandemic. Most of the patients in the post-COVID-19 period had a lower comorbidity score, lower number of debridements and in-hospital stays were also decreased.

Table 2. Therapeutic management.

Variables	Pre-COVID-19 N=17	Post-COVID-19 N=17	*P*
Coinfection, n (%) *S. aureus*	2 (11.6) 2 (100)	3 (17.6) 3 (100)	0.62
Antibiotic, n (%) Betalactams Clindamycin Linezolid Others	 17 (100) 13 (76.5) 2 (11.6) 2 (11.6)	 17 (100) 13 (76.5) 3 (17.6) 1 (5.8)	0.76
Bloodstream infection, n (%)	5 (29.4)	2 (11.8)	0.21
Number of debridements, median (IQR)	4 (2-4)	2 (1-2)	**0.01**

There were not changes in the treatment of the patients between the two periods of study and better outcomes are presented in post-COVID-19 period. The spread of respiratory viruses and their potential to cause pandemic situations is currently a major concern for governments and health organizations worldwide. When these diseases occur, non-pharmacological interventions such as social distancing or the use of masks are commonly employed. As a result of the significant increase in cases of invasive SP infections, some authors have postulated the "immunity theory": this hypothesis suggests that the social distancing may favor, once removed, the development of other infections due to a decrease or loss of the immune response against some microorganisms (4,8,11-13). Post-pandemic studies have reported an increase in infections caused by pathogens such as respiratory syncytial virus, influenza virus, *Streptococcus pneumoniae* and, as in our case, by *S. pyogenes* (12,20-22). Several recent studies have shown that the impact has been greater in the pediatric population (4,7,10,20,21). However, at our center, the incidence of necrotizing fasciitis in adults has almost tripled the existing records of previous years and the estimated overall incidence (2,3). This is consistent with data from other countries that experienced SP outbreaks. For instance, Johannesen *et al*. (2023) (7) estimated a 3.5-fold higher incidence in the Danish population, while in the Netherlands the number of cases doubled (9). Studies conducted in Spain have found that the rise in cases is not linked to a specific strain of SP (8,13). Nevertheless, in other European countries and more recently in Japan, the emm1 M1UK strain has been observed to predominate in SP outbreaks. The M1UK strain has not been associated with more severe conditions, although immune deficits secondary to NPIs may have contributed to worse clinical outcomes (16, 17). Data show that after the COVID-19 pandemic there have been important changes in the characteristics of the population affected by this pathology. Whereas previously the patients were older people (2,3,23), reaching a peak at around 80 years of age, they are now younger, with our study showing a decrease of 9 years in the mean age. These results are consistent with the United Kingdom data (5). Literature reviews estimate that 60-70% of patients with FN have one underlying disease (1-3). In our post-COVID-19 group, only 48% had predisposing comorbidities, with a significant difference in the CCI compared to pre-COVID-19 cases, affecting less medical complexity. These facts may explain

Table 3. Lineal regression of the number of debridements.

Variables	Coeficiente	95%CI	*P*
Age, years	<0.01	-0.04-0.05	0.92
Pre-COVID-19 period	1.97	0.31-3.63	**0.02**
Charlson-index score	-0.02	-0.43-0.49	0.92
LRINEC score >7	1.98	0.07-3.9	0.04
Time to first surgery	<0.01	-0.01-0.01	0.78
Affected area	-1.21	-2.94-0.52	0.16

Table 4. Complications and mortality.

Variables	Pre-COVID-19 N=17	Post-COVID-19 N=17	*P*
Delayed closure, n (%)	4 (23.5)	2 (11.6)	0.30
ICU[1] admission, n (%)	10 (58.8)	8 (47.1)	0.40
Days of ICU admission, median (IQR)	6.5 (2.7-11.7)	6 (1.5-10.5)	0.62
Plastic surgery intervention, n (%)	5 (29.5)	3 (17.6)	0.40
NV[2] sequelae, n (%)	1 (5.8)	1 (5.8)	1
Limb amputation (%)	0	1 (5.8)	0.30
In-hospital mortality, n (%)	3 (17.6)	3 (17.6)	1
Days of hospitalization, median (IQR)	29 (17.5-39.5)	15 (9-27.5)	**0.04**

Abbreviations: [1]ICU = Intensive Care Unit; [2]NV = Neurovascular.

Table 5. Logistic regression of the morbidity.

Variables	Adjusted OR	95%CI	*P*
Age, years	1.2	1.02-1.43	**0.04**
Pre-COVID-19 period	4.66	0.53-40.8	0.09
Charlson-index score	0.43	-0.43-0.49	0.92
LRINEC score >7	1.23	1.12-1.27	**0.04**
Time to first surgery	0.94	0.88-1.11	0.08
Affected area	0.2	0.01-3.31	0.29

why, in our study only one debridement per patient was performed on average in the post-COVID-19 period, which is below the pre-pandemic numbers and quite far from those reported by other authors (3). Patients in the post-pandemic group had fewer and shorter ICU admissions (2,24). Although this difference was not statistically significant, it is likely due to the limited sample size. In terms of mortality, identical numbers were observed between the two groups, lower than the historical series of NF (3). However, it is important to note that the deaths in the post-COVID-19 period were among patients who had a worse baseline condition and significant previous comorbidities. Recently published studies have shown different results regarding the prognosis of these infectious disease outbreaks after the pandemic. Ren *et al*. (2023) (12) and Bordeau *et al*. (2023) (17) have observed a similar or even lower severity of RSV cases, while Metz *et al*. (2023) (20) have reported an increase in complications and mortality in respiratory tract infections. The main limitation of our study infers that is a retrospective single-center with a limited sample size. Additionally, this design was not suitable for comparing overall morbidity rates since it does not analyze the same complications as other included studies. Variability in treatment strategies, such as different betalactams used were not analyses as risk factors for treatment failure. Finally, we did not perform a genetic analysis of the strains involved in our work and for this reason were not able to know if the increase in the incidence derives from the emergence of the MUK1 strain. This study, however, had several strengths: first, we included all patients admitted to the Orthopedics Department during a 12-year period with a SP-NF diagnosis confirmation, and second, we analysed the comorbidities, the surgical procedures and the complications, and trend to correlate these with the management and the time in which the surgery was performed. In conclusion, we observed an increase in the incidence of SP-FN after the COVID-19 pandemic affecting patients with lower comorbidities in comparison to the pre-COVID-19 period. Further studies are necessary to determine whether the loss of immunity is the main cause or if it is due to a change in the virulence of these microorganisms, which would be a long-term concern.

Ethic approval: Institutional review board and ethics committee (Medicine Research Ethics Committee Hospital General Universitario Gregorio Marañón) approved the project (code number COT24.7) on 8 January 2025.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors contribution: A.G.S. planned the study, collected the data, performed the statistical analysis, analyzed and interpreted results, and wrote the manuscript. M.A.G.Q. and J.M.H.N. collected the data, analyzed and interpreted results. S.V. performed the microbiological analysis, interpreted results and helped in manuscript writing. M.S.S. performed the microbiological analysis. P.S.R., J.M., A.B. and J.V. interpreted results, and critically reviewed the manuscript. All the authors read and approved the final version of the manuscript.

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