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Invasive group A *streptococcus* infections in the intensive care unit: an unsupervised cluster analysis of a multicentric retrospective cohort

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Abstract

Background Invasive group A streptococcus (iGAS) infection incidence is rising. These infections have been studied as a whole but can be associated with critical illness in a population with a wide array of underlying conditions, sites of infection and clinical presentations. Using an unsupervised clustering approach, we aimed to identify specific clinical phenotypes regarding presentation, management and outcome.

Methods This was a retrospective multicentric study including all patients admitted to one of 9 ICUs of Paris University Hospitals for an iGAS infection between 01/03/2018 and 01/08/2023. iGAS infection was defined as GAS growth in any microbiological sample from a sterile site. Patients were grouped according to a clustering algorithm (k-prototypes) using a comprehensive set of clinical and biological variables available upon ICU admission. Clusters were described and clinical presentation, management and outcome were compared.

Results 148 patients were included. According to the Silhouette criterion, patients were grouped in 3 clusters, and 7 patients remained unclassified. Cluster 1 (n = 73) comprised a greater proportion of less severely-ill female patients with painful skin and soft tissue infections, a quarter of whom had taken non-steroidal anti-inflammatory drugs. Cluster 2 (n = 42) was characterized by a high rate of respiratory infections with frequent viral co-infections. Cluster 3 (n = 26) included mostly socially deprived patients with high rates of chronic alcohol consumption and psychiatric illness, with severe organ dysfunction related to otherwise pauci-symptomatic skin and soft tissue infections. There was no significant difference in time to source control across clusters (0 [0–0] vs 0 [0–0] vs 0 [0–1] days, p = 0.12). Patients included in cluster 2 less frequently received antitoxin antibiotics than patients from clusters 1 and 3 (79% *vs* 45% *vs* 69%, p < 0.001) and tended to more frequently require ECMO support (3% vs 12% *vs* 0%, p = 0.07), while those from cluster 1 were less likely to receive invasive mechanical ventilation (48% *vs* 74% *vs* 77%, p = 0.005). There was no difference in ICU-mortality between clusters (19% *vs* 29% *vs* 31%, p = 0.32).

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Conclusions Based on simple and readily available clinical admission characteristics of critically ill patients with iGAS, unsupervised clustering analysis identified three specific patient populations that differed regarding ICU management. Whether tailoring management would affect outcome warrants further research.

Keywords Group A streptococcus, Intensive care unit, Critically-ill, Necrotizing soft-tissue infection, Toxic shock, Social deprivation

Background

Invasive group A streptococcus infection (iGAS) incidence is rising worldwide [1]. These infections are associated with an important mortality and morbidity, with frequent need for intensive care unit (ICU) admission [2]. Critically ill patients with iGAS have mostly been described as a whole, but iGAS can occur in a variety of settings, with diverse sources of infection and different, sometimes insidious, clinical presentations [3]. Moreover, their management is still a matter of debate, especially with regard to adjuvant therapies such as antitoxin antibiotics and even more so, polyvalent intravenous immunoglobulins (IVIg). Indeed the benefits of such treatments have been suggested in some patient subgroups (such as patients with toxic shock syndrome) but not others (such as those with necrotizing soft-tissue infections) [4–6]. Using an unsupervised clustering approach, the aim of this study was to identify specific clinical phenotypes of critically ill patients with iGAS in terms of presentation, management and outcome.

Materials and methods

Study design

This was a retrospective multicenter study including all adult patients admitted to one of 9 ICUs of Paris University Hospitals for an iGAS infection between 01/03/2018 and 01/08/2023. These 9 ICUs account for 221 ICU beds of the roughly 1150 available at the Paris University Hospitals, which are set in a region with over 12 000 000 inhabitants. Patients were identified by the microbiology laboratory of each participating center using a dedicated software as patients with *Streptococcus pyogenes* growth in any microbiological sample from a sterile site (blood cultures, perioperative soft tissue sample, joint fluid, lower respiratory tract samples, cerebrospinal fluid, peritoneal fluid) during an ICU stay. Data were extracted from medical charts. All patients received information that data extracted from their medical charts could be used for research purposes. The study was approved by an institutional review board (*Comité d'Ethique de la Société de Réanimation de Langue Française*, n° 23–037).

Statistical analysis

A clustering analysis was performed to group patients using a comprehensive set of clinical and biological variables available at ICU admission. The methodology used is described hereafter and illustrated in supplemental Fig. 1.

The variables used for the construction of the clusters were the following: age, sex, obesity (BMI ≥ 30 kg/m^2), diabetes, immunosuppression (*i.e.* active cancer or cirrhosis or immunosuppressive drugs), chronic renal failure, cardio-vascular comorbidities (*i.e.* peripheral arterial disease of the lower limb or ischemic heart disease or former ischemic stroke or chronic heart failure), chronic alcohol consumption, social deprivation (*i.e.* homelessness or living in a social care shelter or receiving special minimum benefits (*Couverture Maladie Universelle*)), psychiatric comorbidities, non-steroidal anti-inflammatory drug (NSAID) consumption in the week before first symptoms, fever, gastrointestinal signs (*i.e.* nausea or vomiting, diarrhea or abdominal pain), pain, exanthema, acute myocardial dysfunction (defined as mentioned in the medical chart by the treating physician or as an acute alteration of left ventricular ejection fraction $< 30\%$), infection source, Sequential Organ Failure Assessment (SOFA) score, white cell counts, Platelet counts, C-reactive protein (CRP) plasma levels, procalcitonin plasma levels.

To account for missing data, clusters were obtained using a clustering framework for incomplete datasets described hereafter [7]. First, multiple imputation was performed using all variables selected for cluster construction described above, as recommended [8]. For obesity, height and weight were imputed and body mass index (BMI) was then computed. Twenty imputed datasets were computed. A multiple imputation by chained equations algorithm was used to perform the imputations, with predictive mean matching for continuous data, or logistic regression for categorical data. The k-prototypes algorithm with Gower's distance was used to perform clustering from mixed-type data [9]. The number of clusters was selected for each imputed dataset as the one maximizing the Silhouette criterion. The 20 obtained partitions were combined into a single partition (set of clusters) using the MultiCons consensus algorithm

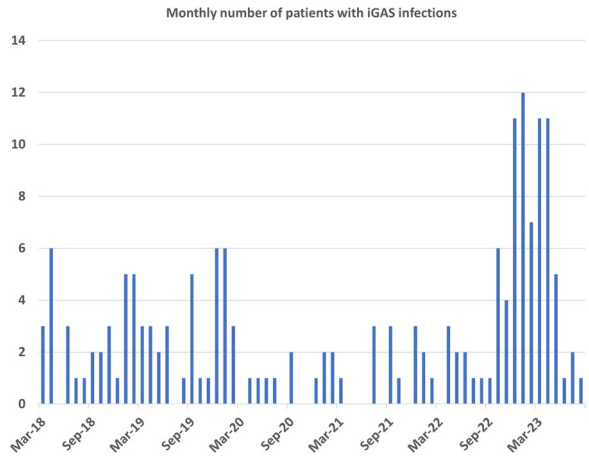

Fig. 1 Monthly number of patients admitted for iGAS infection to any one of the participating ICUs over the study period (blue bars, (n))

[10].'Unclassified'patients correspond to individuals who could not be associated to a cluster due to the uncertainty related to the missing data. To assess the robustness of the identified clustering, a sensitivity analysis was conducted using a Bootstrap framework. A 1000 bootstrap iterations were performed on randomly selected sub-samples of 90% the dataset. The clustering construction was performed on the 1000 sub-samples using strictly the same parameters; then the robustness of the clustering was assessed with two methods: (1) the ARI (Adjusted Rand Index) between the obtained clustering and the sub-sample-based clusterings, described by mean and 95% confidence interval; (2) the *consensus clustering heatmap*, displaying, for each pair of patients, the frequency of co-clustering, ie. the frequency with which the pair of patients were classified in the same cluster.

Clusters were described and clinical presentation, management and outcomes were compared. Data on clusters were presented using the raw (un-imputed) data. Clusters were described using n and percentage (difference between clusters was tested using Fisher's exact test), or median and interquartile range (difference among clusters was tested using Kruskal–Wallis rank sum test), violin plots, and circular bar plots. The association of clusters with selected management or outcome variables (use of anti-toxin antibiotics (clindamycin or linezolid), use of IVIg, need for vasopressors, renal replacement therapy, dobutamine or extracorporeal membrane oxygenation (ECMO) or ICU death), was analyzed using Fisher's exact test and post-hoc pairwise Fisher's exact tests if significant. The association of clusters with ICU death was also assessed with logistic regression model derived likelihood-ratio tests adjusted for age and SOFA or SAPSII. Kaplan–Meier estimators were used to describe ICU survival across clusters. Time-to-ICU-death was defined as the time from ICU admission to death or ICU discharge, whichever occurred first. Deaths after ICU discharge were not considered due to inconsistent availability of this data across centers.

Results

Characteristics of the study population at ICU admission.

GAS growth was identified in a sample from a sterile site for 180 patients admitted to one of the 9 participating ICUs over the 5-year study period. After exclusion of patients not meeting inclusion criteria (n = 4), whose medical charts were not available (n = 6) and whose main reason for ICU admission was not iGAS (n = 22), 148 patients were left for analysis (Supplemental Fig. 2).

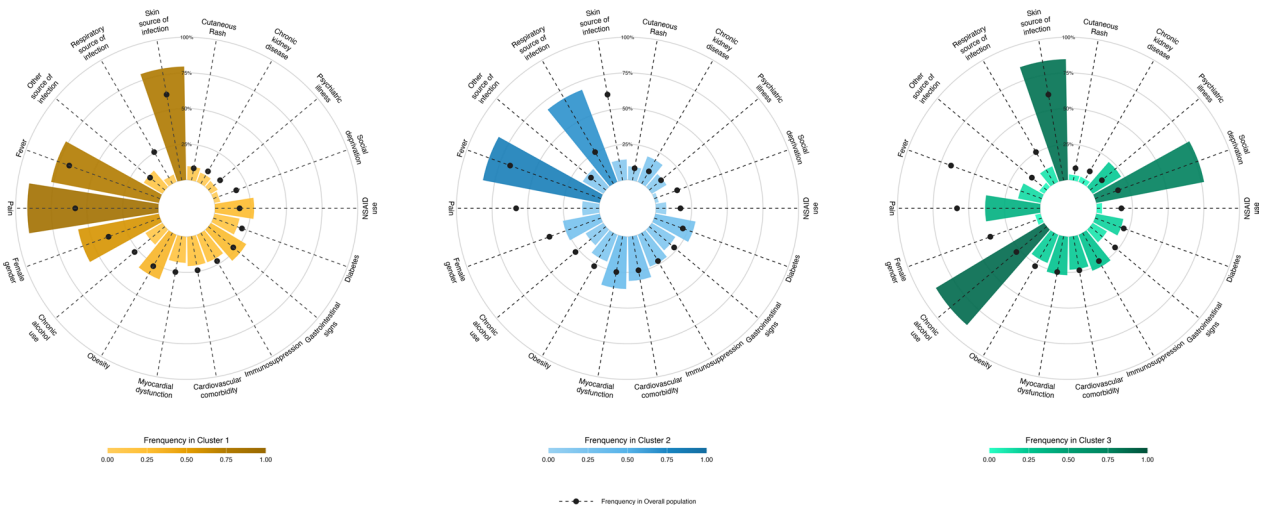

Fig. 2 Frequency of categorical variables used for cluster construction across clusters. Black dots represent the frequency of the variables in the overall population. Binary variables were ordered by increasing frequency in the overall population

The number of iGAS cases admitted to any of the participating ICUs was 2.2 patients/month in the pre-COVID period (2018–2019), dropped to 1.0 patients/month during the COVID pandemic (2020–2021) and rose sharply to 5.1/month afterwards (2022–2023) (Fig. 1). The trend was similar after adjusting for overall admissions in the participating ICUs (2.7 *vs* 1.6 *vs* 5.2 iGAS/1000 ICU admissions).

Infectious foci were mainly cutaneous (61%) and respiratory (26%), with 10% of patients having multiple sources of infection (Supplemental Fig. 2).

Co-infections were found in 36% of the whole population and reached 55% for respiratory infections, with 77% of these respiratory co-infections being viral (55% of influenza and 4.5% each of metapneumovirus, rhinovirus, parainfluenza, SARS-CoV2 and adenovirus). The median duration of symptoms before hospital admission was 3 [2-6] days, and 7% of patients had been receiving antibiotics for more than 24 h prior to ICU admission. Admission characteristics of the overall study population and the identified clusters are shown in Table 1.

Table 1 Patient admission characteristics according to clusters

			Patient Clusters			
	Missing values, n (%)	**Overall, N = 141**	**1, N = 73**	**2, N = 42**	**3, N = 26**	**p-value[2]**
Demographics[1]						
Age (years)	0 (0%)	57 (43, 68)	56 (42, 68)	64 (53, 70)	53 (43, 62)	0.11
Female gender	0 (0%)	54 (38%)	42 (58%)	11 (26%)	1 (3.8%)	< 0.001
Obesity	33 (23%)	29 (27%)	18 (33%)	7 (20%)	4 (21%)	0.3
Diabetes	0 (0%)	30 (21%)	13 (18%)	12 (29%)	5 (19%)	0.4
Immunosuppression	0 (0%)	32 (23%)	15 (21%)	10 (24%)	7 (27%)	0.7
Chronic kidney disease	0 (0%)	14 (9.9%)	5 (6.8%)	8 (19%)	1 (3.8%)	0.081
Cardiovascular comorbidity	0 (0%)	34 (24%)	15 (21%)	13 (31%)	6 (23%)	0.5
Chronic alcohol use	0 (0%)	39 (28%)	10 (14%)	6 (14%)	23 (88%)	< 0.001
Social deprivation	0 (0%)	24 (17%)	3 (4.1%)	1 (2.4%)	20 (77%)	< 0.001
Psychiatric illness	0 (0%)	15 (11%)	4 (5.5%)	5 (12%)	6 (23%)	0.042
Prior NSAID use	1 (0.7%)	24 (17%)	20 (27%)	3 (7.3%)	1 (3.8%)	0.003
Clinical presentation[1]						
Fever	5 (3.5%)	92 (68%)	53 (77%)	35 (83%)	4 (16%)	< 0.001
Gastrointestinal signs	0 (0%)	32 (23%)	21 (29%)	8 (19%)	3 (12%)	0.2
Pain	0 (0%)	82 (58%)	67 (92%)	5 (12%)	10 (38%)	< 0.001
Cutaneous rash	0 (0%)	12 (8.5%)	7 (9.6%)	4 (9.5%)	1 (3.8%)	0.8
Septic shock	0 (0%)	92 (65%)	41 (56%)	28 (67%)	21 (81%)	0.07
Myocardial dysfunction	3 (2%)	35 (25%)	13 (18%)	15 (37%)	7 (27%)	0.10
Suspected toxic shock	0 (0%)	20 (14%)	11 (15%)	5 (12%)	4 (15%)	0.9
Source of infection	0 (0%)					< 0.001
Other		19 (13%)	11 (15%)	7 (17%)	1 (3.8%)	
Skin		86 (61%)	58 (79%)	6 (14%)	22 (85%)	
Respiratory		36 (26%)	4 (5.5%)	29 (69%)	3 (12%)	
Disease severity[1]						
SOFA score	0 (0%)	8.0 (4.0, 11.0)	6.0 (4.0, 10.0)	10.0 (6.0, 12.0)	10.5 (8.2, 12.0)	< 0.001
SAPSII	15 (11%)	53 (34, 70)	42 (31, 62)	68 (40, 80)	65 (47, 71)	< 0.001
Laboratory values[1]						
CRP (mg/L)	72 (51%)	283 (178, 381)	342 (261, 404)	179 (153, 314)	250 (192, 294)	0.066
Procalcitonin (µg/L)	75 (53%)	23 (4, 76)	17 (3, 40)	40 (12, 132)	36 (3, 49)	0.3
Platelets (G/L)	18 (13%)	182 (125, 240)	199 (148, 254)	170 (112, 210)	188 (116, 264)	0.2

[1] n (%); Median (IQR); [2]Fisher's exact test; Kruskal–Wallis rank sum test

Unclassified patients (n = 7) are presented in Supplemental Table 1

Cluster analysis and description

The clustering analysis identified 3 clusters, leaving 7 patients unclassified. Bootstrap analysis yielded satisfactory cluster stability with a mean ARI of 0.63 (95%-CI [0.64; 0.66]) (Supplemental Fig. 4).

The distribution of categorical and continuous variables used for clustering is shown in Fig. 2, Supplemental Figs. 5 and 6.

There was no change in the relative proportion of clusters according to period of inclusion (Supplemental Table 2).

Cluster 1 (n = 73) had a higher proportion of female patients than other clusters (cluster 1: 58%, cluster 2: 26%, cluster 3: 4%, p < 0.001). Patients were less severely ill on admission as evidenced by lower SOFA scores (6 [4–10 *vs* 10 [6–12] *vs* 11 [8–12] p < 0.01 for clusters 1,2 and 3, respectively;) and SAPSII (42 [31–62] *vs* 68 [40–80] *vs* 65 [47–71] p < 0.001). The main focus of infection in this cluster was skin and soft tissue (79%). NSAID consumption prior to admission was the most common in this cluster (27% *vs* 7% *vs* 4%, p = 0.003).

Cluster 2 (n = 42) was characterized by a high rate of lower-respiratory tract infections (6% *vs* 69% *vs* 12%, p < 0.001). On admission blood leucocyte counts were lower (13 [8–19] *vs* 8 [4–13] *vs* 13 [8–21] G/L, p = 0.013) and there was a trend towards more frequent myocardial dysfunction (18% vs 37% *vs* 27%, p = 0.1).

For cluster 3 (n = 26), the most striking feature was the high prevalence of social deprivation (4% *vs* 2% *vs* 77%, p < 0.001) with frequent chronic alcohol use (14% *vs* 14% *vs* 88%, p < 0.001) and psychiatric illness (6% *vs* 12% *vs* 23%, p = 0.042). There was no significant difference in rates of intravenous drug use (3% *vs* 0% *vs* 8%, p = 0.17). The main source of infection was also skin and soft tissue (85%), but compared to other clusters, fever was uncommon (77% *vs* 83% *vs* 16%, p = 0.042) and pain was less common than in cluster 1 (92% *vs* 12% *vs* 38%, p < 0.001). Severity of illness was higher than in other clusters, as indicated by higher SOFA scores (6 [4–10] *vs* 10 [6–12] *vs* 11 [8–12] vs, p < 0.001).

Management and outcome

All patients received antibiotics active against GAS within 24 h of admission. The rate of source control (when applicable) was homogeneous across clusters (Fig. 3). It was not achieved in 7 patients with suspected necrotizing soft tissue infections due to death before surgery (n = 3) or to care consisting of comfort measures only due to expected major sequelae associated with surgical debridement (n = 4). It was achieved within a day of ICU admission in 90% of patients eligible, with no significant difference in time from ICU admission across clusters (0 [0–0] vs 0 [0–0] vs 0 [0–1] days, p = 0.12).

While toxic shock suspicion rates were homogeneous across clusters, patients included in cluster 2 were less likely to receive antitoxin antibiotics than those in clusters 1 and 3 (79% *vs* 45% *vs* 69%, p < 0.001), while IVIg were less commonly prescribed overall, with no statistical difference between clusters (16% *vs* 7% *vs* 12%, p = 0.39). Patients from cluster 1 were less likely to receive

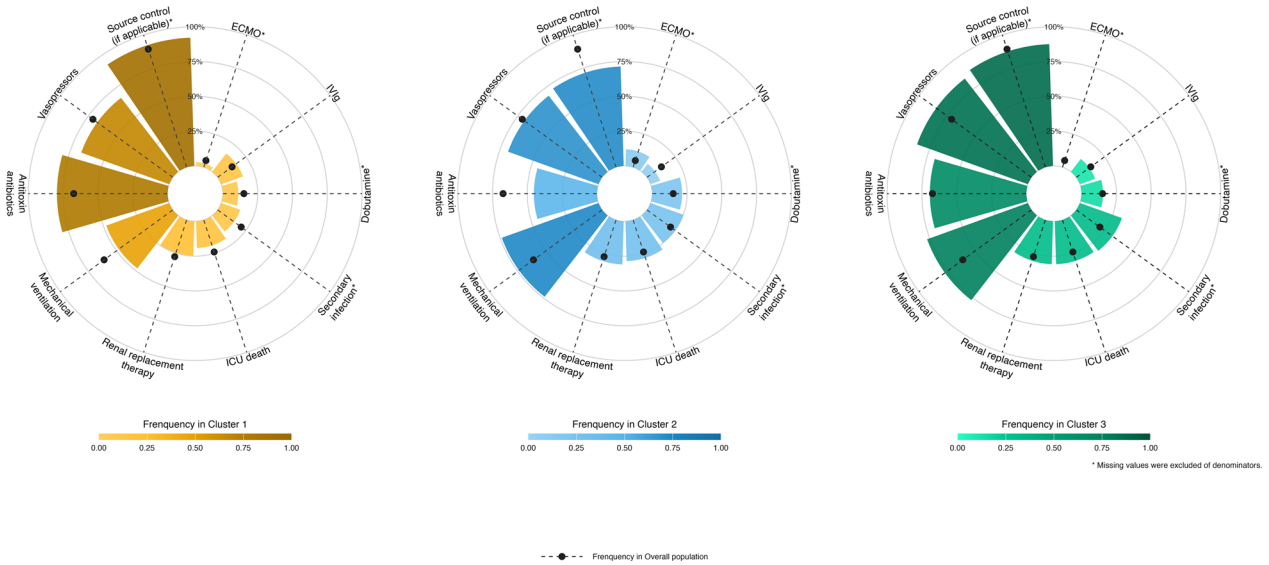

Fig. 3 Frequency of management and outcome variables across clusters. Black dots represent the frequency of the variables in the overall population. Variables were ordered by increasing frequency in the overall population. * The denominator included only patients for whom data was available (for source control only patients for whom it was applicable). ECMO (n = 8) included VA-ECMO (n = 6) and VV-ECMO (n = 2)

invasive mechanical ventilation (48% *vs* 74% *vs* 77%, p = 0.005), while those from cluster 2 tended to more frequently require ECMO support (3% vs 12% *vs* 0%, p = 0.07) (Fig. 3). There was no difference in ICU-mortality between clusters (19% *vs* 29% *vs* 31%, p = 0.32) (Supplemental Fig. 7), even after adjusting for age, SOFA score, SAPSII or the source of infection.

The length of stay in the ICU did not significantly differ between clusters (7 [2–15] *vs* 10 [4–14] *vs* 10 [4–21], p = 0.17) (Supplemental Fig. 8).

Discussion

The main findings of this multicenter cohort of patients admitted to the ICU for iGAS infection are as follows: (1) As in other geographical areas, there was a recent increase in severe iGAS infections in the greater Paris area in late 2022-early2023; (2) Unsupervised clustering analysis based on admission characteristics identified three specific subsets of patients (Cluster 1: a higher proportion of less severely ill female patients with painful skin and soft tissue infections and frequent NSAIDs consumption; Cluster 2: mainly lower-respiratory tract infections with a high rate of viral co-infections; Cluster 3: mostly socially deprived patients with frequent chronic alcohol use and psychiatric illness, with severe organ dysfunction associated with otherwise pauci-symptomatic skin and soft tissue infections); (3) These clusters differed in management, notably the rate of antitoxin antibiotic use, with similar ICU mortality.

The surge in iGAS infections in late 2022-early 2023 following the COVID period has been described worldwide both in adults and children [1, 11–17]. The increase was associated with a shift in clinical presentation to higher rates of pleuro-pulmonary infections particularly in children [18–20]. While in our cohort respiratory infections accounted for 28% of patients in comparison to less than 12% in previous work [2–4], we found no shift in relative proportion of clusters over time. Whether the increase in iGAS in the Paris area described here is associated with the M1UK strain described elsewhere [20–23] is likely but would require confirmation.

While infectious foci may be an obvious difference in patients admitted for iGAS infection, the unsupervised clustering analysis used here highlighted less considered specificities. In particular, social deprivation, chronic alcohol use and psychiatric illness were associated with pauci-symptomatic skin and soft-tissue infections, which may be more difficult to diagnose in the absence of pain or fever, but with severe organ dysfunction. While social deprivation has been reported in 4.3% of ICU patients [24] and in 9% of patients with pneumococcal community-acquired pneumonia [25], the prevalence in our cohort was 17%, highlighting that this population is particularly exposed to iGAS. Our findings are in line with a recent large scale study in the USA, which also identified a tenfold increase in iGAS cases among people experiencing homelessness in the last 10 years [26]. Intravenous drug use had previously been reported to be associated with iGAS in the USA [26, 27], but was anecdotical in our cohort (4% *vs* 15.0–26.4% over the same time period in the work by Gregory et al [26]). Further investigation with longer term outcomes such as rates of re-infection in this population who is likely to be less accessible for contact tracing, decolonization or transmission prevention would be of interest.

Patients from cluster 3, who were mainly patients experiencing social deprivation with pauci-symptomatic skin and soft tissue infections, developed multi-organ failure. One hypothesis is that these patients could suffer from longer diagnosis and therapeutic delays. There was no significant difference in time to source control but aside from a lack of statistical power, we only collected this data in days, whereas an association with mortality has been shown for delays as short as 12 or 6 h [28]. Though impact on outcome cannot be ascertained by our results, they suggest a high index of suspicion for iGAS should be maintained for patients experiencing social deprivation presenting with septic shock. Moreover, as presentation can be pauci-symptomatic, careful and/or repeated skin examination should be performed to identify a cutaneous source of infection, even more so if blood cultures are positive for GAS, in order to ensure prompt source control if needed.

Cluster 2, characterized by the high rate of lower respiratory infections, had a severe course with higher need for mechanical ventilation and the highest need for ECMO, in line with data from Belgium [20]. Viral co-infection was frequent, which has previously been associated with severe disease [29]. In our cohort, use of antitoxin antibiotics was less common in these patients. Babiker and colleagues previously identified younger age, higher severity and necrotizing soft-tissue infection as the source of infection as factors associated with clindamycin use in a population of patients with invasive streptococcal infections (including both group A and non-group A infections and both critically-ill and non-critically-ill patients) [3]. After propensity score matching, they found an overall survival benefit to clindamycin use in iGAS. The prevalence of respiratory infections in their cohort was less than 5%, as in another small scale work focusing on critically-ill iGAS patients [4], and no subgroup analysis allows to confirm this effect in the

subgroup of GAS pneumonia. On the other hand, the viral co-infecting agent is likely to be the main driver of severity in some of these patients (in case of influenza associated acute respiratory distress syndrome for example), and whether a higher rate of antitoxin antibiotic use could improve outcome warrants further research.

The main limitations of our work are inherent to its retrospective design and the relatively small sample size. As such, causality cannot be drawn from our results and data regarding outcome should be considered with caution. Indeed, the absence of a statistically significant difference in time to source control, mortality or length of ICU stay could be due to a lack of statistical power, residual confounding and potential immortal time bias. A significant limitation is that data was extracted from medical charts, and some important clinical variables such as social deprivation, prior NSAID use, acute myocardial dysfunction or suspected toxic shock were recorded based on affirmative chart documentation (*i.e.* considered absent if not mentioned in medical files), introducing a significant risk of measurement bias. Only future prospective work could add robustness to our results. Published indexes of social marginalization such as the Social Deprivation Index [30] were not available in medical charts, and the definition of social deprivation here used had specificities inherent to the French social security system which could limit generalizability. Data regarding GAS strains and virulence factors were not available, nor was clindamycin resistance, though it has recently been reported as low as 3.8% in the greater Paris area [31]. Finally, our study included patients from the greater Paris area and whether results are generalizable to iGAS in other geographical areas remains unknown.

Conclusions

Based on simple and readily available clinical admission characteristics of critically ill patients with iGAS, unsupervised clustering analysis identified three specific patient populations that differed regarding ICU management. Whether tailoring management would affect outcome warrants further research.

Abbreviations

BMI	Body mass index
CRP	C-reactive protein
ECMO	Extra-corporeal membrane oxygenation
ICU	Intensive care unit
iGAS	Invasive group A streptococcus
IVIg	Intravenous polyvalent immunoglobulins
NSAID	Non-steroidal anti-inflammatory drug
RRT	Renal replacement therapy
SAPSII	Simplified acute physiology score II
SOFA	Sequential organ failure assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05469-6.

Supplementary file 1
Supplementary file 2
Supplementary file 3
Supplementary file 4
Supplementary file 5
Supplementary file 6
Supplementary file 7
Supplementary file 8
Supplementary file 9

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Author contributions

TU LF NdP and EM participated in study conception and design. TU, JRL, JM, ML, QdR, MT, WM, MG, GB and DR identified patients and collected data. LF performed statistical analysis. TU wrote the first draft. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

All patients received information that data extracted from their medical charts could be used for research purposes. The study was approved by an IRB (*Comité d'Ethique de la Société de Réanimation de Langue Française*, n° 23–037).

Consent for publication

Consent for publication was provided by all authors.

Competing interests

The authors declare no competing interests.

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