Morbidity and mortality in critically ill patients with invasive Group A streptococcus infection: an observational study

Viveka Björck (✉ viveka.bjorck@med.lu.se)

Lunds universitet Medicinska fakulteten <https://orcid.org/0000-0002-1166-8263>

Lisa I Pålman

Lunds universitet Medicinska fakulteten

Mikael Bodelsson

Lunds universitet Medicinska fakulteten

Ann_Cathrine Petersson

Skanes universitetssjukhus Lund

Thomas Kander

Lunds universitet Medicinska fakulteten

Research

Keywords: emm1/T1-type, group A streptococcus, intensive care unit, sepsis

Posted Date: March 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-17042/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Critical Care on June 6th, 2020. See the published version at <https://doi.org/10.1186/s13054-020-03008-z>.

Abstract

Background Group A streptococci (GAS) are known to cause serious invasive infections but little is known about outcomes when patients with these infections are admitted to intensive care. We wanted to describe critically ill patients with severe sepsis or septic shock due to invasive GAS (iGAS) and compare them with other patients with severe sepsis or septic shock.

Methods Adult patients admitted to a general intensive care unit (ICU) in Sweden (2007-2019) were screened for severe sepsis or septic shock according to Sepsis 2 definition. Individuals with iGAS infection were identified. The outcome variables were mortality, days alive and free of vasopressors and invasive mechanical ventilation, maximum acute kidney injury score for creatinine, use of continuous renal replacement therapy and maximum sequential organ failure assessment score during the ICU stay. Age, simplified acute physiology score (SAPS 3) and iGAS were used as independent, explanatory variables in regression analysis. Cox regression was used for survival analyses.

Results iGAS was identified in 53 of 1021 (5.2%) patients. Patients with iGAS presented lower median SAPS 3 score (62 [56–72] vs 71 [61–81]), $p < 0.001$), had a higher frequency of cardiovascular cause of admission to the ICU (38 [72%] vs 145 [15%], $p < 0.001$) and had a higher median creatinine score (173 [100–311] vs 133 [86–208] $\mu\text{mol/L}$, $p < 0.019$). Of the GAS isolates, 50% were serotyped emm 1/T1 and this group showed signs of more pronounced circulatory and renal failure than patients with non- emm 1/T1, ($p = 0.036$ and $p = 0.007$, respectively). After correction for severity of illness (SAPS 3) and age, iGAS infection was associated with lower mortality risk; 95% confidence interval (CI) of hazard ratio (HR) 0.204–0.746, $p < 0.001$. Morbidity analyses demonstrated that iGAS patients were more likely to develop renal failure.

Conclusion Critically ill patients with iGAS infection had a lower mortality risk but a higher degree of renal failure compared to similarly ill sepsis patients. emm 1/T1 was found to be the most dominant serotype and patients with emm1 /T1 demonstrated more circulatory and renal failure than patients with other serotypes of iGAS.

Background

Sepsis and the more severe form, septic shock, are devastating conditions with high mortality and morbidity caused by a systemic infection leading to organ dysfunction (1, 2). A recent extensive systemic review of observational studies from North America and Europe showed that 10% of patients admitted to intensive care units (ICU) were diagnosed with septic shock, with an ICU mortality of 38% (3). Gram-negative bacteria are the most common group of sepsis-causing organism (62%), but the incidence of gram-positive bacteria has increased in frequency over time (4).

One important gram-positive bacterium that causes sepsis is group A streptococcus (GAS) and it is remarkable how this very common bacterium, usually causing mild diseases such as pharyngitis and impetigo, can cause invasive infections that include necrotising fasciitis and streptococcal toxic shock

syndrome (STSS). From a global perspective, GAS ranks among the top 10 infectious causes of human mortality (5). GAS strains are classified based on serological typing of the T antigen, or genetic differences in the cell surface M protein, encoded by the emm gene. More than 220 different emm types have been described (6, 7). M proteins are virulence factors that contribute to the massive inflammatory effect seen in sepsis via stimulation of immune cells leading to extensive cytokine release (8).

Incidences of invasive group A streptococcus (iGAS) have usually been reported to be around 6 cases per 100 000 people per year (9, 10), with a dominance of emm1 in around 30%. In a prospective epidemiological study of a cohort of 142 adults and children from Greece (11), it was demonstrated that emm1 was associated with more severe infections such as STSS and higher ICU admission rates compared to other iGAS. Another major epidemiological study from North America included 9557 cases of iGAS retrospectively (3.8 cases per 100,000 people per year), with a mortality of 11.7%, and presented the most common emm type to be emm1 (22%) (12). Only 13–15% of patients with iGAS have been described to develop STSS, but the mortality in this group is usually high, with a range between 23% and 44% (13).

There are many valuable studies on iGAS infections where general patients are mixed with critically ill patients (14–18). To the best of our knowledge there is a paucity of studies where critically ill patients with iGAS are studied as a separate cohort and compared to other critically ill patients. Therefore, we performed this observational registry study on patients with iGAS infection who had been admitted to the ICU, with the primary aim to describe these patients in detail and with the secondary aim to evaluate mortality and morbidity in this cohort as compared to other patients with severe sepsis or septic shock admitted to the ICU without iGAS infection. Our hypothesis was that patients with iGAS infection fare worse concerning both morbidity and mortality than other patients with severe sepsis or septic shock admitted to the ICU.

Methods

Subjects

The study was approved by the Swedish Ethical Review Authority in Lund (registration number 2014/916 and 2018/866). All participants were offered an opt-out via an advertisement in the local newspaper and the board waived the requirement for written informed consent. The manuscript was prepared according to the STROBE guidelines for observational studies (19).

All adult sepsis patients (> 18 years old) admitted to the general tertiary, 9-bed ICU at Lund University Hospital, Sweden, between 2007 and 2019 were eligible for inclusion and were screened for severe sepsis (ICD-code R65.1) or septic shock (ICD-code R57.2) according to the Sepsis 2 definition (20). The patients were identified using data from the Swedish Intensive Care Registry. For patients with multiple admissions with a diagnosis of severe sepsis or septic shock, only the first admission was included in the study. Baseline characteristics (such as age, gender, reason for admission, origin of admission,

physiological and laboratory data), as well as outcome variables were collected from raw data; i.e. from the electronic master chart system of the hospital (Melior, Cerner, Kansas City, MO, USA) or from the patient data-management system at the ICU (IntelliSpace Critical Care and Anaesthesia, Philips, Amsterdam, the Netherlands). Mortality data were imported from the Swedish Intensive Care Registry.

Individuals with iGAS infection were identified by cross-referencing the ICU sepsis cohort with the database for cultures at the Clinical Microbiology Laboratory, Region Skåne. IGAS infection was defined as a growth of GAS in cultures from blood or other sterile sites such as tissues or joints. Typing of iGAS isolates was performed at the Clinical Microbiology Laboratory, Region Skåne using T-typing (2007–2011) or emm-typing (2012–2019) (21–23). The correlation between T-type and emm-type is complex; for example, T-type 4 correlates with emm-type 4, 24, 46, 60 and 63. However, T-type 1 is considered equivalent to only emm1 (23).

For the description of iGAS patients, medical records were manually reviewed, identifying the site of infection and other details, including the possible use of intravenous immunoglobulins (IVIG).

Outcomes

The primary aim of the study was to describe the baseline characteristics of patients with iGAS admitted to the ICU. The secondary aim was to investigate if morbidity and mortality differed between patients with iGAS compared to patients without iGAS (controls). For these purposes, the following outcome variables were used: 1) days alive and free (DAF) of vasopressors and invasive mechanical ventilation for the first 28 days after ICU admission. DAF has previously been extensively used to measure the degree of organ failure (24). High numbers in DAF means less need for organ support and lower degree of organ failure. In the present study, we used the definition of DAF without extra penalty for death (24). 2) Maximum acute kidney injury score the first 10 days after admission, according to the acute kidney injury network (AKIN) criteria (AKIN-crea). 3) Use of continuous renal replacement therapy (CRRT). 4) Maximum sequential organ failure assessment score (SOFA-max) during the ICU stay. 5) Length of ICU stay for ICU survivors. 6) Mortality (in the ICU and at 28, 90 and 180 days after admission).

Statistical analysis

Continuous variables are presented as median (interquartile range) and all categorical variables are presented as numbers (percentage). Mann-Whitney or Fisher's exact test (two-tailed) were used for univariate testing of continuous and categorical variables, respectively. A two-sided p-value of less than 0.05 was considered to indicate statistical significance.

For the secondary aim of the study, age, simplified acute physiology score (SAPS 3) (25, 26) and iGAS were used as independent, explanatory variables in all regression analysis. The survival analysis was performed using Cox regression.

The outcomes DAF ventilator, DAF vasopressor, AKIN-crea and CRRT were analysed in separate regression analysis. The distribution of DAF vasopressor and DAF ventilator was U-shaped, with patients

scoring either low or high. Since this distribution pattern does not fit any commonly used regression model, we were forced to dichotomise these variables using more than 24 hours of treatment as a cut off; i.e. DAF < 27. The distribution of AKIN-crea was also U-shaped with the majority of patients with an AKIN score of 0, and was also dichotomised to no AKIN versus AKIN 1–3. Binominal variables were analysed using logistic regression. The distribution of SOFA max and length of stay did not fit any commonly used regression models and were not possible to dichotomise and were therefore not included in any regression models. The goodness of fit for all logistic regression analyses was tested using the Hosmer and Lemeshov goodness-of-fit test.

SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA) were used for all statistical analysis.

Results

Subjects

In total, 1021 unique patients with severe sepsis or septic shock were identified out of 9490 admissions to the ICU during the study period (Fig 1). Of these, 53 patients (5.2%) were diagnosed with iGAS infection based on growth of the bacteria in blood or from other sterile sites. A detailed presentation of baseline characteristics of patients with severe sepsis/septic shock, with and without iGAS, is presented in Table 1. In summary, the median age of patients with iGAS was lower than for patients without iGAS (63 [50–70] vs 68 [59–76] years old, $p < 0.008$), presented a lower median SAPS 3 score (62 [56–72] vs 71 [61–81], $p < 0.001$), had a higher frequency of cardiovascular cause of admission to the ICU (38 [72] vs 145 [15], $p < 0.001$) and the median creatinine score was higher (173 [100–311] vs 133 [86–208] $\mu\text{mol/L}$, $p < 0.02$). Patients with iGAS infection were less likely to be admitted from a general ward (21 [40] vs 527 [54], $p = 0.047$) and 15% arrived at the ICU from the operating room compared to 8% in the non-iGAS group ($p = 0.074$).

In the non-GAS group, culture responses from 749 patients (taken from sterile sites, including blood) were obtained. Of these, 340 (45%) were negative and 95 (12.7%) had positive cultures from more than one of the aggregated groups. For details, including bacterial species, please see Table 2.

Results from *emm1*/T1 typing

Among the 53 patients with iGAS, the isolates from one patient was not subjected to *emm*/T-typing and two isolates were non-typable. The distribution of the different *emm*-types (used after 2012) or T-types (used before 2012) are presented in Figure 2. Of the 50 iGAS isolates with a specific *emm*/T-type, 25 isolates (50%) were classified with *emm1*/T1. Of the patients with iGAS *emm1*/T1, 72% presented with soft tissue infection compared to 44% with other *emm*/T-types ($p = 0.08$), and 48% of *emm1*/T1 had necrotising fasciitis compared to 28% in the group without *emm1*/T1 ($p = 0.24$). The incidences of septic

shock (Sepsis 3 definition) and IVIG treatment were similar between *emm1*/T1 and non-*emm1*/T1 (Table 3).

Outcomes

Non-iGAS versus iGAS patients

Outcome variables including univariate testing are presented in detail in Table 4 and results from survival analysis and multivariable regression analysis are presented in Table 5.

Mortality

Age and high SAPS 3 correlated with higher mortality with 95% confidence interval (CI) of hazard ratio (HR, 1.002–1.016, $p < 0.05$, and 1.033–1.044, $p < 0.001$, respectively). iGAS infection was associated with lower mortality risk (95% CI of HR 0.204–0.746, $p < 0.001$; Table 5). Given that *emm1*/T1 iGAS infection has been associated with more severe infections than many other iGAS serotypes (11, 12), we also performed a secondary Cox regression analysis where iGAS serotyped *emm1*/T1 was compared to the control group. The results were similar, with 95% CI of HR 0.078–0.555, $p < 0.001$, for patients with iGAS *emm1*/T1 positive patients ($n = 25$).

Morbidity

The goodness of fit was good with a valid chi-square value ($p > 0.05$) for all outcomes in the logistic regression analyses. As expected, an increased SAPS 3 score was associated with all measured organ failures. There was no association between any of the other independent variables included in the analysis (age and iGAS), and the development of circulatory failure neither measured with DAF vasopressors nor with CRRT (Table 5). However, higher age seemed to be associated with lower risk of respiratory failure according to DAF ventilator (95% CI of odds ratio [OR] 0.977–0.997) and there was a correlation between iGAS infection and increased risk for renal failure measured with AKIN-crea (95% CI of OR 1.266–4.034, $p = 0.006$).

*Non-*emm1*/T1 versus *emm1*/T1*

Due to the low number of patients in each group ($n = 25$ per group) it was not possible to perform multivariable regression analyses. In the uncorrected univariate analyses (Table 3), patients with *emm1*/T1 showed signs of more pronounced circulatory failure than patients with non-*emm1*/T1,

measured with DAF vasopressor ($p = 0.036$). Furthermore, renal failure measured with AKIN-crea was more pronounced in the *emm1*/T1 group compared to the non-*emm1*/T1 group ($p = 0.007$). However, this was not reflected in the incidence of CRRT.

Discussion

In this single-centre retrospective registry study on critically ill patients with severe sepsis or septic shock, we identified 53 unique patients with iGAS over a 12-year period. Patients with iGAS had a lower median age than the non-iGAS patients, presented a lower median SAPS 3 score at admission and had a higher incidence of cardiovascular cause for admission. After correction for severity of illness and age, iGAS infection was associated with lower mortality risk. Morbidity analyses, also corrected for severity of illness and age, demonstrated that patients with iGAS infection were more likely to develop renal failure measured with AKIN-crea.

Our hypothesis that patients with iGAS infection would fare worse concerning both morbidity and mortality compared to controls was proven wrong with regards to mortality, and proven right in one aspect with regards to morbidity; i.e. renal failure. These are unexpected findings because patients with iGAS infection in general, and those presenting the *emm1*/T1 antigen in particular, have previously been described as having worse survival rates (18, 27, 28). However, it should be noted that these studies were performed in cohorts of general patients and not only in critically ill patients, as in the present study. Furthermore, the control group in the present study included only patients with severe sepsis and septic shock; i.e. a control group with severely ill patients. Beyond that we suggest at least two explanations for our findings. Firstly, iGAS infections are widely recognised as aggressive acute conditions where surgical treatment must be initiated without delay. This surgical treatment is normally very effective as source control and is also complemented with necessary pharmacological treatment with antibiotics and sometimes IVIG. In contrast, patients in the control group were very heterogeneous and source control is rarely as straightforward and effective as with iGAS. Regression analyses were not corrected for the fast and effective treatment in the iGAS group, which may represent a bias in the analyses. Secondly, SAPS 3 may not be sensitive enough to describe the true difference of severity of illness between the groups. As an example, it can be mentioned that comorbidity must be very severe to affect the SAPS 3 score. Considering the higher median age of patients in the control group, it is possible that patients in the control group were more severely ill than SAPS 3 will reflect. In summary, the fast and effective source control in the iGAS group, together with possible underestimated severity of illness in the control group, may contribute to the unexpected results in the corrected regression analyses.

Although studies on critically ill patients with iGAS in the ICU are scarce, studies on all patients admitted to a hospital with iGAS are more common. Mortality in all patients with GAS infection has previously been reported to be 8–23% in the first 7 days (7, 29). Two studies have reported mortality rates of 38–40% in patients with iGAS admitted to the ICU (30, 31). However, in Stockmann and colleagues' large epidemiological study on ICU patients with iGAS infection in Utah, including an impressive 1514 patients over 8 years (2002–2010), they found a mortality rate of 6% in iGAS patients > 18 years old admitted to

the ICU (9). This is in agreement with the present study where ICU mortality was 5.7% for iGAS patients (Table 4). Based on aggregated reports from the Public Health Agency in the region in which we performed our study, and given the catchment of 335 000 inhabitants for the University Hospital in Lund, the incidence of iGAS in our material was estimated at 6.0 per 100,000 inhabitants, which is in agreement with the study from Utah where the incidence was 6.3 per 100,000 inhabitants. Furthermore, in the study from Utah, the proportion of patients with iGAS infection admitted to ICU was 19%, compared to an estimated 18% (53 per 295) in the present study.

In the present study, the incidence of renal failure during the ICU stay was high in the iGAS group. The reasons for acute kidney injury (AKI) in septic patients are multifactorial. Disturbed microcirculation is considered to play an important role, since AKI in sepsis can develop in the presence of normal renal blood flow (32). Overproduction of reactive oxygen, nitrogen species and cytokines that lead to downregulation of cell function to minimise energy demand, and thereby improving cell survival of tubular cells, are other mechanisms (32, 33). M1 protein, situated on the surface of GAS, is a known virulence factor that leads to extensive cytokine release from monocytes and endothelial cells (8). A rare form of acute interstitial nephritis (AIN) has also been described, where the virulence factor streptococcal pyrogenic exotoxin B (SPE B) seems to induce tubule-interstitial damage via T-cell proliferation and cytokine production (34). All this indicates that the renal failure in iGAS infection may be due to the bacteria and the immunological response induced, rather than diminished blood flow as a consequence of the hypotension in sepsis/septic shock. This may, at least in part, explain why patients in the iGAS group developed a higher degree of renal failure measured with AKIN-crea and were still more likely to survive.

A notable finding in our study is that only 50% of patients in the non-iGAS group, and 60% in the iGAS group, were diagnosed with septic shock according to the Sepsis 3 definition. In a study from 2017, Sterling and colleagues reported that, in a cohort of 470 patients diagnosed with septic shock using older definitions, only 43% had septic shock according to Sepsis 3. As expected, the mortality in the two different groups differed (29% in the group meeting Sepsis 3 criteria compared to 14% using the older definition) (35). In a large review and meta-analysis performed by Vincent and colleagues, the overall pooled frequency of septic shock diagnosed at ICU admission was 10% according to Sepsis 2 but decreased to 6.5% using Sepsis 3 criteria (3). Taken together, this points out that Sepsis 2 overestimates the incidence of septic shock compared to Sepsis 3, which is also confirmed in our data.

Fifty patients with iGAS were typed regarding emm/T-type. Of these, 50% were typed as emm1 or T1. This is in agreement with the distribution of emm1 during the years with peak incidences reported from the Public Health Agency of Sweden. In 2017–2018 the incidence of iGAS in Sweden was 7.9 per 100,000 people, with a 30-day mortality of 12%. The most frequent types were emm1 (48%), 3, 4, 12, 28 and 89 (10). In 2012–2013 there was also a peak in the incidence of iGAS (7.8 per 100,000) with emm1 (42%) dominating. The years between 2013 and 2017 reported an incidence of 5.8–6.6 per 100,000 and an emm1 frequency between 20% and 32% (10). This indicates that there is a variation over time of the emm-types and that emm1 is responsible for the peak in incidences.

In our material, the majority of patients with necrotising fasciitis were found in the emm1/T1 group (72% vs 44% in the non-emm1/T1, $p = 0.08$). The severity of the infections in the emm1/T1 group was also underlined by a lower DAF vasopressor and higher AKIN-crea in relation to non-emm1/T1. There was, however, no difference in mortality regarding emm/T-type. This might be explained by the possibility of achieving easier source control by interventions in the operating room regarding the soft tissue infections more common in the emm1/T1 group, in addition to correct antibiotics and in some cases IVIG.

We recognise the limitations of the present study due to its retrospective nature. It should be noted that, as in every study based on results from cultures from sterile sites, there is a risk of false negative cultures; for example, due to cultures taken after the first dose of antibiotics. Another aspect that should be taken into consideration is that, in the multivariable logistic regression analysis, higher age seemed to be associated with lower risk of respiratory failure. This result is not in agreement with the other findings in this study and the reason remains unexplained but may represent a statistical type I error. Furthermore, the number of iGAS patients is rather limited and collected from a single centre, which may not give the study sufficient power for risk prediction of all outcomes and may also question the external validity of the results.

Conclusions

We identified 53 unique patients with iGAS during the study period of 12 years, in a large cohort of 1021 critically ill patients with severe sepsis or septic shock. *emm1/T1* was found to be the most dominant serotype, and patients with iGAS *emm1/T1* demonstrated more renal and circulatory failure compared to patients with iGAS infection caused by other serotypes. When comparing to a control group with substantial severity of illness, patients with iGAS infection demonstrated lower mortality risk.

Abbreviations

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
AKIN	Acute kidney injury network
CI	Confidence interval
CRRT	Continuous renal replacement therapy
DAF	Days alive and free
GAS	Group A streptococcus

HR	Hazard ratio
ICU	Intensive care unit
iGAS	Invasive Group A streptococcus
IVIG	Intravenous immunoglobulins
SAPS 3	Simplified acute physiology score 3
SOFA	Sequential organ failure assessment
STSS	Streptococcal toxic shock syndrome

Declarations

Ethics approval and consent to participate

This study was approved by the Swedish Ethical Review Authority in Lund (registration number 2014/916 and 2018/866).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

Skåne University Hospital Research Funds, the Skåne County Council's Research, Governmental funding of clinical research within the NHS (National Health Service) and Development Foundation and the Anna and Edwin Berger Foundation.

Authors' contributions

TK was the originator of the study and was responsible for the ethical approvals. VB, LP and TK designed the study. TK and AP collected data. VB and TK performed the statistical analyses. VB, LP, MB and TK

contributed to the interpretation of the data. All authors revised the manuscript critically, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Acknowledgements

The authors would like to acknowledge Lena Hyllebusk at the Clinical Microbiology Laboratory in Lund for providing information about culture results from the patients admitted to the ICU 2007–2019.

References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med.* 2017;43(3):304–77.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA.* 2016;315(8):801–10.
3. Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: A systematic review and meta-analysis. *Crit Care.* 2019;23(1):196.
4. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence.* 2014;5(1):4–11.
5. Barnett TC, Bowen AC, Carapetis JR. The fall and rise of group A streptococcus diseases. *Epidemiol Infect.* 2018:1–6.
6. Cunningham MW. Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev.* 2000;13(3):470–511.
7. Walker MJ, Barnett TC, McArthur JD, Cole JN, Gillen CM, Henningham A, et al. Disease manifestations and pathogenic mechanisms of group A Streptococcus. *Clin Microbiol Rev.* 2014;27(2):264–301.
8. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. *Lancet Infect Dis.* 2009;9(5):281–90.
9. Stockmann C, Ampofo K, Hersh AL, Blaschke AJ, Kendall BA, Korgenski K, et al. Evolving epidemiologic characteristics of invasive group a streptococcal disease in Utah, 2002–2010. *Clinical Infect Dis.* 2012;55(4):479–87.
10. Public Health Agency of Sweden Public Health Agency of Sweden [Internet]. [Cited 2019 May 20]. Available from: <https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistik-a-o/sjukdomsstatistik/betahemolytiska-grupp-a-streptokocker-gas-invasiv/>.
11. Zachariadou L, Stathi A, Tassios PT, Pangalis A, Legakis NJ, Papaparaskevas J. Differences in the epidemiology between paediatric and adult invasive streptococcus pyogenes infections. *Epidemiol Infect.* 2014;142(3):512–9.
12. Nelson GE, Pondo T, Toews KA, Farley MM, Lindegren ML, Lynfield R, et al. Epidemiology of invasive group A streptococcal infections in the United States, 2005–2012. *Clinical Infect Dis.* 2016;63(4):478–86.

13. Schmitz M, Roux X, Huttner B, Pugin J. Streptococcal toxic shock syndrome in the intensive care unit. *Ann Intensive Care*. 2018;8(1):88.
14. Darenberg J, Luca-Harari B, Jasir A, Sandgren A, Pettersson H, Schalen C, et al. Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. *Clinical Infect Dis*. 2007;45(4):450–8.
15. Darenberg J, Henriques-Normark B, Lepp T, Tegmark-Wisell K, Tegnell A, Widgren K. Increased incidence of invasive group A streptococcal infections in Sweden, January 2012–February 2013. *Euro Surveill*. 2013;18(14):20443.
16. Efstratiou A, Lamagni T. Epidemiology of streptococcus pyogenes. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes: Basic biology to clinical manifestations*. Oklahoma City: University of Oklahoma Health Sciences Center; 2016. [Internet]. [Cited 2019 June 10]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK343616/>
17. Lamagni TL, Efstratiou A, Dennis J, Nair P, Kearney J, George R. Increase in invasive group A streptococcal infections in England, Wales and Northern Ireland, 2008–9. *Euro Surveill*. 2009;14(5). [Internet]. [Cited 2019 June 10]. Available from: <https://www.eurosurveillance.org/content/10.2807/ese.14.05.19110-en>
18. Luca-Harari B, Darenberg J, Neal S, Siljander T, Strakova L, Tanna A, et al. Clinical and microbiological characteristics of severe streptococcus pyogenes disease in Europe. *J Clin Microbiol*. 2009;47(4):1155–65.
19. Vandembroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *Epidemiology*. 2007;18(6):805–35.
20. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Intensive Care Med*. 2003;29(4):530–8.
21. Beall B, Gherardi G, Lovgren M, Facklam RR, Forwick BA, Tyrrell GJ. Emm and sof gene sequence variation in relation to serological typing of opacity-factor-positive group A streptococci. *Microbiology*. 2000;146(5):1195–209.
22. Centers for Disease and Prevention Department [Internet]. [Cited 2019 May 20]. Available from: <https://www.cdc.gov/streplab/groupa-strep/index.html>.
23. Johnson DR, Kaplan EL, VanGheem A, Facklam RR, Beall B. Characterization of group A streptococci (*streptococcus pyogenes*): Correlation of M-protein and emm-gene type with T-protein agglutination pattern and serum opacity factor. *J Med Microbiol*. 2006;55(2):157–64.
24. Russell JA, Lee T, Singer J, De Backer D, Annane D. Days alive and free as an alternative to a mortality outcome in pivotal vasopressor and septic shock trials. *J Crit Care*. 2018;47:333–7.
25. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3 – From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. *Intensive Care Med*. 2005;31(10):1336–44.

26. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3 – From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med.* 2005;31(10):1345–55.
27. Macheboeuf P, Buffalo C, Fu CY, Zinkernagel AS, Cole JN, Johnson JE, et al. Streptococcal M1 protein constructs a pathological host fibrinogen network. *Nature.* 2011;472(7341):64–8.
28. Aziz RK, Kotb M. Rise and persistence of global M1T1 clone of streptococcus pyogenes. *Emerg Infect Dis.* 2008;14(10):1511–7.
29. Lithgow A, Duke T, Steer A, Smeesters PR. Severe group A streptococcal infections in a paediatric intensive care unit. *J Paediatr Child Health.* 2014;50(9):687–92.
30. Mulla ZD. Invasive group A streptococcal disease and intensive care unit admissions. *Intensive Care Med.* 2002;28(12):1822–4.
31. Mehta S, McGeer A, Low DE, Hallett D, Bowman DJ, Grossman SL, et al. Morbidity and mortality of patients with invasive group A streptococcal infections admitted to the ICU. *Chest.* 2006;130(6):1679–86.
32. Zarbock A, Gomez H, Kellum JA. Sepsis-induced acute kidney injury revisited: Pathophysiology, prevention and future therapies. *Curr Opin Crit Care.* 2014;20(6):588–95.
33. Montomoli J, Donati A, Ince C. Acute kidney injury and fluid resuscitation in septic patients: Are we protecting the kidney? *Nephron.* 2019;143(3):170–3.
34. Chang JF, Peng YS, Tsai CC, Hsu MS, Lai CF. A possible rare cause of renal failure in streptococcal infection. *Nephrol Dial Transplant.* 2011;26(1):368–71.
35. Sterling SA, Puskarich MA, Glass AF, Guirgis F, Jones AE. The impact of the sepsis-3 septic shock definition on previously defined septic shock patients. *Crit Care Med.* 2017;45(9):1436–42.

Tables

Table 1. Baseline characteristics, patients with and without invasive Group A streptococcus.

Values are median (Q1–Q3) or number (%)

	Non-iGAS <i>n</i> = 968	iGAS <i>n</i> = 53	<i>p</i> -value ^a
Age (years)	68 (59–76)	63 (50–70)	0.008*
Female	421 (44)	20 (38)	0.48
SAPS 3 ^b score	71 (61–81)	62 (56–72)	< 0.001*
SAPS 3 EMR ^c (%)	40 (21–61)	22 (14–42)	< 0.001*
Septic shock (Sepsis 3)	486 (50)	32 (60)	0.16
<u>Origin of admission:</u>			
General ward	527 (54)	21 (40)	0.047*
Emergency department	230 (24)	18 (34)	0.10
Operating room	77 (8)	8 (15)	0.074
Other ICU ^d	106 (11)	5 (9.4)	1.00
Postoperative care unit	26 (2.7)	1 (1.9)	1.00
<u>Reason for admission^e:</u>			
Cardiovascular	145 (15)	38 (72)	< 0.001*
Hepatic	56 (5.8)	1 (1.9)	0.36
Abdominal ^f	176 (18)	9 (17)	1.00
CNS ^g	164 (17)	12 (23)	0.27
Renal	320 (33)	21 (40)	0.37
Pulmonary	206 (21)	17 (32)	0.09
Metabolic	189 (20)	9 (17)	0.72
Not coded	124 (13)	4 (7.5)	0.39
<u>Physiological and laboratory variables at admission^h:</u>			
Heart rate	107 (93–122)	108 (94–125)	0.85
SBP ⁱ (mmHg)	103 (86–126)	104 (86–121)	0.94
Lactate (mmol/L)	2.6 (1.5–4.5)	2.5 (1.8–4.9)	0.55
Norepinephrine (µg/min/first 6 h)	2.3 (0–7.7)	2.6 (0–12)	0.10
Temperature (°Celsius)	37.2 (36.5–38.0)	37.5 (36.9–38.0)	0.10
Leucocytes (×10 ⁹ /L)	11 (5.2–19)	10.5 (5.1–18)	0.78
Platelets (×10 ⁹ /L)	160 (92–265)	163 (107–208)	0.42
pH	7.36 (7.27–7.43)	7.36 (7.29–7.42)	0.92
Bilirubin (µmol/L)	15 (9.0–26)	14 (8.0–21)	0.49
Creatinine (µmol/L)	133 (86–208)	173 (100–311)	0.02*
APTT ^j (s)	40 (33–51)	38 (34–44)	0.19
PK-INR ^k	1.4 (1.2–1.7)	1.3 (1.2–1.4)	0.004*

^a = Fisher's exact test or Mann Whitney, * = $p \leq 0.05$

^b = Simplified acute physiologic score 3

^c = Estimated mortality rate

^d = Intensive care unit

^e = Patients may have multiple reasons for admission

^f = Gastro-intestinal bleeding, acute abdomen or pancreatitis

^g = Convulsions, decreased consciousness, coma, delirium or intracranial volume effect

^h = Blood samples taken within 90 minutes after admission

ⁱ = Systolic blood pressure

^j = Activated partial thromboplastin time

^k = Prothrombin time - international normalised ratio

Table 2. Culture results in the control group.

Culture results	Frequency n (%)
Negative culture	340 (45)
<i>Escherichia coli</i>	98 (13)
<i>Staphylococcus aureus</i>	46 (6.1)
<i>Streptococcus pneumoniae</i>	40 (5.3)
Beta-hemolytic streptococci non-GAS	10 (1.3)
<i>Candida</i> species	20 (2.7)
<i>Neisseria meningitides</i>	2 (0.3)
<i>Enterococcus</i> species	32 (4.3)
<i>Pseudomonas aeruginosa</i>	16 (2.1)
Other gram-positive bacteria ^a	126 (17)
Other gram-negative bacteria ^b	71 (9.5)
Mixed flora ^c	3 (0.4)
<i>Fusarium solani</i>	1 (0.1)

Cultures from blood or other sterile sites from 749 of the patients in the control group. Ninety-five patients had positive cultures with microorganisms from more than one of the aggregated groups or the GAS group.

^a *Streptococcus* species (Alpha, *anginosus*, *bovis*, *intermedius*, *lutetiensis*, *mitis* and *salivarius*), coagulase-negative *Staphylococcus* (*S.epidermis*, *haemolyticus*, *hominis* and *sciuri*), *Eggerthella lenta*, *Parvimonas micra*, *Bacteroides* species, *Propionibacterium*, anaerobic gram-positive rods, *Clostridium* species (*cadaveris*, *innocuum*, *paraputrificum*, *septicum*, *ramosum*, *bifermentans* and *perfringens*), *Peptostreptococcus stomatis*, *Cutibacterium* (*Propionibacterium*) *acnes*, *Parabacteroides distasonis*, *Enterococcus gallinarum*, *Gemella* species, *Flavonifractor plautii*, *Globicatella* species, *Granulicatella* species, *Lactobacillus* species, *Anaerococcus* species, *Actinomyces odontolyticus*, *Corynebacterium* species, *Gemella morbillorum*, *Paenibacillus* species and *Peptoniphilus harei*.

^b *Proteus mirabilis*, *Klebsiella* (*aerogenes*, *oxytoca* and *pneumonia*), gram-negative rods, *Prevotella denticola*, *Serratia marcescens*, *Enterobacter cloacae*, *Dialister pneumosintes*, *Citrobacter* (*freundii* and *diversus*), *Morganella morganii*, *Salmonella enterica* serogroup Rissen, *Prevotella* species, *Proteus vulgaris*, *Stenotrophomonas maltophilia*, *Neisseria* species, *Haemophilus* (*influenza* and *parainfluenzae*), *Sphingomonas* species, *Providencia rettgeri*, *Prevotella buccae* and *Fusobacterium necrophorum*.

^c Anaerobic mixed flora, skin flora, mixed flora.

Table 3. Patient characteristics and outcomes in iGAS patients with or without *emm1*/T1.

Values are median (Q1–Q3) or number (%)

<u>Type of infection:</u>			
Soft tissue	11 (44)	18 (72)	0.08
Necrotising fasciitis	7 (28)	12 (48)	0.24
Pneumonia	3 (12)	3 (12)	1.00
Puerperal	2 (8.0)	0	0.49
Arteritis	4 (16)	0	0.11
Pharyngeal/parapharyngeal	1 (4.0)	2 (8.0)	1.00
Mastoiditis	1 (4.0)	0	1.00
Meningitis	0	1 (4.0)	1.00
Unknown focus	3 (12)	1 (4.0)	0.61
Septic shock (Sepsis 3)	11 (44)	10 (40)	1.00
IVIG ^b	7 (28)	13 (52)	0.15
DAF ^c vasopressor	26 (25-28)	25 (23-26)	0.036*
DAF ^c ventilation	26 (20-28)	24 (20-26)	0.23
CRRT ^d	4 (16)	8 (32)	0.32
AKIN-crea ^e	0 (0-3)	3 (0-3)	0.007*
SOFA max ^f	9 (6-13)	12 (7-14)	0.11
Length of stay; survivors	2.7 (1.2-4.7)	5.1 (2.3-7.5)	0.08
SAPS 3 ^g	65 (54-70)	61 (58-78)	0.27
EMR ^h	28 (11-39)	21 (15-54)	0.27
ICU ⁱ mortality	2 (8.0)	1 (4.0)	1.00
28-day mortality	5 (20)	1 (4.0)	0.19
90-day mortality	6 (24)	2 (8.0)	0.25
180-day mortality	8 (32)	3 (12)	0.17

^a = Fisher's exact test or Mann Whitney, * = $p \leq 0.05$

^b = Intravenous immunoglobulin

^c = Days alive and free

^d = Continuous renal replacement therapy

^e = Maximum acute kidney injury network classification score the first 10 days after admission

^f = Maximum sequential organ failure assessment score during ICU admission

^g = Simplified acute physiology score 3

^h = Estimated mortality rate

ⁱ = Intensive care unit

Table 4. Outcomes with univariate testing comparing non-iGAS patients with iGAS patients.

Values are median (Q1–Q3) or number (%)

	Non-iGAS	iGAS	
	<i>n</i> = 968	<i>n</i> = 53	<i>p</i> -value ^a
DAF ^b vasopressor	24 (25–26)	25 (22–26)	0.04*
DAF ^b ventilation	23 (3–28)	25 (20–28)	0.02*
CRRT ^c	185 (19)	12 (23)	0.48
AKIN-crea ^d	0 (0–3)	3 (0–3)	0.045*
SOFA max ^e	11 (8–14)	10 (6–14)	0.16
Length of stay; survivors	3.3 (1.5–6.8)	3.8 (1.8–7.0)	0.77
ICU ^f mortality	237 (25)	3 (5.7)	<0.001*
28-day mortality	354 (37)	7 (13)	<0.001*
90-day mortality	429 (44)	9 (17)	<0.001*
180-day mortality	471 (49)	12 (23)	<0.001*

^a = Mann-Whitney or Fisher’s exact test (two-tailed)

^b = Days alive and free

^c = Continuous renal replacement therapy

^d = Maximum acute kidney injury network classification score the first 10 days after admission

^e = Maximum sequential organ failure assessment score during ICU admission

^f = Intensive care unit

Table 5. Associations between independent variables and outcomes.

All outcomes were analysed in separate multivariable regression models as described in the Methods section. Morbidity outcomes were reported for the first 28 days after admission. * = $p \leq 0.05$.

Outcome	Age	SAPS 3 ^a	iGAS
Severe sepsis or septic shock, <i>n</i> =1021			
Mortality, CI ^b of HR ^c	1.002-1.016*	1.032-1.044*	0.204-0.746*
DAF ^d vasopressor, CI ^b of OR ^e	0.994-1.015	1.044-1.07*	0.897-3.681
DAF ^d ventilator CI ^b of OR ^e	0.977-0.997*	1.046-1.070*	0.694-2.330
CRRT ^f , CI ^b of OR ^e	0.979-1.002	1.031-1.054*	0.862-3.416
AKIN-crea ^g , CI ^b of OR ^e	0.985-1.003	1.030-1.050*	1.246-4.968*

^a = Simplified acute physiology score 3

^b = Confidence interval (95%)

^c = Hazard ratio

^d = Days alive and free

^e = Odds ratio

^f = Continuous renal replacement therapy

^g = Acute kidney injury network (AKIN)-creatinine class 1 or worse

Figures

Figure 1

Flow chart of the patient cohort.

Figure 2

Distribution of emm- and T-type in iGAS isolates. Before 2012, at the Clinical Microbiology Laboratory in Lund, T-typing was performed to determine the serotype of GAS. After 2012 this was replaced by emm-typing. T-type 1 correlates to emm-type 1; other comparisons between T-type and emm-type are more complex.