

GROUP A STREPTOCOCCAL DISEASE IN PAEDIATRIC INPATIENTS: A EUROPEAN PERSPECTIVE

Navin P. Boeddha^{1,2*}, Lucy Atkins^{3*}, Ronald de Groot⁴, Gertjan Driessen^{1,5}, Jan Hazelzet⁶, Werner Zenz⁷, Enitan D. Carrol^{8,9}, Suzanne T. Anderson¹⁰, Federico Martinon-Torres¹¹, Philipp K. A. Agyeman¹², Rachel Galassini¹³, Jethro Herberg¹³, Michael Levin¹³, Luregn J. Schlapbach¹⁴, Marieke Emonts^{3,15,16}, EUCLIDS consortium[#]

*Equal contribution

A list of authors and their affiliations appears at the end of the paper.

1. Erasmus MC-Sophia Children's Hospital, Department of Pediatrics, Rotterdam, the Netherlands
2. Maastad Hospital, Department of Pediatrics, Rotterdam, the Netherlands
3. Great North Children's Hospital, Paediatric Immunology, Infectious Diseases & Allergy, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom
4. Department of Pediatrics, division of Pediatric Infectious Diseases and Immunology and Laboratory of Infectious Diseases, Radboud Institute of Molecular Life Sciences, Radboudumc Nijmegen, the Netherlands
5. Department of Paediatrics, Maastricht University Medical Center, Maastricht, the Netherlands
6. Erasmus MC, Department of Public Health, Rotterdam, the Netherlands
7. Medical University of Graz, Department of General Pediatrics, Graz, Austria
8. University of Liverpool, Institute of Infection, Veterinary and Ecological Sciences Global Health Liverpool, United Kingdom.
9. Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom
10. Medical Research Council Unit The Gambia at LSHTM, Fajara, The Gambia
11. Translational Pediatrics and Infectious Diseases Section- Pediatrics Department, Santiago de Compostela, Spain
12. Inselspital, Bern University Hospital, University of Bern, Switzerland
13. Imperial College of London, Section of Paediatrics Division of Infectious Disease, London, United Kingdom
14. Neonatal and Pediatric Intensive Care Unit, University Children's Hospital Zürich and Children's Research Center, Switzerland
15. Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom
16. NIHR Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Trust and Newcastle University, Newcastle upon Tyne, United Kingdom

29

30 **Corresponding author**

31 Prof. dr. Marieke Emonts

32 Paediatric Immunology, Infectious Diseases & Allergy Dept Great North Children's Hospital

33 RVI, Clinical Resources Building

34 Queen Victoria road Newcastle upon Tyne

35 NE1 4LP, United Kingdom

36 Phone: +44 (0) 191 2825234

37 Email: marieke.emonts@ncl.ac.uk

38

39 **Word count** abstract: 256, total text: 2897 (excl refs), 36 refs

40

41 **KEYWORDS**

42 *Streptococcus pyogenes*, child, hospital, outcome

43

44 **AUTHOR'S SUMMARY**

45 **What is known?**

- 46 • Despite temporal and geographical variability, there is an increase of incidence of infection
- 47 with group A streptococci. However, data on the epidemiology of group A streptococcal
- 48 infections in European children is limited.

49

50 **What is new?**

- 51 • In a large, prospective cohort of children with community-acquired bacterial infection
- 52 requiring hospitalisation in Europe, GAS was the most frequent pathogen.

53 • In children with GAS sepsis, IVIG was used in only 4.6% of patients and Clindamycin in 29% of
54 patients.

55 • We report 2% mortality and 12% disability at discharge.

56

ABSTRACT

Purpose Group A streptococcal (GAS) disease shows increasing incidence worldwide. We characterised children admitted with GAS infection to European hospitals and studied risk factors for severity and disability.

Methods Prospective, multicenter, cohort study (embedded in EUCLIDS and the Swiss Pediatric Sepsis Study) including 320 children, aged 1 month to 18 years, admitted with GAS infection to 41 hospitals in 6 European countries from 2012-2016. Demographic, clinical, microbiological and outcome data were collected.

Results 195 (61%) patients had sepsis. 236 (74%) patients had GAS detected from a normally sterile site. The most common infection sites were the lower respiratory tract (LRTI) (22%), skin and soft tissue (SSTI) (23%), and bone and joint (19%). Compared to patients not admitted to PICU, patients admitted to PICU: more commonly had LRTI (39 vs 8%), infection without a focus (22 vs 8%) and intracranial infection (9 vs 3%), less commonly had SSTI and bone and joint infections ($p<0.001$), and were younger (median 40 (IQR 21-83) vs 56 (IQR 36-85) months, $p=0.01$). Six PICU patients (2%) died. Sequelae at discharge from hospital were largely limited to patients admitted to PICU (29 vs 3%, $p<0.001$; 12% overall) and included neurodisability, amputation, skin grafts, hearing loss and need for surgery. More patients were recruited in winter and spring ($p<0.001$).

Conclusions In an era of observed marked reduction in vaccine-preventable infections, GAS infection requiring hospital admission is still associated with significant severe disease in younger children, and short and long term morbidity. Further advances are required in the prevention and early recognition of GAS disease.

80 **LIST OF ABBREVIATIONS**

81	ANOVA	Analysis of Variance
82	ASOT	Antistreptolysin O titre
83	CPAP	Continuous positive airway pressure
84	CRP	C-reactive protein
85	CSF	Cerebrospinal fluid
86	EUCLIDS	European Childhood Life-threatening Infectious Disease Study
87	GAS	Group A Streptococcus
88	ICD-10	International Classification of Diseases 2010
89	iGAS	Invasive Group A Streptococcus
90	IQR	interquartile range
91	IVIG	intravenous immunoglobulin
92	LRTI	lower respiratory tract infection
93	PCR	Polymerase Chain Reaction
94	PICU	Paediatric Intensive Care Unit
95	PIM2	Paediatric Index of Mortality
96	POPC	Pediatric Overall Performance Category
97	PRISM	Paediatric Risk of Mortality score
98	RST	Rapid streptococcal antigen test
99	SIRS	Systemic inflammatory response syndrome
100	SPSS	Swiss Pediatric Sepsis Study
101	STSS	Streptococcal toxic shock syndrome
102	VZV	Varicella-zoster virus

103

INTRODUCTION

Group A streptococcal (GAS) infection is characterised by a wide variety of phenotypes, from upper respiratory tract and focal skin and soft tissue infections to necrotising fasciitis and streptococcal toxic shock syndrome (STSS), as well as peri-infectious phenomena such as rheumatic fever and post-streptococcal glomerulonephritis.[1] Extensive strain diversity - there are more than 200 emm-types - is presumed to contribute to the diversity of observed clinical syndromes.[2-4]

In Western Europe, GAS was a leading cause of child death until the mid-20th century.[5] Although the incidence fell rapidly during the mid-20th century, it began rising again in the 1980s, and was estimated to be 3-4/100,000 in Northern Europe by the early 2000s.[6] Surges continue in Europe, [7, 8] and further afield, for instance, South Korea [9, 10] and Utah, where a 2010 study found a rate of up to 14.1/100,000 cases in children.[6, 11] Severity of illness also seems to be increasing.[12-14] Mean case fatality rates in affluent countries remain relatively low at 8-16%.[5] However, the mortality of iGAS can rise rapidly up to 60-70% with any delay in antibiotics and interventions against toxins such as clindamycin and intravenous immunoglobulin.[15-17]

Epidemiological studies capturing the full spectrum of GAS disease are challenging. Many cases never present to health care providers, or are treated in the community without microbiological diagnostics (tonsillitis, cellulitis). Studies have shown that *microbiologically-proven* paediatric iGAS occurs most commonly with bacteraemia, soft tissue infections, STSS or necrotizing fasciitis,[18] and that risk factors include other children in the household, preceding coryzal illness and varicella infection.[19] However, it has been difficult to study a wider population of children with severe bacterial infections where GAS is the likely cause but not isolated from a sterile site.

In this large study, we aimed to characterize children admitted with GAS infection to European hospitals and study risk factors for severity and disability. We gathered information about possible risk factors, clinical presentation, progress and outcomes for children presenting with suspected severe bacterial infection for whom the cause was proven or probable GAS.

METHODS

Consortium and study sites

This study used data from the European Childhood Life-threatening Infectious Disease Study (EUCLIDS) and the Swiss Paediatric Sepsis Study (SPSS) [20, 21]. EUCLIDS is a prospective, multicenter, cohort study aimed to identify genes and pathways determining susceptibility and severity of life-threatening bacterial infections. The network included 185 predominantly academic hospitals from 8 European countries. Details of EUCLIDS inclusion and exclusion criteria as well as clinical definitions, have been published elsewhere.[20] In short, for this sub-cohort, children with suspected severe bacterial infection were recruited prospectively from 1-July-2012 to 31-December-2016, as early as possible in admission and before culture results became available. The SPSS is a prospective, national, observational, multicenter, cohort study investigating blood culture-proven sepsis in children under 17 years of age from all 10 major children's hospitals in Switzerland from 1-January-2012 to 31-December-2015.[21] In brief, children with blood culture-proven sepsis meeting the criteria for systemic inflammatory response syndrome (SIRS), as defined by the 2005 pediatric consensus definition[22] at the time of blood culture sampling, were included. Details of the study design and the study protocol have been published elsewhere.[21]

Inclusion criteria

The combined EUCLIDS-SPSS database was used to identify all children for whom GAS was the most likely cause of their illness. Children were included if they met any of the following criteria:

1. Proven GAS: GAS grown from a normally sterile site or positive by pathogen specific PCR (blood, CSF, joint fluid, pleural fluid, peritoneal fluid, tissue, urine, intra-operative pus or internal swab). GAS detection by PCR was performed according to local accredited hospital or specialized molecular microbiology laboratories.

2. Probable GAS: Clinical symptoms consistent with GAS disease, NO other causative organism identified AND at least one of the following:
- a. GAS grown from a potential carriage site (throat, naso-pharynx, eye surface, ear, endo-tracheal tube, broncho-alveolar lavage, skin)
 - b. Antistreptolysin O titre (ASOT) ≥ 300 IU/L[23]
 - c. Local rapid streptococcal antigen test (RST) from pharyngeal sample positive.

Cases were excluded if they had been enrolled retrospectively to avoid selection bias, or were from the non-European EUCLIDS sites. In addition, patients in whom other potential causative pathogens were detected from sterile or non-sterile-site cultures were excluded.

Sepsis, severe sepsis, and septic shock were defined according to Goldstein criteria, and focal infection was used for patients with an organ system identifiable febrile illness not matching sepsis according to Goldstein criteria.[22]

Clinical data collection

Data on demographics, clinical presentation, underlying disease, exposure to varicella-zoster virus (VZV), smoking, recent surgery, illness severity, management, microbiological results, and outcome were collected prospectively. Exposure to VZV or smoking was not available for the Swiss patients. Underlying disease at admission to hospital were classified using the Paediatric Complex Chronic Conditions classification system.[24] Illness severity in PICU patients was measured by the Paediatric Risk of Mortality score (EUCLIDS patients only) [25] and the Paediatric Index of Mortality-2 (PIM2).[26] Lactate values were obtained on PICU admission only, concomitant with PIM2 data collection. Outcome included mortality, disability, PICU-free days and length of hospital stay. Disability was defined as a Pediatric Overall Performance Category (POPC) score greater than one [27], need for skin graft, amputation, hearing loss, neurodisability, or need for surgery. The POPC score was determined either by direct observation or by chart review and ranges from 1 to 6, varying from (1) good overall

performance to (6) brain death.[27] (Supplementary Table 1 for description of categories). PICU-free days (days alive and free from the need for intensive care) were censored at day 28. In patients who died, PICU-free days were considered zero.

Patients were grouped as *no focus* (primary bloodstream infection and sepsis without a known source) versus patients with a clinical focus of infection. All data were collected in web-based case report forms. Monthly telephone conferences, biannual meetings, clinical protocols including case definitions, data audits, and monitoring ensured uniform procedures among study sites.

Statistical analysis

Categorical variables were presented as counts (percentages). Chi-Square or Fisher's exact test were used to compare frequency distributions between two categorical variables. Continuous variables were presented as median (interquartile range (IQR)) for non-parametric data. ANOVA, Kruskal-Wallis, Student's t, or Mann-Whitney U tests were used to test differences between groups, as appropriate. Statistical analysis was performed with IBM® SPSS version 24 (Armonk, USA). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 346/4025 (9%) of the children prospectively enrolled at any of the participating hospitals had proven/probable GAS disease. Other commonly identified pathogens were *Neisseria meningitidis*, *Staphylococcus aureus* and *Streptococcus pneumoniae* in about 8% of patients each.[20] 22 GAS patients were excluded because they had been recruited retrospectively as part of the genetics study, and 4 because they were from non-European EUCLIDS sites (Figure 1), leaving 320 patients for analyses.

Demographics and clinical spectrum

161 (50%) were male, with median age 47 (IQR 27-84) months. 47 (15%) presented without a clinical focus of infection. In children with a focus of infection, bone/joint, soft tissue or respiratory tract infection were the predominant presentations. One or more underlying conditions were present in 117 (37%) of patients of which the most common were recent VZV (n=21, 6.6 %), congenital or genetic conditions (n=18, 5.6%) and eczema (n=11, 3.4 %). Further details are presented in Table 1.

Characteristics of PICU cases and risk factors for severe disease

148 (46%) children were admitted to PICU. 105 (71%) patients in PICU required invasive ventilation, with a median (IQR) of 5 (3-8) days (n=92). 88 (59%) PICU patients required inotropes, with a median (IQR) of 3 (2-4.3) days (n=74). None of the patients required extracorporeal membrane oxygenation. The median (IQR) PRISM score was 14 (8-20, n=72) and PIM2 6.1% (1.4-11.5, n=88) predicted death rate. Median lactate on PICU admission was 1.5 mmol/L (IQR 0.9-2.4, n=90). The number of PICU-free days at day 28 in the PICU group was 23 days (IQR 18-25).(Table 1)

The proportion of patients admitted to PICU differed between countries ($p=0.026$, Supplementary Figure 1). Patients admitted to PICU, compared to those not admitted to PICU, were younger (40 [21-83] vs 57 [36-85] months, respectively, $p=0.01$), had more frequent epilepsy ($p=0.01$) and congenital and genetic defects ($p=0.005$) as underlying conditions, and more often had LRTI , intracranial infection, and infection without a focus, whereas SSTI and bone and joint infections were more common in patients not requiring PICU ($p<0.001$).(Table 1) Also, the maximum CRP in PICU patients was significantly higher and hospital admission was associated with a two-fold increase in duration. Time from onset of symptoms to admission to hospital did not differ between PICU and non-PICU patients. Eczema (n=11) and recent VZV infection (n=21) were not associated with PICU admission. Also, there was no difference in exposure to smoking between PICU and non-PICU patients (20 (12%) and 29 (20%), respectively, $p=0.13$).

42 children (13%) had a severe infection (defined as a clinical syndrome suspected for severe invasive bacterial disease such as septicaemia, toxic shock syndrome, pneumonia, empyema,

meningitis, osteomyelitis and septic arthritis) in the previous medical history, but this was not related to increased risk of PICU admission. In fact, those with a severe infection in the past were less often admitted to PICU (7.4 vs 18%, $p=0.02$). This could not be explained by a difference in onset of symptoms until admission. ($p=1.0$)

Microbiology

The diagnosis of GAS infection was based on a positive culture and/or PCR from a normally sterile site in 236 (74%) of the patients, of which 145 (61%) in blood and 37 (16%) in pleural fluid were the most common sites (Table 1). For the remaining patients, GAS clinical syndrome was determined by the local team based on positive culture and/or PCR from a potential carriage site ($n=68$, 21%), elevated ASOT ($n=7$, 2%), and a positive pharyngeal RST ($n=9$, 3%). Streptococcal titres were measured with a median of 16 days (IQR 10-28) after onset of symptoms and 8 days (IQR 5-12) after admission to the hospital. There was no difference in the means of GAS identification between non-PICU and PICU patients ($p=0.11$).

Seasonality

A seasonal pattern was noted with more GAS infected patients recruited in the winter and spring months ($n=223$ (70%), December-May) compared to the rest of the year ($n=97$ (30%), June-November, $p<0.001$; Figure 2).

Sepsis versus focal infection

195 (61%) patients had sepsis, of which 47 (24%) without a focus, and in 125 (39%) patients disease was limited to a focal infection. Patients with sepsis tended to be younger (median 44 months) compared to patients with focal infection (median 57 months, $p=0.07$). Sex distribution was not significantly different for patients with sepsis or focal infection. Patients with sepsis relatively more often had LRTI (25.1 vs 17.6%) as focus of infection compared to the other foci ($p<0.001$). Sepsis was

associated with a higher CRP than focal infection (median 228 (IQR 114-303) vs 111 (IQR 53-211); $p<0.001$). The proportion of patients with sepsis was higher in PICU ($n=116$, 78%) than in those not requiring PICU admission ($n=79$, 46%, $p<0.001$) (Table 2). All but one (73/74 (99%)) patient with septic shock or toxic shock were admitted to PICU. Patients with sepsis more often had GAS identified from a normally sterile site than those with focal infection ($n=168$, 86% vs $n=68$, 54%; $p<0.001$).

With regard to adjunctive treatment of patients with sepsis, intravenous immunoglobulin (IVIG) was administered in 9/195 (4.6%) patients and administration did not differ between countries (7/86 (8.1%) patients with sepsis from the UK and 2/39 (5.1%) patients with sepsis from The Netherlands; $p=0.32$). However, Clindamycin was prescribed in 57/195 (29%) sepsis patients and prescription rate was different between countries (39/86 (45%) from the UK, 8/39 (21%) from The Netherlands, 4/7 (57%) from Spain, 4/56 (7%) from Switzerland, 1/3 (33%) from Austria, and 1/4 (25%) from Germany; $p<0.001$).

Outcome

Six children died, reflecting a crude mortality of 2% (Table 3). Overall, 231 (72%) children survived without disability and 39 (12%) with disability, including 23/168 (14%) children who did not have an underlying condition at hospital admission, i.e. previously healthy children. For the remaining 44 (14%) patients, information on disability was not classified. The majority of patients where disability was not classified were transferred back to their local hospital for ongoing care, from which point no reliable judgment could be made regarding full recovery. The proportion of survivors without disability was lower for those admitted to PICU (57%, $p<0.001$). Age was not associated with outcome (disability vs no disability). Skin graft and need for surgery were seen in patients with sepsis and focal infection, but other complications such as death, amputation, and neurodisability, were observed at discharge in patients with sepsis only, and limited to those admitted to PICU (Figure 3).

DISCUSSION

In this European cohort, GAS is a significant cause of probable or confirmed severe bacterial infection, with a significant burden of mortality and persistent morbidity. Risk factors for PICU admission were lower age, LRTI, intracranial infection, and infection without a focus. The need for PICU admission did not seem to be related to delayed presentation. The proportion of patients admitted to PICU differed between countries. A survey among participating centres showed that criteria for PICU admission and availability of resources differed between centres. In some centres non-invasive ventilation (e.g. CPAP) was only supported in PICU, while in others it could be offered on a paediatric ward or high dependency unit. (Unpublished) In addition, except for Switzerland, the participating centres were not representing the entire population, and selection bias may contribute to differences.

Data from this study originates from two separate cohorts; EUCLIDS and SPSS. In EUCLIDS, recruitment of patients took place on admission and largely before the causative pathogen was known. Only patients with suspected severe bacterial infection admitted to the hospital were recruited, which means those with milder infections not requiring admission were not included. Also, due to the nature of the study it is not clear exactly what proportion of overall eligible children was recruited for the study. In SPSS, only children with blood culture-proven sepsis were recruited, meaning that children with GAS disease and negative blood culture were omitted. Therefore, data from our study could be an underestimation of the true impact of GAS disease in Europe and should be interpreted with caution.

The overall mortality (2%) was comparable to other studies on bacteraemic children including all patients in hospital [21, 28]; but was lower than most previously-reported mortality rates in patients admitted to PICU.[5] When assessing severity, considering mortality alone risks underestimating the true impact of iGAS. While for most patients full recovery at hospital discharge was noted, significant sequelae were identified in 12% overall, increasing to 23% for those admitted to PICU. As patients were not followed after hospital discharge, no information is available on potential resolution of some of the sequelae and longer term morbidity and functional outcome related to iGAS disease. In addition, no data on baseline POPC scores were available, which means

pre-existing comorbidity could not be taken into account assessing the difference in functioning pre and post infection.

Overall, 74% of patients had GAS identified from a sterile site. For 26% of patients, a positive potential carriage site, a rapid antigen test or raised ASOT was the only method of microbiological GAS confirmation. We acknowledge these diagnostic methods as a limitation of our study. However, while analysis of proven GAS infections might be the gold standard, it is recognised that GAS cannot be cultured in all patients. By including probable cases, we better reflected the actual demographics of GAS disease. We reduced the risk of including non-GAS cases by excluding patients in whom other potential causative pathogens were detected from sterile or non-sterile-site cultures. Only patients in whom diagnostics exclusively identified GAS were included.

As not all GAS isolates were kept, we were unable to obtain their M types to assess potential association with phenotype and severity. The variability in these proteins, associated with diversity in disease phenotypes, makes development of a generic GAS vaccine challenging.[2, 29, 30] Future research focussing on bacterial phenotypes related to LRTI, intracranial infection and sepsis might help prioritise vaccine development, in order to prevent most severe disease.

Interestingly, only a few patients with recent VZV infection were identified. While it is well-known that VZV increases vulnerability to iGAS infection[16], our study confirms that GAS infection predominantly occurs in individuals with no obvious risk factors. It has to be acknowledged that for patients recruited in Switzerland, unfortunately, VZV and other exposures were not recorded.

Despite the fact that this study was not purposely designed to study epidemiology, a seasonal variation was noted. Patients were recruited to the study early during the admission when the cause of infection was not yet known, limiting recruitment bias. Most patients with GAS infection were recruited in winter and spring, with a clear reduction in the summer months, while recruitment took place year-round. Seasonal increase has also been noted in Australian children, where iGAS coincides with the influenza season.[31] An increased incidence over the winter months has also been reported in Hong Kong, South Korea, the USA, Iceland and other European countries.[6, 10, 32-36]

334

335 **CONCLUSION**

336 Our study showed that LRTI, intracranial infection, and infection without a focus more commonly
337 resulted in severe GAS disease requiring admission to PICU. PICU admission for GAS infection was
338 associated with worse outcome with regard to mortality and disability. With increasing incidence of
339 iGAS disease worldwide, and increased morbidity and mortality in those requiring PICU, future
340 research should focus on prevention of iGAS infection. Vaccination development should target iGAS
341 serotypes associated with severe disease requiring PICU admission.

342

REFERENCES

1. Dietrich ML, Steele RW. Group A Streptococcus. *Pediatr Rev.* 2018;39(8):379-91. doi: 10.1542/pir.2017-0207.
2. Shulman ST, Tanz RR, Dale JB, Steer AC, Smeesters PR. Added value of the emm-cluster typing system to analyze group A Streptococcus epidemiology in high-income settings. *Clin Infect Dis.* 2014;59(11):1651-2. doi: 10.1093/cid/ciu649.
3. Davies MR, McIntyre L, Mutreja A, Lacey JA, Lees JA, Towers RJ, et al. Atlas of group A streptococcal vaccine candidates compiled using large-scale comparative genomics. *Nat Genet.* 2019;51(6):1035-43. doi: 10.1038/s41588-019-0417-8.
4. Sanderson-Smith M, De Oliveira DM, Guglielmini J, McMillan DJ, Vu T, Holien JK, et al. A systematic and functional classification of Streptococcus pyogenes that serves as a new tool for molecular typing and vaccine development. *J Infect Dis.* 2014;210(8):1325-38. doi: 10.1093/infdis/jiu260.
5. Steer AC, Lamagni T, Curtis N, Carapetis JR. Invasive group a streptococcal disease: epidemiology, pathogenesis and management. *Drugs.* 2012;72(9):1213-27. doi: 10.2165/11634180-000000000-00000.
6. Lamagni TL, Darenberg J, Luca-Harari B, Siljander T, Efstratiou A, Henriques-Normark B, et al. Epidemiology of severe Streptococcus pyogenes disease in Europe. *J Clin Microbiol.* 2008;46(7):2359-67. doi: 10.1128/JCM.00422-08.
7. Plainvert C, Loubinoux J, Bidet P, Doloy A, Touak G, Dmytruk N, et al. [Epidemiology of Streptococcus pyogenes invasive diseases in France (2007-2011)]. *Arch Pediatr.* 2014;21 Suppl 2:S62-8. doi: 10.1016/S0929-693X(14)72262-6.
8. Scaber J, Saeed S, Ihekweazu C, Efstratiou A, McCarthy N, O'Moore E. Group A streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England. *Euro Surveill.* 2011;16(5).

367 9. Filleron A, Jeziorski E, Michon AL, Rodiere M, Marchandin H. Current insights in invasive group A
368 streptococcal infections in pediatrics. *Eur J Pediatr.* 2012;171(11):1589-98. doi: 10.1007/s00431-012-
369 1694-8.

370 10. Park DW, Kim SH, Park JW, Kim MJ, Cho SJ, Park HJ, et al. Incidence and Characteristics of Scarlet
371 Fever, South Korea, 2008-2015. *Emerg Infect Dis.* 2017;23(4):658-61. doi: 10.3201/eid2304.160773.

372 11. Stockmann C, Ampofo K, Hersh AL, Blaschke AJ, Kendall BA, Korgenski K, et al. Evolving
373 epidemiologic characteristics of invasive group a streptococcal disease in Utah, 2002-2010. *Clin Infect*
374 *Dis.* 2012;55(4):479-87. doi: 10.1093/cid/cis422.

375 12. Lithgow A, Duke T, Steer A, Smeesters PR. Severe group A streptococcal infections in a paediatric
376 intensive care unit. *J Paediatr Child Health.* 2014;50(9):687-92. doi: 10.1111/jpc.12601.

377 13. Nasser W, Beres SB, Olsen RJ, Dean MA, Rice KA, Long SW, et al. Evolutionary pathway to increased
378 virulence and epidemic group A *Streptococcus* disease derived from 3,615 genome sequences. *Proc*
379 *Natl Acad Sci U S A.* 2014;111(17):E1768-76. doi: 10.1073/pnas.1403138111.

380 14. Al-Shahib A, Underwood A, Afshar B, Turner CE, Lamagni T, Sriskandan S, et al. Emergence of a
381 novel lineage containing a prophage in emm/M3 group A *Streptococcus* associated with upsurge in
382 invasive disease in the UK. *Microb Genom.* 2016;2(6):e000059. doi: 10.1099/mgen.0.000059.

383 15. Carapetis JR, Jacoby P, Carville K, Ang SJ, Curtis N, Andrews R. Effectiveness of clindamycin and
384 intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal
385 infections. *Clin Infect Dis.* 2014;59(3):358-65. doi: 10.1093/cid/ciu304.

386 16. Laupland KB, Davies HD, Low DE, Schwartz B, Green K, McGeer A. Invasive group A streptococcal
387 disease in children and association with varicella-zoster virus infection. Ontario Group A Streptococcal
388 Study Group. *Pediatrics.* 2000;105(5):E60.

389 17. Whitehead BD, Smith HV, Nourse C. Invasive group A streptococcal disease in children in
390 Queensland. *Epidemiol Infect.* 2011;139(4):623-8. doi: 10.1017/S0950268810001378.

18. Zachariadou L, Stathi A, Tassios PT, Pangalis A, Legakis NJ, Papaparaskevas J, et al. Differences in the epidemiology between paediatric and adult invasive *Streptococcus pyogenes* infections. *Epidemiol Infect.* 2014;142(3):512-9. doi: 10.1017/S0950268813001386.
19. Factor SH, Levine OS, Harrison LH, Farley MM, McGeer A, Skoff T, et al. Risk factors for pediatric invasive group A streptococcal disease. *Emerg Infect Dis.* 2005;11(7):1062-6. doi: 10.3201/eid1107.040900.
20. Martinon-Torres F, Salas A, Rivero-Calle I, Cebey-Lopez M, Pardo-Seco J, Herberg JA, et al. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study. *Lancet Child Adolesc Health.* 2018;2(6):404-14. doi: 10.1016/S2352-4642(18)30113-5.
21. Agyeman PKA, Schlapbach LJ, Giannoni E, Stocker M, Posfay-Barbe KM, Heininger U, et al. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. *Lancet Child Adolesc Health.* 2017;1(2):124-33. doi: 10.1016/S2352-4642(17)30010-X.
22. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric S. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2-8. doi: 10.1097/01.PCC.0000149131.72248.E6.
23. Pagana KDP, T.J.; Pagana, T.N. *Mosby's Diagnostic & Laboratory Test Reference.* 14 ed. Elsevier; 2019.
24. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr.* 2014;14:199. doi: 10.1186/1471-2431-14-199.
25. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med.* 1988;16(11):1110-6.
26. Slater A, Shann F, Pearson G, Paediatric Index of Mortality Study G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med.* 2003;29(2):278-85. doi: 10.1007/s00134-002-1601-2.

416 27. Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr.* 1992;121(1):68-74. doi:
417 10.1016/s0022-3476(05)82544-2.

418 28. Odetola FO, Gebremariam A, Freed GL. Patient and hospital correlates of clinical outcomes and
419 resource utilization in severe pediatric sepsis. *Pediatrics.* 2007;119(3):487-94. doi:
420 10.1542/peds.2006-2353.

421 29. Steer AC, Law I, Matatolu L, Beall BW, Carapetis JR. Global emm type distribution of group A
422 streptococci: systematic review and implications for vaccine development. *Lancet Infect Dis.*
423 2009;9(10):611-6. doi: 10.1016/S1473-3099(09)70178-1.

424 30. Safar A, Lennon D, Stewart J, Trenholme A, Drinkovic D, Peat B, et al. Invasive group A streptococcal
425 infection and vaccine implications, Auckland, New Zealand. *Emerg Infect Dis.* 2011;17(6):983-9. doi:
426 10.3201/eid1706.100804.

427 31. Oliver J, Thielemans E, McMinn A, Baker C, Britton PN, Clark JE, et al. Invasive group A
428 Streptococcus disease in Australian children: 2016 to 2018 - a descriptive cohort study. *BMC Public*
429 *Health.* 2019;19(1):1750. doi: 10.1186/s12889-019-8085-2.

430 32. Lee CF, Cowling BJ, Lau EHY. Epidemiology of Reemerging Scarlet Fever, Hong Kong, 2005-2015.
431 *Emerg Infect Dis.* 2017;23(10):1707-10. doi: 10.3201/eid2310.161456.

432 33. Smeesters PR, Laho D, Beall B, Steer AC, Van Beneden CA. Seasonal, Geographic, and Temporal
433 Trends of emm Clusters Associated With Invasive Group A Streptococcal Infections in US Multistate
434 Surveillance. *Clin Infect Dis.* 2017;64(5):694-5. doi: 10.1093/cid/ciw807.

435 34. Nelson GE, Pondo T, Toews KA, Farley MM, Lindegren ML, Lynfield R, et al. Epidemiology of
436 Invasive Group A Streptococcal Infections in the United States, 2005-2012. *Clin Infect Dis.*
437 2016;63(4):478-86. doi: 10.1093/cid/ciw248.

438 35. O'Loughlin RE, Roberson A, Cieslak PR, Lynfield R, Gershman K, Craig A, et al. The epidemiology of
439 invasive group A streptococcal infection and potential vaccine implications: United States, 2000-2004.
440 *Clin Infect Dis.* 2007;45(7):853-62. doi: 10.1086/521264.

441 36. Olafsdottir LB, Erlendsdottir H, Melo-Cristino J, Weinberger DM, Ramirez M, Kristinsson KG, et al.
442 Invasive infections due to *Streptococcus pyogenes*: seasonal variation of severity and clinical
443 characteristics, Iceland, 1975 to 2012. *Euro Surveill.* 2014;19(17):5-14.

444

445

STATEMENTS AND DECLARATIONS

Funding

This work was supported by the European Seventh Framework Programme for Research and Technological Development (FP7) under EUCLIDS Grant Agreement n°. 279185. The Swiss Pediatric Sepsis Study was funded by grants from the Swiss National Science Foundation (342730_153158/1), the Swiss Society of Intensive Care, the Bangerter Foundation, the Vinetum and Borer Foundation, and the Foundation for the Health of Children and Adolescents. These funders were not involved in the design of the study, collection, analysis, interpretation of data, or in writing the manuscript.

Competing Interests

The authors declare no competing interests.

Author Contributions

FMT, JH, EDC, ME, RdG, WZ, and ML designed the study and obtained funding. JH, NPB, PA, LJS, GJD, STA, ME, LJS and EDC assisted with recruitment of patients, data collection, and sample collection. ME and NPB did the statistical analyses. LA and RG provided database and informatics support. LA, ME, NPB, LJS, and GJD wrote the first draft of the manuscript. FMT, JAH, RdG, WZ, EDC, STA, FMT, PA, RG, JH and ML contributed to writing of the manuscript. All authors approved the final manuscript.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by at least one ethical review board in every country (Coordinating center Research Ethics Committee reference: 11/LO/1982). Written informed consent was obtained from parents or legal guardians. In the Swiss study, consent was obtained for collection

471 of research blood, but waiver of consent for collection of anonymized epidemiological data was
472 approved.

473

474

TABLES

Table 1: Characteristics of children admitted with GAS infection

	All patients (n=320)	No PICU admission (n=172)	PICU admission (n=148)	P
Sex (male n, %)	161 (50%)	86 (50%)	75 (51%)	0.9
Age (months) (IQR)	47 [27-84]	57 [36-85]	40 [21-83]	0.01
Time interval onset symptoms to hospital admission (n=251, days)	3.0 [1.8-6.0]	3.5 [1.8-6]	3.0 [1.8-5.7]	0.67
Immunizations up-to-date (n=222)	211 (95%)	103/110 (94%)	108/112 (96%)	0.06
Number of underlying conditions				
None	203(63%)	107 (62%)	96 (65%)	0.11
1	77 (24%)	48 (28%)	29 (20%)	
≥2	40 (13%)	17 (10%)	23 (16%)	
Underlying conditions				
Congenital or genetic defect	18 (5.6%)	4 (2.3%)	14 (9.5%)	0.006
Prematurity	10 (3.1%)	5 (2.9%)	5 (3.4%)	0.11
Immunodeficiency	6 (1.9%)	1 (0.6%)	5 (3.4%)	0.19
Cardiac condition	5 (1.6%)	2 (1.2%)	3 (2.0%)	0.47
Epilepsy	5 (1.6%)	0	5 (3.4%)	0.01
Respiratory	9 (2.8%)	6 (3.5%)	3 (2.0%)	0.12
Haematological	1 (0.3%)	0	1 (0.7%)	0.28
Oncological	1 (0.3%)	1 (0.6%)	0	0.35
Inflammatory	2 (0.6%)	1 (0.6%)	1 (0.7%)	0.36
Liver disease	1 (0.3%)	0	1 (0.7%)	0.28
Renal disease	0	0	0	NA
Metabolic disease	2 (0.6%)	1 (0.6%)	1 (0.7%)	0.36
Recent surgery	3 (0.9%)	1 (0.6%)	2 (1.4%)	0.48
Eczema/dermatitis	11 (3.4%)	6 (3.5%)	5 (3.4%)	0.96
Recent chickenpox	21 (6.6%)	10 (5.8%)	11 (7.4%)	0.09
Primary infection site				<0.001
None	47 (15%)	14 (8%)	33 (22%)	
Lower respiratory tract	71 (22%)	14 (8%)	57 (39%)*	
Skin/Soft tissue	73 (23%)	50 (29%)	23 (16%)	
Bone/joint	60 (19%)	52 (30%)	8 (5%)	
Upper respiratory tract	46 (14%)	34 (20%)	12 (8%)	
Intracranial	18 (6%)	5 (3%)	13 (9%)	
Peritoneal	3 (1%)	1 (1%)	2 (1%)	
Renal	2 (1%)	2 (1%)	0	
Microbiology				0.11
Sterile site positive culture or PCR [^]	236 (74%)	120 (70%)	116 (78%)	
Blood	145 (61%)	80 (67%)	65 (56%)	
CSF	5 (2%)	2 (2%)	3 (3%)	
Joint fluid	18 (8%)	17 (14%)	1 (1%)	
Pleural fluid	37 (16%)	3 (3%)	34 (30%)	
Peritoneal fluid	1 (0.4%)	0	1 (1%)	
Tissue	4 (2%)	1 (1%)	3 (3%)	
Urine	1 (0.4%)	1 (1%)	0	
Abscess/pus	26 (11%)	15 (13%)	11 (10%)	
Intraoperative swab	13 (6%)	6 (5%)	7 (6%)	
GAS clinical syndrome, AND	84 (26%)	52 (30%)	32 (22%)	
- Potential carriage site positive	68 (21%)	40 (23%)	28 (19%)	
- Elevated ASOT	7 (2%)	4 (2%)	3 (2%)	

- Pharyngeal RST positive	9 (3%)	8 (5%)	1 (1%)	
Inflammatory markers				
Max CRP (n=256, mg/L)	185 (80-286)	119 (62-228)	256 (149-328)	<0.001
Hospital length of stay (n=318, days)	11 [6-18]	8 [4-13]	17 [11-26]	<0.001
PICU free days at day 28 (n=318)	28 (23-28)	28	23 [18-25]	<0.001

Abbreviations: ASOT=Antistreptolysin O titre; CRP=C-reactive protein; CSF=cerebrospinal fluid; GAS=group A streptococcal; PCR=Polymerase chain reaction; PICU=Pediatric Intensive Care Unit; RST=rapid streptococcal antigen test.

*34/57 ((69%) of patients in PICU and 4/14 (29%) of patients not requiring PICU for lower respiratory tract infection had pleural empyema.

^Breakdown exceeds 100% as GAS could have been identified from multiple sources per patient.

509 **Table 2. Sepsis in iGAS infection**

Sepsis severity	No PICU N=172	PICU N=148	<i>P</i>
None	93 (54%)	32 (22%)	P<0.001
Sepsis	74 (43%)	34 (23%)	
Severe sepsis	4 (2%)	9 (6%)	
Septic shock	1 (1%)	58 (40%)	
Toxic shock syndrome		15 (10%)	

510
511 Abbreviations: iGAS=invasive group A streptococcal; PICU=Pediatric Intensive Care Unit.
512

513
514

Table 3. Outcome of patients with GAS disease

	All patients (n=320)	No PICU admission (n=172)	PICU admission (n=148)	P
Died	6 (2%)	0	6 (4%)	<0.001
Survived with disability	39 (12%)	5 (3%)	34 (23%)	
Mild overall disability	20 (6%)	2 (1%)	18 (12%)	
Moderate overall disability	5 (2%)	0	5 (3%)	
Severe overall disability	3 (1%)	0	3 (2%)	
Amputation	4 (1%)	0	4 (3%)	
Skin graft	9 (3%)	0	9 (6%)	
Amputation and skin graft	2 (1%)	0	2 (1%)	
Need for surgery	10 (3%)	4 (2%)	6 (4%)	
Neurodisability	2 (1%)	0	2 (1%)	
Survived without disability	231 (72%)	146 (85%)	85 (57%)	
Unknown	44 (14%)	21 (12%)	23 (16%)	

Abbreviations: GAS=group A streptococcal; PICU=Pediatric Intensive Care Unit.

541 **FIGURE LEGENDS**

542 **Fig. 1 Study design**

543 CONSORT flow chart including and excluding patients.

544

545 **Fig. 2 Numbers of patients with GAS disease per month**

546 Accumulated numbers of patients with GAS disease over the five year study period per month
547 of presentation. Total n=320.

548

549 **Fig. 3 Outcome of GAS disease in PICU and ward patients**

550 Relative outcomes of patients with GAS per admission category (PICU or non-PICU)

551

FIGURES

Fig. 1 Study design

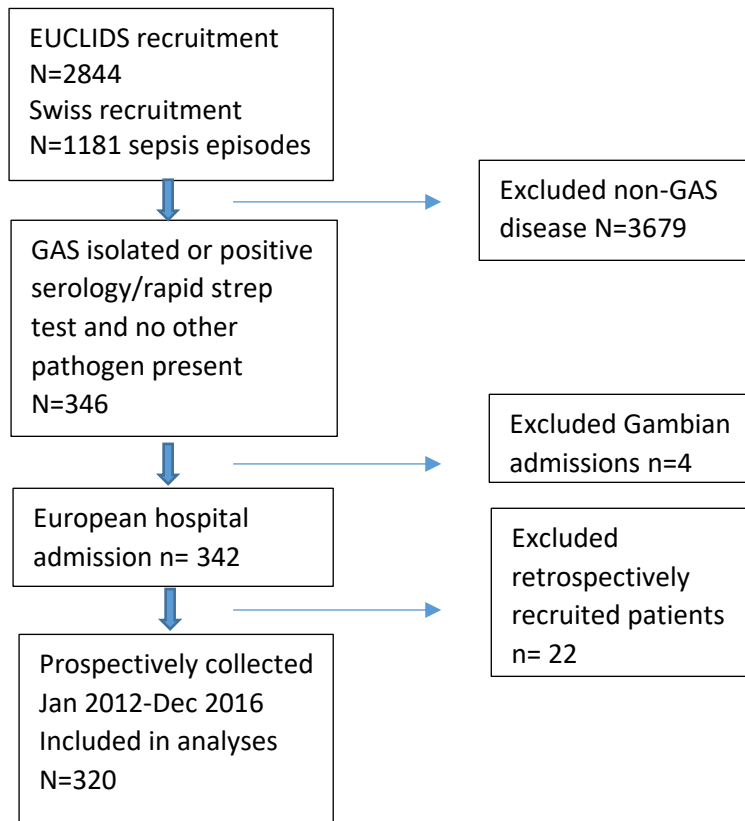


Fig. 2 Numbers of patients with GAS disease per month (2012-2016 combined)

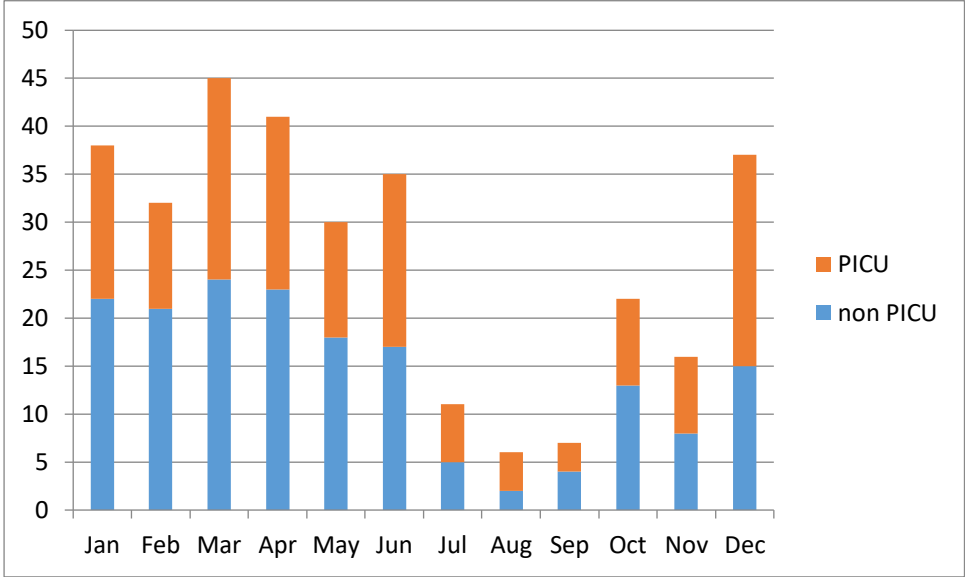
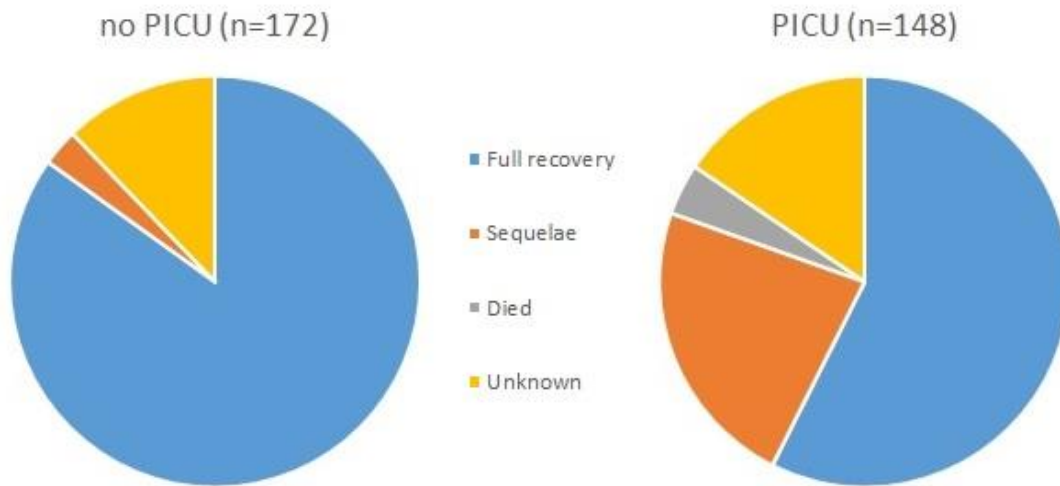


Fig. 3 Outcome of GAS disease in PICU and ward patients



627 **SUPPLEMENTARY FILE**

628

629 **Supplementary Table 1 Description of Pediatric Overall Performance Category (POPC) scores**

630 The POPC scale ranges from 1 to 6; (1) good overall performance, (2) mild
631 overall disability, (3) moderate overall disability, (4) severe overall disability,
632 (5) coma or vegetative state, and (6) brain death

633

634 **Supplementary Fig.1 Percentage of patients with GAS admitted in PICU or on the ward in**
635 **different countries**

636 The relative distribution of patients admitted to PICU differs between
637 countries. $P=0.026$. Numbers are too small to allow meaningful analysis taking
638 into account other risk factors.

639

640 **Consortium EUCLIDS consortium – list of members**