Clinical and microbiological features of a case series of group A streptococcus pleural empyema cases in children: results from a Scottish national surveillance study

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Main text

In the autumn of 2022, clinicians working at the Royal Hospital for Children, Glasgow observed an unusually high number of admissions for paediatric pleural empyema. We questioned whether this was occurring nationally and in this preliminary report present the clinical, epidemiological and microbiological characteristics of these cases. Utilising routine clinical records, microbiology laboratory reports, procedure lists for chest drain insertion, and a list of hospital admissions provided by Public Health Scotland, we identified community acquired pleural empyema cases requiring chest drain insertion from 1 January 2022 onwards at the three tertiary centres performing this procedure in Scotland (Glasgow, Edinburgh and Aberdeen). In 2022, Scotland had an estimated population of 5.47 million[1], with 899,854 children and young people (CYP) under the age of 16 years (16.4%). In the period 1 January 2022 to 27 December 2022 we identified 33 cases of pleural empyema requiring chest drain insertion (36.7 cases per million CYP aged <16 years). Up to the end of August 2022 the most common organism identified in such cases was *Streptococcus pneumoniae* (5/10 cases up until that point). However, from September 2022 onwards a rise in pleural empyema associated with group A streptococcus (GAS) infection was noted, with 16 cases (17.8 cases per million CYP aged <16 years) out of a total of 23. To provide context for our findings, we also queried clinical records and microbiology laboratory reports at the study sites for the period 1 January 2017 to 31 December 2021 (Figure 1, panels A-E). We found an increase in GAS cases in the winter of 2017-18 (four confirmed GAS empyema cases, Figure 1, panels A and B) but not to the degree seen in 2022 (Figure 1, panel F).

Ages for children with pleural empyema with confirmed GAS infection ranged from 10 months to 11 years (median 3 years, IQR 1.6-5); nine out of the 16 cases were males. Two children had significant pre-existing co-morbidities (both born moderately prematurely). Three out of the 16 children were of non-white ethnicity. Most children were resident in and around the city of Glasgow, with three children admitted to the Royal Hospital for Children and Young People, Edinburgh, and none to the Royal Aberdeen Children's Hospital. A review of information held by Public Health Scotland and the Greater Glasgow & Clyde NHS Board did not identify any epidemiological links between the iGAS cases reported in this case series (Eisin McDonald, personal communication). Of the 16 patients in this case series, all presented with fever, 15/16 (93.8%) with lethargy/malaise, 14/16 (87.5%) with cough, 14/16 (87.5%) with difficulty breathing, 8/16 (50%) with rash, and 2/16 (12.5%) with a sore throat. Low rates of reporting a sore throat as a presenting symptom may relate to disease pathogenesis, but more likely reflects the young median age of our patient group. Nine children were admitted to a paediatric intensive care unit. Of these, five were invasively mechanically ventilated out with the periprocedural period of the insertion of a chest drain, and five received inotropic support. There were no deaths amongst the children presented in this case series. Two children remained inpatients at the time of writing; the median length of hospital stay for those who had been discharged was 15.5 days (IQR 13.3-19.8).

An empyema case was judged to be caused by GAS if a sample from a sterile site (blood or pleural fluid) tested positive for *S. pyogenes*. GAS was isolated from pleural fluid culture in eight cases, throat swabs in six cases, and blood cultures in three cases (numbers are not cumulative and can represent cultures from more than one sample type in a single case). GAS was detected in six out of 16 (37.5%) cases only after 16s rRNA sequencing (5 cases) or GAS specific RT-PCR of the *CsrR* gene (1 case) of culture-negative pleural fluid samples. Comparing

time from antibiotic administration to pleural fluid sampling for pleural culture positive (8/16) and negative (8/16) cases showed a significant difference between the two groups (mean of 1.0 days in culture positive cases vs. 2.6 days in culture negative cases, p= 0.007 using unpaired two-side Welch two sample t-test). In 15 cases, a full RT-PCR panel for respiratory viral pathogens was performed, and in nine (9/15, 60 %) a virus was identified: human metapneumovirus (hMPV) in four cases (in one case alongside rhinovirus), respiratory syncytial virus (RSV) in two cases, and Influenza A, varicella and rhinovirus as a sole viral pathogen in three further cases.

In the nine cases that had a *Streptococcus pyogenes* isolate from a sterile site available from culture, eight had been sent to the Scottish Microbiology Reference Laboratory, Glasgow at the time of submission for sequencing of the hypervariable region of the M protein (*emm* typing). The predominant type identified was *emm* 1.0 (6/8), with single *emm* 12.0 and *emm* 1.25 isolates identified. Querying the Scottish National *S. pyogenes* Reference Laboratory database showed that in 2022 the overall number of GAS isolates from sterile sites (21) was in keeping with annual cases from the period 2017-2020 (median 22.5, range 21-24). A striking exception to this trend was 2021, when only one isolate (*emm* type 12) was reported to the Reference Laboratory (Supplementary Table 1a). In 2022*, emm* types 1.0 and 12 were found to be the most common circulating types isolated from sterile sites in children <15 years of age (Supplementary Table 1b), in keeping with UK wide data[2]. Examining isolates from sterile respiratory sites, in 2022 *emm* type 1.0 predominated, in contrast to previous years, where a number of other types were found (Supplementary Table 2).

Recent news reports[3] and alerts from the UK Health Security Agency[4] have highlighted increased rates of invasive GAS (iGAS) disease in children, and associated deaths. Here we present a case series from Scotland of 16 children with iGAS with a primary presentation of empyema. Cases were associated with subtype *emm* 1.0, and testing of nine out of 15 children with a full RT-PCR panel for respiratory viral pathogens found evidence of an associated respiratory tract infection. A clear single cause for the rise in iGAS cases reported here, and seen across the United Kingdom, has not yet been identified[5]. Given the low number of cases of GAS empyema, and iGAS more generally, seen in Scotland post-pandemic up until the autumn of 2022 (with only one GAS case isolated from a sterile site in children <15 years of age in 2021, Supplementary Table 1b), it is possible that a waning in herd immunity may play a role[5]. Another factor may be an increase in viral respiratory tract infections following the easing of lockdown restrictions; these are recognised as risk factors for iGAS[6], and over half (9/15) of patients tested in this case series were positive for such a pathogen on their admission. Finally, it is possible that changes in the *S. pyogenes* genome may have made GAS more transmissible or virulent[5,7]; we found that the majority of cases in our series were associated with the *emm* 1.0 subtype

A limitation of our study is the small sample size, even though we performed a national audit. A UK-wide study is urgently needed to confirm these initial findings, and accurately establish the morbidity as well as mortality caused by iGAS in the current outbreak. Accurate and timely information on demographic risk factors for iGAS will inform the implementation of an effective group A streptococcus vaccine (e.g. TeeVax[8]), once this becomes available. In the context of the current increase in iGAS cases, we recommend a high index of suspicion for empyema in children presenting with respiratory symptoms, and widespread use of 16s rRNA sequencing or GAS specific RT-PCR for culture negative pleural fluids, particularly if there was a lag between start of antibiotic administration and pleural fluid sampling. We also argue for the utility of respiratory tract RT-PCR testing for associated respiratory viruses to better understand risk factors for such infections. This

information will inform the implementation of existing vaccinations (influenza, varicella), as well as the potential rollout of future vaccines for pathogens such as RSV[9] and hMPV[10].

Competing interests: Thomas C Williams is Principal Investigator for the BronchStart project, which is funded by the Respiratory Syncytial Virus Consortium in Europe (RESCEU), with data collection supported by the National Institute for Health Research. None of the other authors declare any competing interests.

Ethics statement: The Public Health Scotland Order 2019 in Article 9(2)(i) places an obligation on Public Health Scotland to engage in the control of spread of infectious diseases in accordance with section 43 of the National Health Service (Scotland) Act 1978. In accordance with Sections 15, 16(5), and 21(2) of the Public Health etc. (Scotland) Act 2008, Public Health Scotland is obliged to process data in relation to notifiable diseases, health risk states of patients, notifiable organisms, and carrying out public health investigations, and as such, individual patient consent is not required. The study was reviewed by the Scientific Officer of the West of Scotland Research Ethics Service (Ward 11, Dykebar Hospital, Grahamston Road, Paisley PA2 7DE) who judged that the study fell within the scope of Health Surveillance as defined by the UK Policy Framework for Health and Social Care Research, and therefore did not require review by an NHS research ethics committee. Data collection for iGAS positive cases was conducted at the Royal Hospital for Children Glasgow, NHS Greater Glasgow and Clyde (1345 Govan Rd, Glasgow G51 4TF, United Kingdom) and the Royal Hospital for Children and Young People Edinburgh, NHS Lothian (50 Little France Cres, Edinburgh EH16 4TJ, United Kingdom) and approval was given for the publication of this study by the Caldicott Guardian at both Trusts.

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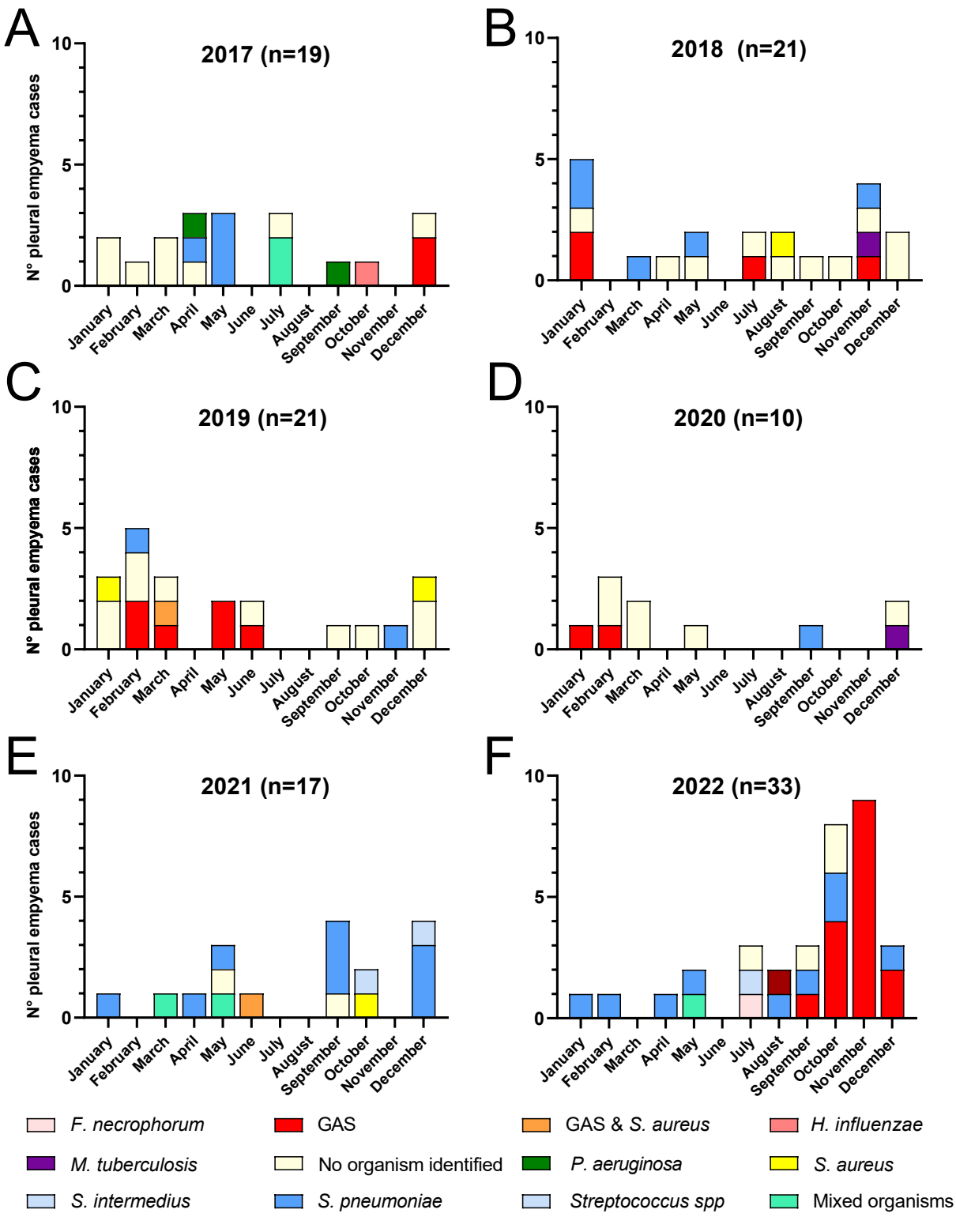

Figure 1 Microbiology of pleural empyema cases across Scotland by month of admission from 1 January 2017 to 27 December 2022. Of note, 2/4 culture-negative pleural samples from 2022 (from July and September) did not undergo 16S rRNA sequencing and therefore group A streptococcus infection cannot be completely excluded. Abbreviations: *F. necrophorum* (*Fusobacterium necrophorum*); GAS (group A streptococcus); *H. influenzae (Haemophilus influenzae)*; *M. tuberculosis (Mycobacterium tuberculosis)*; *P. aeruginosa (Pseudomonas aeruginosa); S. aureus (Staphylococcus aureus); S. intermedius (Streptococcus intermedius); S. pneumoniae (Streptococcus pneumoniae); Streptococcus spp (Streptococcus species)*