Invasive group A streptococcal disease

Joannu Ann Varughese,1 Mahesh Katre,2 Birendra Rai,2 Debkrishna Mallick1

SUMMARY
We report on two children who had presented in a poor clinical state after an initial bout of cough, sore throat and fever for a few days. Both of them had multisystemic involvement with fluid-refractory septic shock requiring ionotropic support, intubation and care in the paediatric intensive care unit. Recent significant rise in scarlet fever has led to a significant increase in the number of invasive group A streptococcal infections with increased mortality in paediatric patients. Both of them had co-infection with influenza, which could have led to an increased risk of invasive group A streptococcal (iGAS) infection. After prompt treatment, including early initiation of antibiotics, they both recovered well. To our knowledge, there are no reported cases of iGAS infection from the UK in any medical journal though the fatal cases have been reported to the health statistics department by various National Health Service trusts individually.

BACKGROUND
The UK has seen a very steep rise in the cases of scarlet fever during the winter of 2022, with a number of cases going far above the cases seen during the previous comparable years in 2017–2018. Seen in line with this rise are the cases of invasive group A streptococcal (iGAS) disease, with children dying of it in significant numbers. Our case series is the first such in any medical journal from this season, which depicts the importance of early recognition and prompt treatment of any such suspicious cases to help improve the mortality and morbidity rate of this hitherto scared illness.

CASE PRESENTATION
Case 1
A teenage boy presented to the emergency department (ED) with a 6-day history of fever, sore throat and cough. His cough had progressively gone worse over the previous 2 days and fever occurred daily with spikes up to 39°C on most of the days. On the day of presentation, he had started vomiting blood both with and without a cough. He had eight episodes of haemoptysis at home and continued to pass watery black/dark-coloured stool while being treated in ED.

He was a previously fit and well child with no allergies and with up-to-date vaccination. He had no history of travel outside and has not come in contact with any animals or humans with tuberculosis or respiratory illness in the last few weeks. Everybody in the family was healthy, with no history of atopy.

The initial clinical assessment revealed tachycardia (heart rate 175) with hypotension (blood pressure (BP) 80/43 mm Hg) and raised capillary refill time of 3 s with cold peripheries.

The initial venous blood gas revealed normal pH and gases but raised lactate of 6.2 and hyponatraemia with sodium 129 mmol/L. He was treated for septic shock after collecting initial blood and other samples for analysis in the laboratory as per the local sepsis pathway.

Systemic examination revealed mild red throat with no exudates. He had no increased signs of work of breathing, but auscultation revealed crackles on the left base. The abdomen was guarded with diffuse tenderness.

Case 2
A child in his mid-childhood had presented to the ED with coryzal symptoms for 1 week and fever in the last 3 days. Parents mentioned that he had become more confused and agitated over the course of the day, which worsened by the night he presented to ED. He also had four episodes of vomiting before the arrival to ED with no diarrhoea. They noticed a rash around his neck which had spread to the chest through the course of the day.

He was known to have trisomy 21 with no congenital defects. He previously had sepsis requiring intubation, ventilation and extracorporeal membrane oxygenation approximately 2 years prior to this presentation. No other significant history was present.

Multiple members of the family were also having coryzal symptoms recently.

His early warning scores were 8 at presentation for heart rate 149 bpm, temperature 38.1 degree C, respiratory rate 32 per minute, BP 88/48 mm Hg and oxygen saturation 97%.

Systemic examination revealed a prolonged capillary refill time of 5 s with cold peripheries. The child was listless. The chest had bilateral equal vesicular breath sounds and no added sounds. He had no signs of respiratory distress. Heart sounds were normal with no murmur. The abdomen showed a palpable spleen of 2 cm below the right costal margin, with normal rest of the abdominal examination. Tonsils were red and enlarged with no exudates. The lips appeared to be cracked. He also had a maculopapular rash around the neck.

INVESTIGATIONS
Case 1
Initial venous gas showed pH 7.335, PCO₂ 4.9, PO₂ 7.6, bicarbonate (HCO₃⁻) 21.9, base excess –2.9, sodium (Na) 129, glucose 5.7, lactate 6.2 and...
Case report

Varughese JA, et al. BMJ Case Rep 2024;17:e254646. doi:10.1136/bcr-2023-254646

Haemoglobin (Hb) 124. Repeat venous gas after three boluses of normal saline (500 mL each) did not show any improvement in lactate (6.7), but the rest of the gas remained unremarkable with an improvement in sodium level to 131.

Blood tests revealed white cells 3.0×10⁹/L, neutrophils 2.4, lymphocytes 0.3, Hb 124 g/L, platelets 113×10⁹/L, C-reactive protein 205 mg/L, Na 129 mmol/L, potassium (K) 3.8 mmol/L, urea 8.2 mmol/L, creatinine 126 µmol/L, eGFR (estimated glomerular filtration rate) 54 with acute kidney injury stage 2, prothrombin time (PT) 12.8s, activated partial thrombin time (APTT), lactate dehydrogenase 430 IU/L, amylase 39 IU/L and ferritin 406 ng/mL.

Chest X-ray (CXR) revealed cavitating pneumonia in the left mid-zone with further air space shadowing in the left lower zone (figure 1). CXR repeated on day 4 of admission revealed left-sided pleural effusion, which required drainage (figure 2).

CT scan of the thorax, abdomen and pelvis revealed extensive left lower lobe consolidation with areas of cavitation within (figure 3). Mild infiltrates were seen in the right lower lobe. No pericardial or pleural effusions were noted. The abdomen and pelvis were looking normal except minimal free fluid in the pelvis. The rest of the scan was within normal limits.

Nasal swab was positive for influenzae A PCR and blood culture grew group A beta-haemolytic streptococci after 8.4 hours of incubation, which was sensitive to penicillin, erythromycin, doxycycline, clindamycin, vancomycin, teicoplanin and linezolid. His throat swab also grew group A beta-haemolytic streptococci sensitive to similar antibiotics.

Case 2

Initial venous blood gas showed lactate 5.49, glucose 4.2 and sodium 130, and the rest of the gas was unremarkable. Repeat

---

Figure 1  CXR showing cavitating pneumonia in the left mid-zone.

Figure 2  CXR on day 4 showing left-sided pleural effusion with chest drain in situ.
blood gas after three boluses of normal saline showed a worsening lactate of 7.65 with some improvement in sodium level to 131.

Blood tests revealed WCC (White blood cells) 23.9 × 10^9/L, neutrophils 22.5 × 10^9/L, Hb 108 g/L, platelets 107 × 10^9/L, lymphocytes 0.4 × 10^9/L, PT 16.5 s, APTT 34.5 s, sodium 132 mmol/L, potassium 4.0 mmol/L, urea 10.9 mmol/L, creatinine 114 mmol/L and CRP (C Reactive protein) 138.

CXR showed a marked perihilar inflammatory change with some non-specific air space shadowing. The heart size was normal (figure 4).

Blood culture grew gram-positive group A beta-haemolytic streptococci after 9.9 hours of incubation, which was sensitive to penicillin, erythromycin, vancomycin, teicoplanin, linezolid and clindamycin.

DIFFERENTIAL DIAGNOSIS
Case 1 and case 2
Though the invasive group A streptococcal disease was upfront differential due to the current prevailing situation, among the probable differentials were septic shock secondary to acute abdomen with upper gastrointestinal bleeding and influenza A. Cavitary parenchymal disease of the lung suspicious of round pneumonia leading to profound haemoptysis was also thought of as differentials. Among the cavitatory pneumonitis lesions, Staphylococcus and Klebsiella are the most common causes.

Among the rarer differentials were septic emboli and granulomatosis with polyangitis, which can present with chest pain, dyspnoea and haemoptysis.

TREATMENT
Case 1
With the initial presentation showing features of septic shock, he received three normal saline boluses of 500 mL each, but his systolic BP stayed below 90. Hence, he was commenced on peripheral intravenous epinephrine infusion, which maintained his systolic BP in the range of 90–100 mm Hg. Central venous access was obtained by the transport team, and his epinephrine infusion was changed to the central route before transport. In light of fluid-refractory septic shock, reduced alertness and increased work of breathing, he was electively intubated before being transferred to a tertiary paediatric intensive care unit (ICU).

He initially received intravenous ceftriaxone and clindamycin as per local hospital policy. It was later changed to intravenous benzylpenicillin and clindamycin after the sensitivity results were available, and he completed a total of 10 days course of these antibiotics.

A surgical consult was sought for acute abdomen, who recommended CT scan of the thorax, abdomen and pelvis. No surgical intervention was required anymore after the results were satisfactory.

He developed left-sided pleural effusion while on ventilation on day 4 of admission. A chest drain was inserted, which relieved the requirement of ventilation, and he successfully came off ventilator support on day 5 of admission. Gradually, his inotrope support was weaned off and he was no longer on any inotropes from day 3 of admission. His haemoptysis improved and was transferred out of ICU on day 6. His blood parameters including raised urea and creatinine and low sodium completely normalised by day 6. He is currently well with no residual functional impairment whatsoever.

Case 2
He was treated for septic shock in line with local policy and received the first intravenous bolus of normal saline followed by intravenous antibiotics (ceftriaxone and clindamycin) after the blood was taken for culture and other tests. He continued to be tachycardic with heart rate 140, hypotensive with systolic BP 82 mm Hg and blood gas showing rising lactate up to 6.5 in spite of having received two boluses of normal saline. In view of fluid-refractory septic shock, he was commenced on intravenous epinephrine infusion that improved his BP marginally. As his alertness has been progressively declining since presentation to ED, he was electively intubated and ventilated prior to transfer to the paediatric ICU.

Prior to transfer, central venous lines were inserted and added ionotropic support was provided with dopamine, epinephrine, vasopressin and hydrocortisone. Potassium and calcium were also replaced.

In the territory centre, his antibiotics were changed to benzylpenicillin and clindamycin after seeing blood culture results, and he received a total of 10 days of antibiotics. He remained ventilated for a total of 5 days and was extubated onto high-flow oxygen before completely coming out of oxygen support by the sixth day of admission. His ionotropic support was stopped completely by day 5 of admission. He is currently stable with no residual functional impairments whatsoever.

DISCUSSION
The UK Health and Safety Agency has reported 27 486 notifications of scarlet fever in the winter of 2022, until 18 December 2022, in comparison to 3287 cases reported at a similar point in
the comparable year of the 2017–2018 season. This has resulted in 88 cases of iGAS disease in children aged 5–9 years, and 21 children have died of iGAS so far under the age of 18 years.1

Continued rise of group A streptococcal throat cases with a significant number of invasive diseases has not only raised concerns among parents but also affected National Health Service resources in terms of its common antibiotics such as penicillin and amoxicillin being stocked out due to the increased use in recent weeks.

The WHO issued an alert with advisory on 15 December 2022 after five major European countries including the UK reported a steep rise in cases of group A streptococcal infection with deaths of children under 10 years of age in significant numbers.2

Group A beta-haemolytic streptococcus (GAS) is a gram-positive beta-haemolytic bacteria. It is responsible for multiple infections, such as tonsillitis, scarlet fever, impetigo, cellulitis, necrotising fasciitis, acute rheumatic fever, streptococcal toxic shock syndrome and glomerulonephritis.

The incubation period is approximately 2–5 days. Skin, throat and anogenital tract are the common reservoirs for GAS. GAS can be transmitted through direct skin contact or close human contact and respiratory droplets.

It presents with multiple signs and symptoms, with generalised features such as fever, headache, vomiting, abdominal pain and lymphadenopathy or more specific features based on the site of infection. Scarlet fever presents with high-grade fever, strawberry tongue, sandpaper rash and a sore throat. Though most of the scarlet fever patients improve on their own after a week of illness, some of them could go on to develop invasive diseases which can rarely lead to fluid-refractory septic shock and impair the function of other vital organs such as kidneys and lungs.

As suggested by both the WHO and the European Centre for Disease Prevention and Control, the recent increase in viral co-infection such as influenza and respiratory syncytial virus might have increased the risks of invasive group A streptococcal infection, especially in the aftermath of the relatively reduced number of cases in the intervening COVID pandemic periods.3

High risk of invasive GAS infection has also been noted in the past in England in the winter months when influenza virus activity was on high levels.4

Both of our cases had presented similarly with fluid-refractory shock and raised lactate, after initial bouts of fever and coryzal symptoms for a few days. Awareness of the hitherto prevailing situation regarding group A streptococcal infections helped us narrow down our differentials to it and manage the patients proactively.

The diagnosis of GAS infection can be done by isolating GAS bacteria in cultures of throat swabs, skin swabs, blood, tissue samples and other body fluids. In case of negative results, molecular diagnostic tests could help in the identification of the organism, but its availability at every centre could be an issue.

Treatment poses challenges in terms of identifying the rapidly deteriorating patients quickly and making arrangements for advanced treatments such as ventilatory support, inotropes and management of complications of pneumonia (pleural effusions and empyema) in a timely fashion by liaising with tertiary centres. Though our patients did not require intravenous immunoglobulins (IVIGs), there are reports of it being effective when used early and cautiously.5 The Pan American Health Organization supports the use of IVIG as an adjunctive therapy, as IVIG has shown to be effective in serious cases of septic shock and toxic shock syndrome.6

Luckily, there have not been any increases in the reports of drug-resistant GAS or the emergence of any new strains of GAS to date. The antibiotic of choice for oral treatment still remains phenoxymethylpenicillin or macrolide in case of penicillin allergy. For invasive GAS, we recommend that antibiotic treatment should be guided by the sensitivity noted on the culture and the local hospital policies.

Invasive GASs and scarlet fever are notifiable diseases. In accordance with the UK Health Security Agency guideline, the health protection team identifies the close contacts. Close contacts are defined as contact with the patients 7 days before the start of symptoms and up to 24 hours after starting treatment. Antibiotic treatment is commenced in close contact with suspected infection or confirmed iGAS infection and high-risk contacts. The antibiotic of choice for prophylaxis in close contact is phenoxymethylpenicillin for a duration of 10 days.

Group A beta-haemolytic streptococci isolated from both of our patients were sensitive to penicillin and responded well to it. This supports the British Society for Allergy and Clinical Immunology’s drive for penicillin allergy de-labelling service, as almost 95% of penicillin allergy patients turn out to be non-allergic after proper testing.8–10

### Learning points

- Invasive group A streptococcus disease most frequently affects respiratory system with some structural lesions in the lung but has potential to affect both liver and renal system leading to deranged liver and renal function test results.
- Prompt management of septic shock with fluid resuscitation and inotropes along with early administration of appropriate antibiotic would help tide over the crisis and reduce mortality.
- Early liaison with paediatric intensive care unit helps initiating prompt treatment as rapid deterioration could ensue without much warning.
- Despite recent rise in invasive group A streptococcus diseases, there is no report of any drug resistance or emergence of any new strain whatsoever.
- Group A Streptococcus identified during the current epidemic situation is still sensitive to benzylpenicillin, and it supports the drive to de-label penicillin allergy initiated by BSACI (British Society for Allergy and Clinical Immunology).

### Twitter

Birendra Rai @BirendraRai

### Contributors

The following authors were responsible for drafting of the text, sourcing and editing of clinical images, investigation results, drawing original diagrams and algorithms and critical revision for important intellectual content: IV, MK, BR and DM. The following authors gave the final approval of the manuscript: BR and DM.

### Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

### Competing interests

None declared.

### Patient consent for publication

Consent obtained from parent(s)/guardian(s)

### Provenance and peer review

Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

### REFERENCES

1 UKHSA update on scarlet fever and invasive group A Strep. Govt of UK 2022. Available: https://www.gov.uk-government/news/ukhsa-update-on-scarlet-fever-and-invasive-groupa-strep [Accessed 4 Jan 2023].
World Health Organization. Increased incidence of scarlet fever and invasive group A Streptococcus infection - multi-country. 2022. Available: https://www.who.int/emergencies/diseases/outbreak-news/item/2022-DON429 [Accessed 6 Jan 2023].

European Centre for disease prevention and control. Increase in invasive group A Streptococcal infections among children in Europe, including fatalities. 2022. Available: https://www.ecdc.europa.eu/en/news-events/increase-invasive-group-a-streptococcal-infections-among-children-europe-including [Accessed 5 Jan 2023].

Zakikhany K, Degail MA, Lamagni T, et al. Increase in invasive Streptococcus Pyogenes and Streptococcus pneumoniae infections in England. Euro Surveill 2011;16:2131507.

Mahmut Can K. 2023 Consecutive seven serious cases with invasive group A Streptococcal infections at December 2022–January 2023. Pediatr Infect Dis J 2023;42(2):208–11.

UK health security agency. UK guidelines for the management of contacts of invasive group A Streptococcus (iGAS) infection in community settings. 2022. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1124085/management-of-contacts-of-invasive-group-a-streptococcus.pdf [Accessed 6 Jan 2023].

Savic I, Ardern-Jones M, Avery A, et al. BSACI guideline for the set-up of penicillin allergy de-labelling services by non-Allergists working in a hospital setting. Clin Exp Allergy 2022;52:1135–41.

Macy E, Ngor EW. 2013 Safely diagnosing clinically significant penicillin allergy using only.

Blumenthal KG, Huebner EM, Fu X, et al. Risk-based pathway for outpatient penicillin allergy evaluations. J Allergy Clin Immunol Pract 2019;7:2411–4.