education

FROM THE JOURNALS Edited highlights of weekly research reviews

Pregnancy: the natural stress test

This national Swedish cohort study of more than two million women found that any of five major adverse pregnancy outcomes (preterm delivery, small for gestational age, pre-eclampsia, other hypertensive disorders, and gestational diabetes) was associated with increased mortality risks that remained elevated up to 46 years later. The major causes of death included cardiovascular and respiratory disorders and diabetes.

But are these pre-existing risks that were going to play out anyway or are they new risks? This study suggests the latter. It used co-sibling data and found that familial factors accounted for only a small part of the effect. This suggests that all five major adverse pregnancy outcomes are independent risk factors for premature mortality. That's a stark message to hear, but it can be framed as an early warning system to trigger enhanced monitoring, prevention, and treatment of chronic disease.

JAMA Intern Med doi:10.1001/jamainternmed.2024.0276

Time-restricted eating: is it a myth?

Does it matter when we eat? Michael Mosely and others argue that giving the body a break from eating by fasting intermittently, only eating within a 12 hour period, or at least avoiding food in the three hours before bedtime, can have myriad health benefits.

This 12 week, single site study included 41 women with average age of 59 years and mean body mass index of 36. The study looked at whether adults with obesity and pre-diabetes or diet-controlled diabetes lost more weight if they stuck to time-restricted eating (TRE) of 10 hours with 8% of calories eaten before 1 pm or ate the same number of calories and proportion of nutrients but in a usual eating pattern of ≥16 hours per day with at least half their calories consumed after 5 pm. There was no difference in weight loss (−2.3 *v* −2.6 kg) and no change in glycaemic measures.

Ann Intern Med doi:10.7326/M23-3132

How do we solve a problem like CKD?

This US study of 15 966 patients with moderate to high risk chronic kidney disease (CKD) found that a multipronged primary care intervention (using the electronic health record, an e-consultation with a nephrologist, pharmacist-led medication review, and patient education) didn't reduce the risk of CKD progression or improve hypertension control compared with usual care delivered by a primary care physician over a 17 month follow-up. More people took ACE inhibitors or angiotensin receptor blockers in the intervention group (rate ratio 1.21), but that didn't translate into better hypertension control or substantial differences in the rate of fall in estimated glomerular filtration rate or progression to end stage kidney disease (7.6% *v* 8.6%). It was a lot of effort for minimal, if any, gains.

JAMA Intern Med doi:10.1001/jamainternmed.2024.0708

Leaking valves

Severe aortic regurgitation is treated by replacing the aortic valve. But for those at high surgical risk or with age related degenerative aortic regurgitation, transcatheter aortic valve implantation (TAVI) is an option. However, the transcatheter heart valve devices are tricky to position and anchor properly when treating aortic regurgitation. A new device—the JenaValve Trilogy—has been developed to try to overcome some of these technical problems.

This study of 180 patients, funded by JenaValve Technology, gave Trilogy transcatheter heart valve a guarded thumbs up. It was safe (2% deaths, 2% strokes at 30 days) and effective (technical success in 95% patients) for patients at high surgical risk with symptomatic aortic regurgitation in terms of short term outcomes and improved cardiac output. But there was a relatively high need for pacemaker implantation (24%), and a problem in identifying who is at highest risk and standardising frailty scoring.

Lancet doi:10.1016/S0140-6736(23)02806-4

Pembrolizumab for kidney cancer

Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer. Improvements in disease-free survival have been found in patients given post-surgical adjuvant pembrolizumab (an anti-programmed death 1 (PD-1) antibody). The question remains whether overall survival improves too. In this interim phase 3 randomised study involving 994 patients with ccRCC who had undergone nephrectomy within the past three months and were at increased risk of recurrence, adjuvant pembrolizumab was associated with a significant improvement in overall survival compared with placebo (91.2% *v* 86% at 48 months). This translates to a 38% lower risk of death. There were more serious adverse events in the pembrolizumab group (20.7% v 11.5%), but no deaths attributable to the drug.

N Engl J Med doi:10.1056/NEJMoa2312695

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Cite this as: ***BMJ*** **2024;385:q917**

WHAT YOUR PATIENT IS THINKING

The ever looming shadow of caregiving

David Kang shares what it is like to live with and care for someone with profound autism

CPD READING
0.5 HOURS

PRIYA SUNDRAM

Our household doesn't rely on alarm clocks. Instead, it's the consistent thumping of my 18 year old brother's foot against the side of his crib that signals 6 am. His profound autism and developmental delay are woven into the fabric of our family's daily routine, and his silent cues shape our interactions. Breakfast, a simple meal for many, is an intricate dialogue for us. My brother doesn't communicate with words, but his actions speak volumes. A fleeting smile and hand rub mean yes, while a whine or deliberate head turn signals no.

The complexity of caregiving

My life is completely mapped out by my caregiving role. Home based care requires understanding of the unique environment my brother needs to feel secure and happy. This means that after he is tucked in bed at 7 pm, the whole house must maintain a library voice to avoid waking him up. It means always remembering to close doors around the house to keep my brother safe. These are only some of the many considerations for an autism-friendly environment.

In addition, the routine of my brother's caregiving dictates my family's schedule. Once my brother wakes up, our family adheres to the daily itinerary. One of us must keep an eye out for him at all times, and it is only when he goes to school that the rest of us can do our own things without worry. It is these daily routines that keep my brother and the rest of our family balanced. To keep the bright smiles on his face, our family must work hard without breaks every day.

Unrelenting

Chronic stress is an unspoken part of caregiving and casts an ever looming shadow on caregivers. Recent events in my family have highlighted the unrelenting nature of caregiving. When my mother was admitted to hospital following a serious road traffic incident, my brother's needs didn't pause. With my father juggling visits to the hospital and his job, the full weight of my brother's care fell on me. Amid managing his daily routine, my own concern for my mother's health, and preparing for my exams, the days became a relentless cycle of responsibilities.

During this time, the absence of a support system for caregivers like myself became glaringly apparent. Managing my brother's care solo highlighted the need for accessible caregiver groups and recognition from healthcare professionals of our critical role. During my brother's numerous medical appointments, the focus remains squarely on him, with no healthcare professional extending the conversation to inquire about my wellbeing. This gap in care suggests a need for a dual focus approach in medical practices: one that cares for the patient and also checks in on the caregiver's health.

What the future holds

During my brother's medical appointments, decisions were sometimes made without considering my input, despite my deep understanding of my brother's needs. I can feel like a bystander in these appointments, and I've often wished to play a more active role in planning for my brother's future, as I will eventually become his primary caregiver. I want to live an ambitious life and I have many goals, and the thought of my brother's future is a puzzling concern.

Yet, this caregiver responsibility, initially seen as burdensome, has given me important skills. I have developed patience, empathy, and the ability to communicate without words, which are now cornerstones of my identity. If it weren't for my brother, I wouldn't have the same depth of understanding about the intricacies of non-verbal cues, something that surprisingly comes in handy even outside my caregiving role. Envisioning a future where I continue to care for my brother, I'm armed with resilience, empathy, and advocacy lessons. I may be his caregiver but he has also given me so much.

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Cite this as: *BMJ* 2024;385:q726

WHAT YOU NEED TO KNOW

- Being a caregiver of someone with profound autism is complex and involves the whole family
- Ask caregivers how they are, and regularly screen for caregiver stress or provide other means of assistance
- Consider involving siblings in decision making; they may become the main caregiver in the future

EDUCATION INTO PRACTICE

- How could you ensure that you are involving caregivers in treatment plans?
- What resources or information could you share to provide support to a family of caregivers?

GUIDELINES

Secondary prevention of cardiovascular disease, including cholesterol targets: summary of updated NICE guidance

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Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

CPD READING
0.5 HOURS

While mortality from acute cardiovascular disease (CVD) has been falling in most developed countries, more people are now living with established CVD, including coronary heart disease, peripheral arterial disease, and stroke or transient ischaemic attack. These individuals remain at high risk of subsequent cardiovascular events and mortality. In the UK, the cost of treating a myocardial infarction is £1310 higher in the first year for someone with established CVD than for a first event.[1] Secondary prevention interventions, such as lowering of low density lipoprotein cholesterol (LDL-C), mitigate this risk and improve outcomes.[2]

Statins, ezetimibe, bempedoic acid, and injectable therapies are approved as lipid lowering therapies in the UK. However, use of these agents is variable,[3] with about one fifth of people with CVD in England receiving no lipid lowering therapy.[4] This is partly because of the absence of nationally agreed LDL-C targets for people with CVD to inform need for therapeutic escalation. Targets between 1.4 mmol/L and 1.8 mmol/L have been advocated by specialist societies and expert consensus, based on data from randomised controlled trials (RCTs),[5 6] and achievement of these targets has been poor.

This article summarises the most recent recommendations from the National Institute for Health and Care Excellence (NICE), first published in 2014, and updated in December 2023, incorporating for the first time LDL-C targets for people with CVD.[8] This guideline is the first to incorporate economic modelling and cost effectiveness in the calculation of cholesterol targets, which could mean that it is more easily implemented.

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are on bmj.com.

WHAT YOU NEED TO KNOW

- Offer 80 mg atorvastatin (unless contraindicated or previously not tolerated) as soon as possible to people with atherothrombotic cardiovascular disease (CVD)
- 2.0 mmol LDL-C (or 2.6 mmol/L non-HDL) is the most cost effective target for patients with established atherothrombotic CVD
- Consider ezetimibe for patients with atherothrombotic CVD, even if their cholesterol level is below the target

Initial treatment

The evidence for these recommendations has not been revisited since the last update[9]; however the wording has been updated to ensure consistency across the guideline. Randomised controlled trials have shown consistently that reduction of LDL-C by prescribing statins reduces the risk of major cardiovascular events and cardiovascular mortality by approximately one fifth for each 1 mmol/L reduction in LDL-C.[2] For people with established CVD, cost utility analysis in an NHS setting showed that high intensity statins are highly cost effective when compared with no treatment or any other statin regimen.[9]

- Offer atorvastatin 80 mg to people with CVD, whatever their cholesterol level.
- Offer a lower dose of atorvastatin if any of the following apply:
  - It could react with other drugs
  - There is a high risk of adverse effects
  - The person would prefer to take a lower dose.
- Do not delay statin treatment for secondary prevention of CVD but discuss lifestyle changes at the same time if appropriate.
- If a person has acute coronary syndrome do not delay statin treatment. Measure full lipid profile on admission and two to three months after starting treatment.

Lipid targets for people with CVD taking lipid lowering treatments

In people with CVD, LDL-C should be as low as possible to minimise the risk of re-admission to hospital and mortality, based on data from RCTs, genetic studies, and observational cohorts. At a population level, however, this is not cost effective, given that many potent non-statin therapies are expensive.

To inform this new recommendation, a cost utility analysis was developed using estimates of the impact of lipid lowering treatments on LDL-C (from an original network meta-analysis of RCTs),[10] combined with estimates of the impact of LDL-C reduction on major cardiovascular events (from a published meta-analysis of statin RCTs).[2] The economic model measured the impact of lipid lowering treatments across a range of baseline LDL-C levels (0.3 to 4.0 mmol/L), on reduced admissions to hospital (stroke, myocardial infarction, and cardiovascular procedures), increases in life expectancy, and improvements in quality of life. Hospitalisation cost savings were offset against the cost of lipid lowering treatments and associated monitoring costs. The lowest LDL-C target that was cost effective at the benchmark pre-specified in NICE's principles of £20 000 per quality adjusted life year gained,[11] was 2.0 mmol/L or an equivalent non-HDL of 2.6 mmol/L.

- For secondary prevention of CVD aim for LDL-C levels of 2.0 mmol per litre or less, or non-HDL cholesterol levels of 2.6 mmol per litre or less.

Escalating treatment for people treated with statins

For people who are above the LDL-C target while already being treated with statin monotherapy, the GC refers healthcare practitioners to NICE's relevant technology appraisals to allow an informed choice to be made on the basis of the treatment specific expected LDL-C lowering that would achieve the LDL-C target, local availability, and patient preference.

This guideline newly recommends healthcare practitioners consider use of ezetimibe for people at or below the target. The low acquisition price (£1.51 for 28 tablets, at one tablet a day[12]) and its effectiveness (an average 7% reduction in major cardiovascular events) makes ezetimibe highly cost effective for use in people with CVD at all cholesterol levels, and supports the principle of lowering LDL-C as much as possible for maximal risk reduction.

- Make decisions about escalating lipid lowering treatment after an informed discussion between the clinician and the person about the risks and benefits of additional lipid lowering treatments.
- Take into account potential benefits from lifestyle changes, the person's preferences, the presence of any comorbidities, whether they are on multiple medications, whether they are frail, and their life expectancy (see also NICE's guideline on multimorbidity[13]).
  - If the person is taking the maximum tolerated dose and intensity of statin but the lipid target for secondary prevention of CVD is not met (see above), consider additional lipid lowering treatments (see the NICE technology appraisals on alirocumab,14 evolocumab,[15] ezetimibe,[16] and inclisiran[17]).
- Consider ezetimibe in addition to the maximum tolerated intensity and dose of statin to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is met (see above).

Secondary prevention of CVD when statins are contraindicated

People with CVD should take statins when they can be tolerated safely. However, approximately 9% of patients report an intolerance to all forms of statin therapy.[18] In this context, this guideline newly recommends ezetimibe as a cost effective alternative first line therapy.

- Offer ezetimibe instead of a statin to people for whom statins are contraindicated or if after documented discussion, it is recognised the person cannot tolerate statins of any intensity or dose. This applies whatever the person's cholesterol level (see the NICE technology appraisal on ezetimibe[16]).
- If the person is taking ezetimibe but the lipid target for secondary prevention is not met, consider alternative or additional lipid lowering treatments (see the NICE technology appraisals on alirocumab,[14] bempedoic acid,[19] evolocumab,[15] and inclisiran[17]).

Annual medication review

This recommendation has been updated to focus treatment on people at greatest risk. Healthcare practitioners should measure a full lipid profile annually, to allow estimation of LDL-C, as well as evaluation of familial hypercholesterolaemia and quantification of triglycerides that could inform use of additional approved cholesterol lowering therapies, such as icosapent ethyl.

- Offer an annual full lipid profile to inform discussions about secondary prevention of CVD.

Implementation

The high resource costs of some lipid lowering therapies may create a barrier to implementation, but are likely to be offset by costs related to cardiovascular events prevented.

The slightly lower LDL-C target in existing guidelines, 1.8 mmol/L, seems close to the 2.0 mmol/L newly presented in this guideline; however, the economic model suggests that the additional cost to achieve a target of 1.8 mmol/L for everyone with CVD was considerable. We anticipate the Qualities and Outcome Framework indicator CHOL002[20 21] will be realigned to the guideline target in the 2024/25 GP contract, which will incentivise implementation in primary care. This guideline does not preclude aiming for a lower LDL-C target on an individual basis, with wider use of ezetimibe with statin therapy.

Healthcare practitioners might find it difficult to provide further escalation to patients taking maximal statin and ezetimibe therapy who have LDL-C between 2.0 and 2.6 mmol/L. No national funding mandate exists for advanced therapies, such as inclisiran or PCSK9 inhibitors, for use in patients in this range. Therefore, the escalation option of ezetimibe or inclisiran should be chosen carefully to reduce occurrence of this scenario.

Competing interests: See bmj.com.

How patients were involved in this article: see bmj.com

Cite this as: *BMJ* 2024;384:q637

Find the full version with references at http://dx.doi.org/10.1136/bmj.q637

PRACTICE POINTER

Group A beta-haemolytic streptococcal infection in children

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CPD READING

0.5 HOURS

LEARNING MODULE

See learning.bmj.com for linked learning module

A 5 year old girl presents to her GP with a three day history of fever up to 39°C, sore throat, myalgia, headache, lack of appetite, and lethargy. When afebrile, her observations are within normal limits. On examination, both tonsils are red, inflamed, and have exudate. The child's parents work in healthcare, and have a recent history of sore throats that were not medically treated. A clinical diagnosis of suspected streptococcal pharyngitis is made and a 10 day course of penicillin V prescribed. The child re-presents 48 hours later with persistent fevers and new onset vomiting and diarrhoea. She has managed to take only half of her prescribed doses of penicillin V. On examination, she is tachycardic and has cool peripheries. She has developed a sandpaper rash on her trunk, and her tonsils remain inflamed, with exudate. Her forearm is moderately swollen, and she screams when it is palpated lightly.

Group A beta-haemolytic streptococci (GAS) are Gram positive bacteria resembling chains ("streptos") of berries ("kokkus") that colonise mucous membranes and damaged skin. They are spread by skin contact and respiratory droplets. People of all ages are susceptible, but especially children, pregnant women, and older adults. Invasive GAS (iGAS) refers to when GAS moves from "colonising" skin or mucosal surfaces, reaching normally sterile sites such as blood, cerebrospinal, synovial, or pleural fluids, or deep tissues.

Manifestations of GAS infection reflect the type of toxins produced. Scarlet fever occurs following a hypersensitivity reaction to "erythrogenic" exotoxins. Exotoxins acting as enterotoxins cause diarrhoea and vomiting, whereas collagenases, hyaluronidase, streptokinase, and lipases aid the spread of organisms through tissue in necrotising fasciitis.

With seasonal increases in influenza and respiratory syncytial virus infection, healthcare practitioners working in community and acute settings may find making a clinical diagnosis of GAS pharyngitis (and more serious complications) challenging. This article aims to increase understanding and recognition of GAS infection in children, highlight clues that inform earlier recognition of invasive disease, and inform on how to manage the condition.

WHAT YOU NEED TO KNOW

- Group A beta-haemolytic streptococcal (GAS) infections, including pharyngitis and more complex invasive infections, can be difficult to diagnose clinically
- In December 2022, rates of invasive infection in the UK increased substantially, with a high number of children presenting with empyema
- Suspect invasive infection, including necrotising fasciitis and streptococcal toxic shock-like syndrome, in any child who is unwell and presents with severe or disproportionate pain in the setting of recent varicella zoster virus or GAS infection

How common is GAS infection?

In 2022, notifications of scarlet fever in the UK quadrupled, and iGAS infections increased.[1] In England, Scotland, and Wales all cases of iGAS and scarlet fever, including children admitted to hospital, are notifiable to national public health bodies and feed into national reporting data. During the 2022 epidemic, the incidence of children under 10 diagnosed with scarlet fever in northwest England was 957/100 000,[2] compared with 185.7/100 000 in in 2014.[3]

The overall hospital admission rate for GAS infection in children under 15 in December 2022 was 16.16/100 000 population, seven-fold higher than in 2021,[4] and higher proportions of GAS empyemas were also reported at this time.[5 6] Similar increases in GAS infection were reported throughout Europe, the US, and Australia.[7 8]

The rate of iGAS, including septicaemia, meningitis, streptococcal toxic shock, and necrotising fasciitis, is far less common than the more superficial infection such as pharyngitis and scarlet fever, but has a high case fatality rate. In 2022-23 the rate of iGAS in children under 1 did not change substantially in the UK (1.3/100 000); however, the case fatality rate in this age group from September 2022 to June 2023 was 9.5% (9/95 cases), four times that of 2018-19 (2.1%).[2] Rates of iGAS for children aged 1-4 and 5-9 almost quadrupled, to 2.3/100 000 and 1.2/100 000 population, respectively, with case fatality rates of 6.3% and 5.6% respectively.[2]

As a result, national guidance recommended prescribing empirical antimicrobial treatment for suspected scarlet fever, temporarily lowering the clinical scoring threshold for treatment of presumed streptococcal pharyngitis. The guidance also recommended early notification to public health bodies of iGAS and scarlet fever to enable antimicrobial prophylaxis for susceptible individuals within 24 hours.[9]

Table 1 | Common clinical presentations of GAS in children

Condition	Epidemiology	Presentation, notable features
Pharyngitis	Causes 17-22% of pharyngitis in children under 5[11] Uncommon (1.9-7.1%) in children under 2[12]	Symptoms: - Acutely painful sore throat (especially in children under 5) - Difficulty swallowing - Headache - Vomiting Signs: - Pharyngeal exudate - Palatal petechiae - Tender, anterior cervical lymphadenopathy
Scarlet fever	Usually affects children under 10 (especially 2-8 years)[13]	Symptoms: - Initial non-specific symptoms include sore throat, headache, fever (38.3°C or higher) - Nausea and vomiting[14] Signs: - Blanching, maculopapular rash that begins on the trunk or face, spreads to the limbs, but spares palms and soles, then fades and desquamates over a week - Palpable "sandpaper" rash aids diagnosis on darker skins - "Strawberry tongue" and circumoral pallor are typical but not diagnostic - "Pastias lines" (accentuated erythema, linear petechiae) occur in skin folds—antecubital fossae, groin, axillas
Pneumonia	GAS infection is increasingly associated with viral coinfection and empyemas. Studies have found rates of viral co-infection in children with GAS pneumonia ranging from 30-100%[5 6]	Symptoms - Those consistent with lower respiratory tract infection; cough (88%) and fever (94%) - Pharyngitis (13%)[5] - Lethargy Signs: - Rash (50%)[5]Large pleural effusions are characteristic of GAS[15] and often associated with streptococcal toxic shock-like syndrome[16]

How does GAS infection present?

Pharyngitis is the commonest manifestation of GAS infection in children, and is responsible for more than 25% of cases in a systematic review of pharyngitis from 19 countries.[10] In a meta-analysis of prevalence data gathered over 70 years from mainly high income countries, GAS pharyngitis was responsible for about a quarter of GAS infections in children[11] (table 1).

Scarlet fever is common in children under 10, with large outbreaks occurring at nurseries and schools. Inflammation of mucous membranes and damage to the mucociliary escalator following viral co-infection is thought to facilitate translocation of pharyngeal GAS into the bloodstream or descent into the lungs.[5] This may lead to pneumonia and viral co-infection, possibly explaining the increase in childhood GAS empyemas noted in the UK during 2022.[5]

Early clinical features to suspect necrotising fasciitis when assessing a child with possible GAS

- Fever is present in about 75% of childhood necrotising fasciitis[20]
- Recent varicella zoster infection is a major risk factor, the mean time from onset of rash to hospital admission is about five days[21]
- Warm, swollen area, with rapidly progressive cellulitis
- Extreme pain out of proportion to visible signs is pathognomonic of fasciitis, but may be difficult to discern in children, especially if masked by analgesics early in illness
- Woodiness of subcutaneous tissues; "bruising" and bullae are late features
- Altered mental state
- Tachycardia and tachypnoea in the setting of a possible skin infection
- Rapidly deteriorating clinical picture

GAS is also associated with otitis media. In one cohort study of 11 311 children with acute otitis media and inner ear fluid analysed, GAS was observed in 3.1%, and aggressive disease was associated with higher rates of perforation.[17] A systematic review including 2560 children with acute otitis media found an increased incidence of GAS in those with discharge and, overall, five times higher risk of mastoiditis (11.6/100 episodes) compared with *Streptococcus pneumoniae*.[18] Very rarely, GAS meningitis can result.

Although GAS is the third commonest cause of septic arthritis in children, it remains uncommon, affecting 0.46/100 000 population per year.[19] GAS necrotising fasciitis is even more uncommon. A systematic review of paediatric GAS necrotising fasciitis reported an incidence between 0.022/100 000 children per year (Finland) and 0.843/100 000 children per year (US).[20] Early GAS necrotising fasciitis typically presents with subtle changes and misleading symptoms such as gastroenteritis or features compatible with viral illness (box).

Streptococcal toxic shock-like syndrome affects 0.38/100 000 children per year.[22] Like necrotising fasciitis, it is associated with varicella zoster virus infection, whereby skin lesions allow entry of organisms into host tissue. Exotoxins acting as superantigens cause non-specific flu-like symptoms, vomiting, diarrhoea, persistent fever, and sepsis with late hypotension. However, the defining sunburn rash of staphylococcal toxic shock is present in only 50% of cases of GAS toxic shock.[23] Patients with features of streptococcal toxic shock should be examined carefully for features of necrotising fasciitis as the two commonly co-occur.

Immunologically mediated post-streptococcal infections such as rheumatic fever and acute glomerulonephritis are now very rare in the UK and other high or middle income countries.

Table 2 | Risk factors in history taking for GAS infection

Question	Significance of question
Has the child been in contact with a case of streptococcal infection, eg, scarlet fever, pharyngitis, impetigo?	Children with a diagnosis of scarlet fever have unwell family or contacts commonly, with one small cross-sectional study estimating 43% of cases.[13] Risk of iGAS is significantly increased if a household contact has confirmed scarlet fever[24]
Has the child been reviewed by a clinician recently?	Children re-presenting to healthcare professions with fever after initial evaluation and discharge may be more likely to have GAS than viral illness. In one surveillance study, 15 (54%) of children admitted with iGAS had presented to a medical practitioner for review in the 48 hours before eventual admission, including 7 of 10 patients with severe iGAS infection[25]
Has the child had recent varicella zoster virus infection?	Increased risk of iGAS, streptococcal toxic shock- like syndrome, and necrotising fasciitis
Has the child had diarrhoea or vomiting?	Gastrointestinal symptoms, including abdominal pain, nausea, and vomiting, are clinical features suggestive of GAS pharyngitis,[26] whereas gastroenteritis associated with viral pharyngitis rarely produces a high temperature. GAS strains can produce exotoxins that act as enterotoxins
Has the child taken non-steroidal anti-inflammatory drugs (NSAIDs)?	NSAIDs may prevent neutrophils killing the GAS they ingest, promoting infection.[27 28] They also may mask temperature, lessen pain, and inflammation, making evaluation of severity and identification of the focus more difficult

How can I differentiate viral from bacterial pharyngitis clinically?

In table 2 we outline five questions to ask for any patient presenting with pharyngitis to help determine whether GAS infection should be suspected. The questions are based on our clinical experience and appraisal of the available evidence. Viral pharyngitides typically produce a cough, coryza, oral ulceration (herpangina, enteroviruses), croup, laryngitis, hoarseness, or conjunctivitis (adenovirus). Distinguishing bacterial from viral infection on clinical grounds alone becomes more difficult when they co-exist. For example, a cough following a typical viral pharyngitis could also herald secondary bacterial pneumonia,[5 6] and present in up to 88% of children with empyema.[5] Pharyngitis resulting from Epstein-Barr virus (EBV) typically manifests in adolescents with fever, cervical adenopathy (especially posterior chain), and fatigue. Less common features of EBV include generalised lymphadenopathy, hepatosplenomegaly, stomatitis, a faint maculopapular rash, and periorbital oedema.

No single symptom is diagnostic of bacterial pharyngitis,[29] however clinical decision rules (scoring systems incorporating typical bacterial symptoms and signs) are used in clinical practice. UK guidelines suggest combining a Centor or FeverPAIN score with history and examination to make a clinical diagnosis, and recommend treating children empirically based on scoring cut-off values.[30] Routine diagnostic testing is discouraged.[30 31]

A systematic review of eight different clinical prediction rules found that none showed sufficient diagnostic accuracy, nor identified children at low risk (probability ≤12%) or high risk (probability ≥85%) of infection.[32] Furthermore, since presentation differs with age, even fewer prediction rules apply to children under 5. Of two rules validated for children under 3, the one judged most useful clinically[33] was time consuming to complete and missed 16% of positive cases.[25] Hence, a meta-analysis[25] and systematic reviews[32 34] conclude that scoring systems are insufficient to justify empirical prescribing without microbiological confirmation, which is consistent with most international guidelines.[34]

What microbiological tests are available?

Culturing bacterial throat swabs takes up to 48 hours and requires laboratory resources and processing, but results in an isolate of GAS that can be tested for antimicrobial sensitivity. This approach is considered the gold standard for diagnosis of GAS infection in practice. Rapid antigen detection tests (RADT) enable diagnosis of GAS using minimal resources within minutes, but do not provide antimicrobial sensitivities. They are 70-90% sensitive and 95% specific when compared with throat swab culture.[35] In the UK, national guidance has been issued for healthcare professionals on how to interpret patients' self-testing results from RADTs.[36] Molecular methods, such as real time polymerase chain reaction (PCR) testing, take about 15 minutes to make a diagnosis, but necessitate access to more complex laboratory equipment and reagents, and because they are ultra-sensitive may also detect incidental pharyngeal carriage, which affects about 8% of children.[11] They have a sensitivity of >82% and specificity of >91% for diagnosis of GAS infection.[32] Difficulties in obtaining a high quality posterior pharyngeal swab may be obviated in future by salivary nucleic acid testing, with one trial currently under way in France.[37]

In most high income countries, children under 3 are not swabbed routinely because they rarely acquire GAS related tonsillo-pharyngitis,[29] and are unlikely to develop rheumatic heart disease as a complication. Although no international consensus exists, 2012 US guidelines[26] and two thirds of international guidelines[38] recommend RADTs for children over 3 to confirm GAS pharyngitis on the grounds that diagnoses based on clinical features alone are unreliable. Some advocate bacterial throat culture in children with negative RADT results to reduce false negative results,[26 39] which may be as high as 10%.[35] Evidence underlying the utility of RADTs in clinical practice remains mixed.

What treatment should I choose?

Non-steroidal anti-inflammatory drugs (NSAIDs) are more effective than antibiotics in relieving pharyngeal related pain and fever,[27] but it is unclear how much NSAIDs delay presentation and potentially promote development of invasive disease by inhibiting neutrophil killing of ingested streptococci.[27] No evidence supports avoidance of systemic NSAIDs in routine GAS pharyngitis, but children with varicella zoster and GAS symptoms should avoid them because of concerns about possible predisposition to necrotising soft tissue infection.[27 28]

Red flags/red traffic light system (high risk criteria)—if one red flag is present, recommend urgent review in secondary care	Amber flags (intermediate risk of sepsis)
Child appears ill to health professional Unresponsive to social cues/difficult to rouse Pale/mottled/ashen/blue/non-blanching rash Cyanosis of skin, lips or tongue Weak, high pitched, or continuous cry Reduced skin turgor	Abnormal response to social cues Not smiling Wakes only with prolonged stimulation Decreased activity Dry mucous membranes Parent or carer concerned child behaving differently to usual
Under 3 months Temperature >38°C **Any age** Temperature <36°C	**3-6 months** Temperature ≥39°C **Any age** Fever ≥5 days
Grunting respiration or apnoeic episodes Moderate or severe chest indrawing SpO_2 <90% in air Severe tachypnoea (see below)	Nasal flaring Tachypnoea (see below) Oxygen saturation ≤95% in air OR nasal flaring Crackles on auscultation
Severe tachycardia or bradycardia <60 Age / Severe tachypnoea / Severe tachycardia <1 year / ≥60 / ≥ 160 1-2 years / ≥50 / ≥150 3-4 years / ≥40 / ≥140	Tachycardia Age / Moderate tachypnoea / Moderate tachycardia <1 year / 50-59 / 150-159 1-2 years / 40-49 / 140-149 3-4 years / 35-39 / 130-139 Capillary refill time ≥3 seconds
No wet nappies/not passed urine in past 18 hours Temperature <36°C	Reduced urine output Poor feeding in infants Leg pain Cold hands or feet
Non-blanching rash Bulging fontanelle Neck stiffness/neurological signs/seizures	Swelling limb or joint Non-weight bearing limb or not using an extremity

Signs and symptoms suggesting sepsis in suspected GAS infection. NICE "traffic light system" criteria,[45] NICE guideline [NG51][46]

Antibiotics shorten illness duration by a day, and limit the period of communicability of GAS from children with proven GAS from two weeks (if untreated) to 24 hours in 80-90% of cases.[40] Treatment reduces the risk of suppurative complications. A Cochrane review of randomised trials including children found a reduced risk of peritonsillar abscess (risk ratio 0.15) and otitis media (risk ratio, 0.30).[41] Consult local guidelines for the recommended treatment of GAS pharyngitis. In the UK, phenoxymethylpenicillin for five to 10 days (or five days of clarithromycin for children with mild/severe penicillin allergy) is recommended by the National Institute for Health and Care Excellence (NICE),[30] whereas in the US[29] 10 days of oral first generation cephalosporins, clindamycin, or macrolides are alternative options. Consider local macrolide resistance rates when treating empirically. Clarithromycin is unlicensed for children under 12 months. For toddlers declining unpalatable liquid phenoxymethylpenicillin, amoxycillin is more palatable, with good oral bioavailability.[30 42] Five days of oral penicillin may be enough for symptomatic cure, but 10 days may result in an increased microbiological cure[30] and less recurrence of infection. Ten days' treatment is advocated for scarlet fever[43] and also prophylaxis of rheumatic fever in countries where the risk is higher.

Children with GAS infection should not return to nursery or school until at least 24 hours after starting treatment with an appropriate antibiotic,[9] and have no fever and are feeling well. After 24 hours of an appropriate antibiotic, the risk of transmission is considered minimal.[9]

In the UK, once public health bodies have been notified, prophylaxis is recommended for close contacts of scarlet fever (risk of infection being 12 times increased).[24] For iGAS household or close contacts, the risk of iGAS is increased almost 2000-fold, hence prophylaxis is recommended for contacts with open wounds, especially varicella, at extremes of age, or who are pregnant.[9]

Despite a lack of high quality evidence proving a direct effect, avoidance of NSAIDs is usually advised in patients with varicella infection.[28]

When should I refer to secondary care?

If sepsis is strongly suspected, refer the child to secondary care urgently. Although uncommon in these age groups, neonates (<1 month) and infants (1-3 months) with iGAS often present with non-specific signs and symptoms.[44] In children >3 months and pre-school and school aged children, features of systemic inflammatory response syndrome are typical. These include an abnormal core temperature (<36°C or >38.5°C), an abnormal heart rate, or an abnormal respiratory rate (figure).

However, the presence of an altered mental status only or reduced perfusion without other listed features also might indicate sepsis.

Case outcome

With a clinical diagnosis of probable GAS sepsis and possible necrotising fasciitis, the patient is transferred by ambulance to hospital immediately. There she is resuscitated, treated with intravenous ceftriaxone and clindamycin, and admitted to intensive care. The plastic surgery team confirms necrotising fasciitis, and after debridement, GAS is cultured from the forearm tissue and blood culture. She improves rapidly, and is discharged home after a week on oral amoxycillin to complete 14 days' treatment. Following UK national guidelines,[9] her mother, who is 36 weeks pregnant, receives prophylactic penicillin V for 10 days.

Competing interests: None declared.

Cite this as: *BMJ* 2024;385:e077561

Find the full version with references at doi: 10.1136/bmj-2023-077561

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two of the authors are parents of three children admitted to secondary care with GAS infection: one following scarlet fever, one with mastoiditis, and one with erysipelas. They raised several points, of which the following was considered in the drafting of the manuscript: potential masking of symptoms when reviewing children who have recently taken antipyretics.

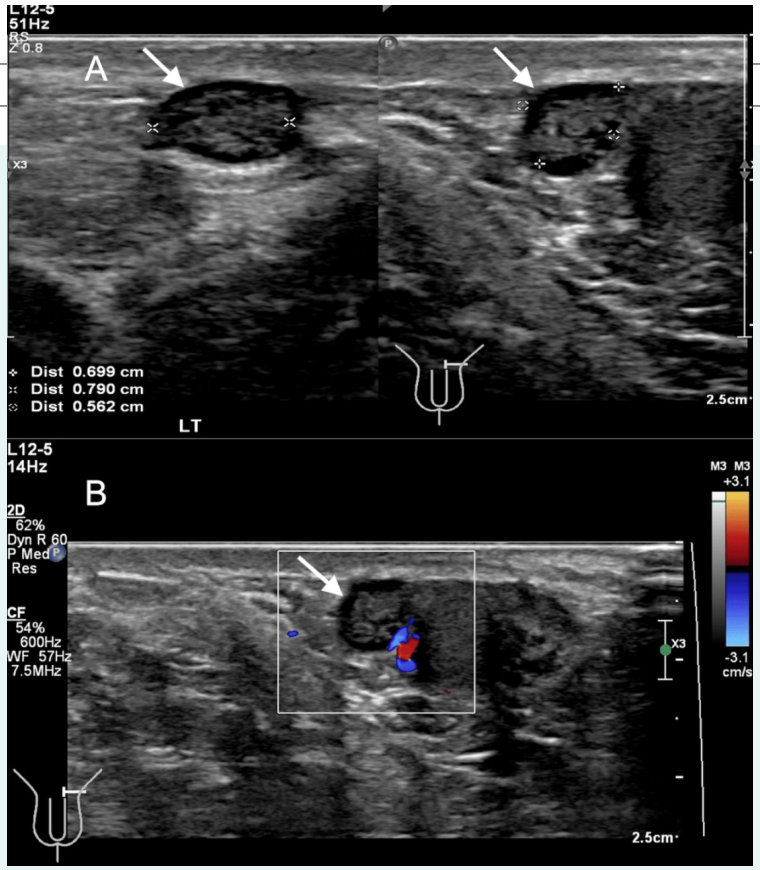
EDUCATION INTO PRACTICE

- How do you document your rationale for prescribing antimicrobials for pharyngitis in clinical records?
- How often do you ask about contact with GAS infection when assessing unwell children?

CASE REVIEW

Acute left testicular pain in a child

A 10 year old boy presented to the emergency department with a one day history of left testicular pain and swelling. He had no history of scrotal trauma, fever, nausea, abdominal pain, or urinary symptoms. Clinical examination showed a small, tender, palpable nodule at the upper pole of the left testis. Bilateral cremasteric reflexes were present and both testes showed a normal vertical lie. No appreciable changes were seen to the overlying skin of the scrotum. Urinalysis results were unremarkable. In view of persistent pain, urgent scrotal ultrasonography was performed for further evaluation (figure), which showed a small tender nodule between the left testis and epididymis. The sonographic features of both testes were otherwise normal.



Greyscale longitudinal/transverse (A) and colour Doppler ultrasonography (B) of the left testicular superior pole. A shows a subcentimetre nodule with heterogenous salt and pepper echotexture (arrow) situated in between the left testis and epididymis, which was tender during scanning, in keeping with a testicular appendage. B shows no vascularity within the nodule (arrow), worrisome for torsion

1 What are the differential diagnoses?

2 What is the most likely diagnosis?

3 How would you manage this condition?

Submitted by Shin Yin Ooi and Timothy Shao Ern Tan

Patient consent obtained.

Cite this as: *BMJ* 2024;385:e077516

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answers

CASE REVIEW **Acute left testicular pain in a child**

1 What are the differential diagnoses?

Differential diagnoses of acute testicular pain include ischaemia (testicular torsion, torsion of testicular appendage), infection (acute epididymo-orchitis), or trauma (testicular contusion or rupture).

2 What is the most likely diagnosis?

Torsion of the left testicular appendage.

Torsion of the left testicular appendage is the most common reason for acute testicular pain in prepubertal children, typically affecting the left side. Although the cause remains unclear, torsion of the testicular appendage has been associated with trauma or prepubertal testicular enlargement of the testes, which may account for its peak incidence in boys aged 7 to 12 years.

3 How would you manage this condition?

Torsion of a testicular appendage is generally self-limiting. Management is conservative, with analgesia, and the patient may be as active as can be tolerated. Surgery should be reserved for patients with persistent symptoms suspicious for testicular torsion that cannot be excluded on clinical and imaging findings alone. Generally, sonographic follow-up is not required, as symptoms usually resolve within a week without any substantial complication or risk of recurrence. If symptoms persist or worsen beyond this timeframe, however, re-evaluation should be considered.

LEARNING POINTS

- Torsion of the testicular appendage is the most common cause of testicular pain in prepubertal children and may mimic testicular torsion clinically.
- Ultrasonography remains the preferred imaging modality to distinguish a torsed testicular appendage from other important mimics of testicular pain.
- Torsed testicular appendages may be managed conservatively and often resolve spontaneously without any major sequelae.

PATIENT OUTCOME

The patient was managed conservatively with supportive treatment and his symptoms subsequently resolved. No complication was detected at the latest follow-up.

CPD READING
0.5 HOURS

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

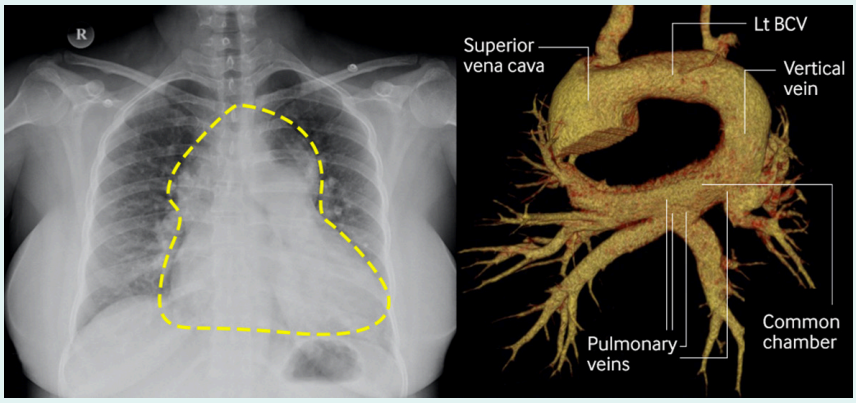
LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at learning.bmj.com.

A change of heart

This chest radiograph (figure, left panel) and reconstructed cardiac computed tomography angiography scan (figure, right panel) show a rare example of unobstructed supracardiac total anomalous pulmonary venous connection (TAPVC). The patient, a woman in her 30s, presented with worsening dyspnoea, cyanosis, and digital clubbing of the fingers and toes.

In this congenital malformation a common chamber is formed by all four pulmonary veins (figure, right panel) coursing into the superior vena cava through a vertical vein and the left brachiocephalic vein (BCV). Left atrial inflow is through an obligatory right to left shunting atrial septal defect. The radiograph (figure, left panel) shows an enlarged cardiac silhouette in a classic "figure of 8" or "snowman" appearance, as a result of the enlarged superior vena cava and vertical vein giving rise to an additional spherical configuration above an enlarged cardiac silhouette. Dilated pulmonary arteries and multiple end-on vessels suggestive of increased pulmonary blood flow are also seen. Survival of uncorrected TAPVC into adulthood is rare.



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Patient consent obtained.

Cite this as: *BMJ* 2024;385:e076278

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Selective serotonin reuptake inhibitors and oral anticoagulants

SSRIs are among the most frequently prescribed antidepressants, at least in part because of their favourable safety profile. However, serotoninergic mechanisms are involved in haemostasis, and the potential adverse effects of these drugs may have been underestimated. A study used a UK primary care database to compare the risk of major bleeding in people already taking SSRIs who were starting oral anticoagulants because of atrial fibrillation with controls using oral anticoagulants alone. Risk of bleeding increased by 33% in the first few months for people taking both SSRIs and oral anticoagulants (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2024.3208).

Mixed connective tissue disease

A retrospective study in France which reviewed 300 patients who fulfilled criteria for mixed connective tissue disease reveals the variability of the prognosis. Over a median follow-up of eight years, nearly half achieved remission. On the other hand, a third progressed to interstitial lung disease or pulmonary hypertension, and around a quarter developed a differentiated connective tissue disease—most frequently systemic sclerosis or systemic lupus erythematosus (*J Intern Med* doi:10.1111/joim.13752).

Treating presbyopia

Presbyopia, in the absence of optical correction, is disabling for people carrying out near vision intensive tasks. A randomised trial from Bangladesh shows how much of an impact the provision of reading glasses has. Participants, aged 35 to 65 with presbyopia and who had never owned glasses, were randomly selected to receive free reading glasses immediately or to have glasses provided at the end of the trial. At eight months, nine of 10 people in the immediate intervention group were still wearing their glasses. What's more, the median income for people in this group had risen by a third (*PLoS One* doi:10.1371/journal.pone.0296115).

The remarkable properties of water

Three ingredients are essential for life: water, energy, and organic molecules. Energy and organic molecules are abundant in the universe but water, at least in its liquid form, is rare. Next time you see the reflection of a white cloud in a puddle of water pause for a moment to appreciate what an odd substance water is. No other compound with a molecular weight as low as 18 and a boiling point as high as 100°C exists. It's a surprising fact that one of the most ubiquitous substances on our planet is, thanks largely to its hydrogen bonding, a chemical outlier (https://www.chemistryworld.com/opinion/water-isnt-normal/4019218.article).

Vibrating insoles

By installing vibratory motors and piezoelectric actuators in the insole of a shoe, it's possible to deliver vibrating stimuli to the heel and forefoot as a person walks. An experiment in which 22 men with diabetic peripheral neuropathy used these insoles finds that they contribute to mobility. When the vibrating stimuli were activated, speed of walking and speed while climbing and descending stairs increased by around 10%. Postural balance also improved (*Diabetes Care* doi:10.2337/dc23-1858).

Surgery for cerebellar infarcts

Surgical decompression of the posterior fossa is often undertaken in patients presenting with a cerebellar infarct, but in a series of more than 500 patients with cerebellar infarcts treated at centres within Germany, there was no difference in mortality or other outcomes between surgically and medically managed patients either at discharge or at follow-up one year later. A secondary analysis, in which cerebellar infarcts were stratified by volume, suggested that larger cerebellar infarcts had a better outcome if managed surgically, while smaller infarcts were better managed conservatively (*JAMA Neurol* doi:10.1001/jamaneurol.2023.5773).

Cite this as: *BMJ* 2024;385:q884