education

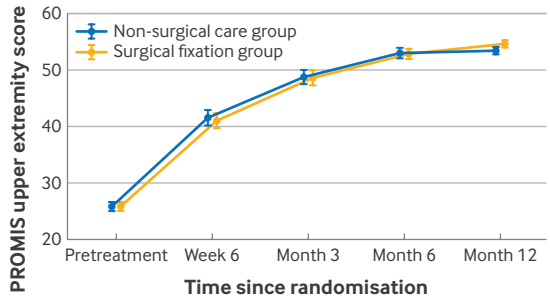
RESEARCH REVIEWS Fortnightly round up from the leading medical journals

AI timesavers

As we race to implement artificial intelligence (AI) into healthcare, it's worth asking what problems it's trying to solve. If only it could do all those time consuming things doctors aren't trained for, so we could get on with the things we were trained for. A randomised controlled trial in a primary care setting in China found

that consultation times were reduced when a patient-facing large language model chatbot was used to take a history and suggest preliminary diagnoses and tests. One striking feature of the study was that the average length of primary care appointments in the control group was only 4.41 minutes—which also happens to be the average time it takes to print off a blood test form with the labels the right way round. Average consultation time in the chatbot group was only 3.14 minutes, my personal best for finding a dermatoscope and taking a photo that isn't too blurry. It's a relief to know we'll have more time to fit these tasks into appointments in the future.

Nat Med doi:10.1038/s41591-025-04176-7



Patient Report Outcomes Measurement System (PROMIS) upper extremity scale scores at each trial timepoint in non-surgical care and surgical fixation groups

Study fixates on paediatric elbow fractures

Medial epicondyle fractures account for around 10% of paediatric elbow injuries. Debate about whether surgical fixation or non-surgical care (eg, resting the elbow in a cast) leads to better outcomes has been fuelled by a lack of high quality evidence—until now. A multicentre, randomised controlled trial enrolled 335 children aged 7-15 with a recent displaced medial epicondyle fracture across 59 sites in the UK, Australia, and New Zealand. No clinically important difference in upper limb function was found between the groups after 12 months. Follow-up will continue until participants are age 16, to assess long term function.

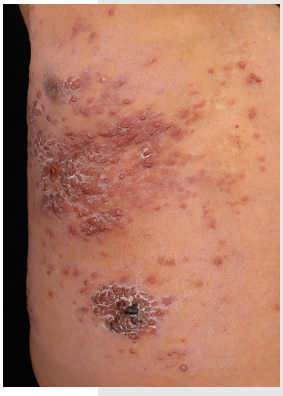
Lancet doi:10.1016/S0140-6736(25)02098-7

PERRY DC, ACHTEN J, ZIMMERMANN A, ET AL. *LANCET* 2026 DOI: 10.1016/S0140-6736(25)02098-7

Ticking the boxes for alpha-gal syndrome

Writing the phrase "patient reports" in the notes tends to signal a degree of scepticism about what really happened. "Patient reports now allergic to meat after eating pastrami sandwich in Katz's deli in New York. Reaction witnessed by diner at nearby table who quipped, 'I'll *not* have what she's having,' then called 911." If you find yourself writing this history, as well as exploring which 1980s romcoms the patient has watched recently, ask if they've been bitten by a lone star tick. Alpha-gal syndrome is a rare allergic response to a sugar (alpha-

CLINICAL PICTURE



Zosteriform nodules and plaques on the trunk

A man in his 70s presented with a one month history of painless, non-pruritic nodules and plaques on the right side of his trunk, which had progressively increased in number and coalesced. He reported no systemic symptoms, comorbidities or regular medication use.

Physical examination showed multiple firm, non-ulcerated, erythematous nodules and plaques on his right anterior trunk, exhibiting a zosteriform distribution predominantly across the T3-T8 dermatomes, with some lesions crossing the midline. Hard, mobile, non-tender lymph nodes were palpated in the right inguinal region and right axilla.

Differential diagnoses included herpes zoster, cutaneous malignancy, and inflammatory dermatoses. Histopathological examination of the skin lesions identified epithelioid cell clusters in the dermis with marked nuclear atypia. Immunohistochemistry was positive for CKPan, CDX2, and CK20 cell markers, and negative for CK7. Together these results indicated that the skin lesions were cutaneous metastases from a colorectal primary tumour.

Contrast enhanced computed tomography demonstrated segmental mural thickening of the sigmoid colon with significant enhancement, and enlarged lymph nodes in the retroperitoneal, right inguinal and right axillary regions, supporting a diagnosis of sigmoid

gal) found in the saliva of some ticks, typically the lone star tick that has recently spread into New York and New England. Typical presentations are gastrointestinal symptoms 2-8 hours after consuming meat, and can progress to anaphylaxis and shock.

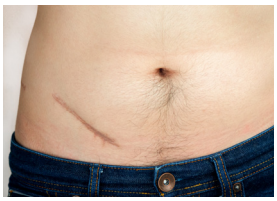
N Engl J Med doi:10.1056/NEJMc250880

quality of life between the two groups.

JAMA Netw doi:10.1001/jama.2025.25921

Finishing the Finnish appendicitis trial

Having appendicitis these days doesn't always leave a scar. Results from the 10 year follow-up of a trial of antibiotics versus appendicectomy support the option of antibiotics in adults with uncomplicated appendicitis. Two hundred and fifty three of 257 participants in the antibiotic arm of a multicentre study set in Finland were followed up, and found to have a cumulative appendicectomy rate of 44.3%. Complication rates were lower in the appendicectomy group and there were no differences in



SGLT-2 benefits for kidney outcomes in diabetes

As no randomised controlled trials have yet compared sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors with glucagon-like peptide-1 (GLP-1) receptor agonists for kidney outcomes in people with diabetes, a target trial emulation study published in *JAMA Internal Medicine* offers the next best thing. The study used nationwide, population data from Denmark to compare renal outcomes in people with type 2 diabetes who were already taking metformin and started either an SGLT-2 inhibitor or a GLP-1 receptor agonist. It found a weighted 5 year risk of chronic kidney disease of 6.7% for SGLT-2 inhibitor initiators, versus 8.2% for GLP-1RA initiators—with a risk ratio of 0.81 (95% CI 0.76 to 0.87) favouring SGLT-2 inhibitors.

JAMA Intern Med doi: 10.1001/jamainternmed.2025.7409

Tom Nolan, clinical editor, *The BMJ*, London; sessional GP, Surrey

Cite this as: *BMJ* 2026;392:s158

colon adenocarcinoma with multiple lymph node metastases (stage T3N2M1b).

It is estimated that around 2-6% of patients with colorectal cancer develop cutaneous metastases, which usually signify advanced disease and poor prognosis. They typically present as single or multiple nodules on the abdominal wall, particularly in the periumbilical region or at surgical scar sites. Cutaneous metastases with a zosteriform distribution may mimic herpes zoster, but skin lesions tend to be progressive, non-pruritic, painless, and firm in texture, aiding differentiation.

Yicen Yan; Hang Li (drlihang@126.com), Peking University First Hospital, Xicheng District, Beijing, China

Patient consent obtained.

Cite this as: *BMJ* 2026;392:e085472

MINERVA From the wider world of research

Slow tapering of antidepressants

For adults who have recovered from depression with the help of antidepressant drugs, a combination of slow tapering and psychological support prevents relapse as effectively as remaining on medication, according to a systematic review and network meta-analysis of 76 randomised controlled trials. Relapse rates were substantially higher when antidepressant drugs were stopped abruptly or tapered rapidly. *Lancet Psychiatry* doi:10.1016/S2215-0366(25)00330-X

Genetics of psychiatric disorders

Forty years ago, following the identification of single-gene neurological disorders such as Huntington's disease, many expected that psychiatric disorders would yield to the same approach. It turns out, however, that most psychiatric illness is highly polygenic. Genome wide association data from more than one million people identified very few disorder specific loci. Genetic risk factors also cut across diagnostic boundaries. Schizophrenia and bipolar disorder show extensive overlap, as do depression, anxiety, and post-traumatic stress disorder. *Nature* doi:10.1038/s41586-025-09820-3

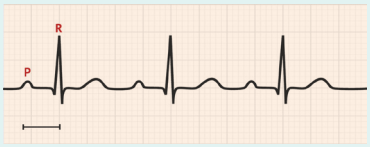
Coffee staining for electron microscopy

In transmission electron microscopy, biological tissue is almost invisible without chemical staining. Standard methods require uranyl acetate, which is both toxic and radioactive. A search for less hazardous alternatives found that coffee, particularly espresso, produced images comparable to those obtained with uranyl acetate—safer, and a lot cheaper. *Methods* doi:10.1016/j.ymeth.2025.08.009

Azathioprine for Parkinson's disease

The increased incidence of Parkinson's disease among people with inflammatory bowel disease, and the attenuation of this risk by anti-TNF therapy, suggest that systemic inflammation is involved in the pathogenesis of the disease. So it is disappointing that a 12 month randomised controlled trial of the immunosuppressant azathioprine found no evidence that it slowed disease progression. Although treatment was well tolerated, gait and motor symptoms did not differ from those in the placebo group. *Lancet Neurol* doi:10.1016/S1474-4422(25)00386-2

PR intervals



By linking data from more than nine million electrocardiograms to national patient registries, Danish investigators showed that both short and prolonged PR intervals were associated with small increases in the risk of atrial fibrillation, heart failure, ventricular arrhythmias, and mortality. Longer PR intervals, unsurprisingly, were associated with syncope and advanced atrioventricular block. *Heart* doi:10.1136/heartjnl-2025-327183

Cardiorespiratory fitness and colorectal cancer

In a large cohort of US veterans followed for 10 years, higher cardiorespiratory fitness was associated with a lower incidence of colorectal cancer. Among more than 640 000 participants who completed a standard exercise treadmill test, incidence declined progressively with increasing fitness. Compared with the least fit group, those with the highest fitness were only half as likely to develop the disease. *Mayo Clin Proc* doi:10.1016/j.mayocp.2025.03.015

Cite this as: *BMJ* 2026;392:s160

EASILY MISSED?

Giant cell arteritis

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. To suggest a topic for this series, please email us at practice@bmj.com. Advisers to this article series are Anthony Harnden, professor of primary care, Department of Primary Care Health Sciences, University of Oxford, and Dr Kevin Barraclough, School of Social and Community Medicine, University of Bristol.

CPD READING
0.5 HOURS

An 80 year old woman experienced jaw pain for four weeks. The pain occurred multiple times a day, shortly after she started to eat. She also experienced right intermittent painless loss of vision, mild scalp tenderness on brushing her hair, and headaches similar to her usual long term headaches. Subsequently, she developed bilateral, intermittent painless loss of vision which progressed to a constant blurriness over two weeks. She visited her dentist, who found no underlying dental cause for the jaw pain.

She sought a private ophthalmology review owing to her visual symptoms. A diagnosis of giant cell arteritis was suspected, and she was referred urgently for blood tests and ultrasound scan of temporal and axillary arteries. Full blood count, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were normal, and ultrasound was reported as equivocal (no evidence of non-compressible halo; possible stenosis of one branch vessel).

Giant cell arteritis was no longer the working diagnosis, but, at follow-up ophthalmology review one month later, she had a thickened non-pulsatile left temporal artery and bilateral anterior ischaemic optic neuropathy. At this point, CRP and repeat temporal artery ultrasound were normal. The ophthalmologist referred her urgently to acute medicine.

WHAT YOU NEED TO KNOW

- Giant cell arteritis is a medical emergency, and delayed treatment may lead to end-organ ischaemia, including permanent visual loss
- Limb claudication, jaw claudication, and temporal artery thickening have the highest positive likelihood ratios for giant cell arteritis and should increase clinician suspicion of the diagnosis
- About 4% of biopsy-proven giant cell arteritis cases have normal inflammatory markers, therefore consider this diagnosis in a patient with a suggestive history
- Treat all patients with suspected giant cell arteritis with high dose glucocorticoids immediately and refer urgently for specialist review

What is giant cell arteritis?

Giant cell arteritis is a medium-to-large vessel vasculitis, which can lead to end organ ischaemia. Because it can affect multiple organs, the spectrum of giant cell arteritis includes multiple phenotypes, and is most commonly classified as classical cranial arteritis and extra-cranial giant cell arteritis.[1]

When the small muscular cranial arteries are affected in the classic phenotype, symptoms include new or altered headache, scalp tenderness, jaw claudication, and visual changes, which, according to a literature review of 634 patients, can result in some degree of permanent visual loss in 50% of untreated patients.[2] When large arteries such as the aorta and its branches are involved in extracranial disease, patients may present with polymyalgic symptoms or limb claudication.[3]

How common is it?

A 2021 meta-analysis of the international incidence of giant cell arteritis found that, in people aged 50 years or older, incidence was highest in Scandinavia (21.6/100 000 people) and lowest in East Asia (0.3/100 000). Across the world, rates vary: 10.9/100 000 in North and South America, 7.9/100 000 in Oceania, 7.3/100 000 in Europe, 5.7/100 000 in the Middle East, and 4.6/100 000 in Africa.[4]

In the UK, it is estimated that a full time GP will see one new case of giant cell arteritis every one to two years.[5] Poor outcomes are more common in areas of socioeconomic deprivation, which may be due, in part, to delayed presentation. For example, a retrospective observational study of 271 patients with giant cell arteritis across eight UK sites found that, after controlling for the age at onset, area level socioeconomic deprivation was an independent predictor of irreversible ischaemic complications in giant cell arteritis.[6] Compared with the least deprived quartile, people in the most deprived quartile were three times more likely to experience an irreversible ischaemic complication (odds ratio 3.0 (95% CI 1.1 to 7.9), P=0.029).

Why is it missed?

The diagnosis of giant cell arteritis can be challenging to make because it is relatively uncommon, there may be limited access to diagnostic services, and presentations may be atypical or non-specific.

Over-reliance on certain clinical features may lead healthcare professionals to rule out the diagnosis prematurely. In the UK, one multi-methods study of 1249 general practitioners reported limited awareness of the

thebmj Visual summary

Giant cell arteritis

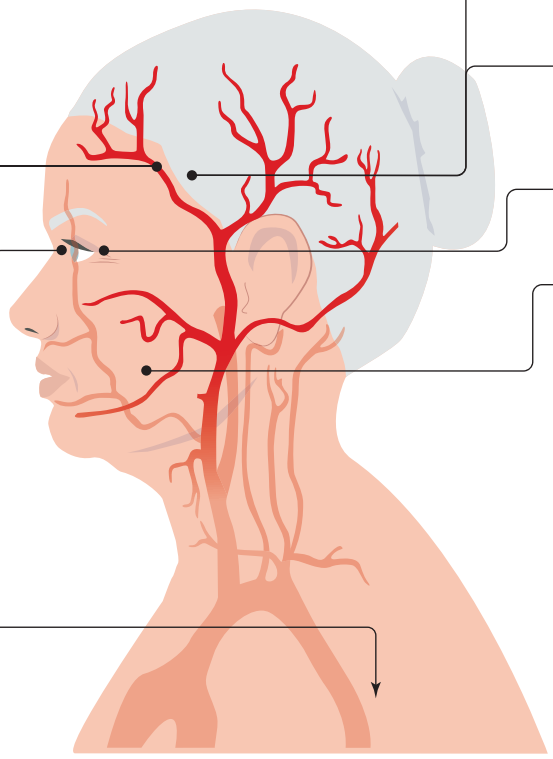
Selected diagnosis and referral considerations

from British Society of Rheumatology, European Alliance of Associations for Rheumatology, and American College of Rheumatology.

The diagnosis of giant cell arteritis can be challenging to make because it is relatively uncommon, there may be limited access to diagnostic services, and presentations may be atypical or non-specific. It is diagnosed using a combination of clinical, biochemical, and histological features.

Signs

- Tenderness and/or thickening of the superficial temporal arteries with or without reduced pulsation
- **Ophthalmological findings:**
  - Anterior ischaemic optic neuropathy
  - Oculomotor cranial nerve palsy/palsies
  - Central retinal artery occlusion
  - Branch retinal artery occlusion
  - Choroidal ischaemia
- Bruits (particularly in the axilla)
- Reduced pulses/difference in blood pressure of upper limbs



Symptoms

- Temporal/scalp tenderness (ask if they notice new pain on brushing hair)
- New onset persistent localised headache, often in the temporal area
- Acute visual symptoms such as amaurosis fugax, acute visual loss, diplopia
- Jaw/tongue claudication (pain after a few minutes of eating)
- **Constitutional symptoms such as:**
  - Weight loss >2kg
  - Low grade fever
  - Fatigue
  - Night sweats
- Symptoms of polymyalgia rheumatica (pain and stiffness of the shoulder and hip girdles)
- Limb claudication

Investigations

Blood Tests

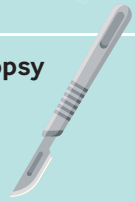
- **First presentation**
  - Erythrocyte sedimentation rate/plasma viscosity
  - C reactive protein
  - Full blood count
- **Major organ system function**
  - Plasma glucose
  - Renal and liver function tests
  - Calcium and alkaline phosphatase
- **Screening tests for osteoporosis risk, which may include:**
  - Thyroid function tests
  - Vitamin D

Imaging

Ultrasound UK and European guidelines recommend ultrasound of temporal and axillary arteries as first line.

MRI/PET-CT High-resolution magnetic resonance imaging, or 18F-fluorodeoxyglucose positron emission tomography can be used as alternatives.

Biopsy



If diagnosis not confirmed by clinical picture and ultrasound, consider temporal artery biopsy.

Referral

Refer all suspected cases of giant cell arteritis immediately for specialist review via local pathways:

03 — All cases should be seen within 3 working days as in UK guidelines

If new visual symptoms present, should be seen by ophthalmologist on the same calendar day

Selected diagnostic recommendations from British Society of Rheumatology,[9] European Alliance of Associations for Rheumatology,[3 16] and American College of Rheumatology[17]

History and examination

Signs:

- Tenderness and/or thickening of the superficial temporal arteries with or without reduced pulsation
- Bruits (particularly in the axilla)
- Reduced pulses or difference in blood pressure of upper limbs
- Pathological findings during ophthalmological examination, including anterior ischaemic optic neuropathy, oculomotor cranial nerve palsies, central retinal artery occlusion, branch retinal artery occlusion, and choroidal ischaemia

Symptoms:

- Limb claudication
- Jaw or tongue claudication (pain after a few minutes of eating)
- Temporal or scalp tenderness (ask if patient notices new pain on brushing hair)
- New onset persistent localised headache, often in the temporal area
- Constitutional symptoms (such as weight loss >2 kg, low grade fever, fatigue, night sweats)
- Acute visual symptoms such as amaurosis fugax, acute visual loss, diplopia
- Symptoms of polymyalgia rheumatica (pain and stiffness of the shoulder and hip girdles)

Investigations

Bloods:

- Perform erythrocyte sedimentation rate (ESR) or plasma viscosity, C reactive protein (CRP), and full blood count at first presentation as a minimum
- Baseline laboratory tests of major organ system function (plasma glucose, renal and liver function tests, calcium and alkaline phosphatase)
- Screening tests for osteoporosis risk (may include thyroid function tests, vitamin D)

First line confirmatory tests:

- British and European guidelines recommend ultrasound of temporal and axillary arteries as first line
  - If diagnosis not confirmed by clinical picture and ultrasound, consider temporal artery biopsy
  - High resolution magnetic resonance imaging, or 18F-fluorodeoxyglucose ([18F]FDG) positron emission tomography (PET) can be used as alternatives to ultrasound for the assessment of cranial arteries in patients with suspected giant cell arteritis
- US guidelines recommend temporal artery biopsy within 2 weeks of starting oral glucocorticoids as first line
  - In the cases of suspected giant cell arteritis and a negative temporal artery biopsy, imaging of the large vessels is conditionally recommended to provide additional evidence of disease. Potential diagnostic imaging modalities include magnetic resonance or computed tomography angiography of the neck, chest, abdomen, or pelvis; ultrasonography; and [^{18}F]FDG PET

Referral

- Refer all suspected cases of giant cell arteritis immediately for specialist review via local pathways:
  - All cases should be seen within 3 working days (UK guidelines)
  - If new visual symptoms present, patient should be seen by ophthalmologist on the same calendar day

full range of potential symptoms associated with the condition and demonstrated that about 1 in 5 GPs would exclude giant cell arteritis as a diagnosis if headache was absent despite wider features of the condition being present.[7] However, a 2025 meta-analysis of 9971 patients with giant cell arteritis found that headache was present only in about three quarters of patients (75.7% (95 CI% 72.2 to 79.0%)).[8]

In the UK, guidelines from the British Society for Rheumatology recommend that patients with suspected giant cell arteritis should be evaluated by a specialist on the same working day if possible and that all cases should be evaluated within three working days. For those presenting with new visual loss (transient or permanent) or double vision, evaluation by an ophthalmologist should be on the same calendar day.[9] This is in line with European recommendations, which recommend urgent referral of suspected giant cell arteritis to specialist teams, but are less prescriptive about specific timelines.[3]

In practice, however, diagnostic delays across healthcare settings are common. A 2024 Dutch retrospective cohort study of 205 patients in whom giant cell arteritis was suspected analysed the timeline of the diagnostic delay from symptom onset to diagnosis over 33 months.[10] Median time between onset of symptoms and first GP visit was 10.5 days, and median time between first GP visit and referral to a rheumatology fast-track clinic was 10.0 days. Patients may have had multiple consultations with the GP or have been referred

Complications can arise within days and are often prevented only with timely treatment with glucocorticoids

to other specialties before rheumatology. Median time after onset of symptoms to first fast-track clinic visit was 31 days. Patients were generally seen at the fast-track clinic within one day after referral. In contrast, a 2017 worldwide systematic review and meta-analysis of studies from primary to tertiary care settings reporting diagnostic delay between onset of giant cell arteritis symptoms and diagnosis for 2474 patients found that mean diagnostic delay was nine weeks (95% CI 6.5 to 11.4 weeks).[11] A limitation of this study is that the reason for delay was not included, and therefore delay may be related to factors other than referral time or clinician error—such as time for patients to seek medical attention, receive an appointment, or availability of diagnostic tests.

Both studies identified longer diagnostic delays for patients with atypical extracranial presentations. In the 2017 systematic review, patients with cranial giant cell arteritis (defined as those who presented with cranial features such as headache and scalp tenderness or who went on to receive a positive temporal artery biopsy) received a diagnosis after eight weeks. In comparison, patients with extracranial giant cell arteritis (defined as those who presented with constitutional symptoms such as fever, anorexia, or polymyalgia, or other non-cranial presentation) received a diagnosis after 18 weeks. In the

2024 Dutch study, for patients with isolated cranial giant cell arteritis, median delay from onset of symptoms to treatment initiation was 21 days, whereas the delay was 57 days in patients with extracranial giant cell arteritis.

Why does this matter?

Giant cell arteritis, if left untreated, can cause permanent vision loss, cerebrovascular events, and other end organ ischaemia.[12] These complications can arise within days and are often prevented only with timely treatment with glucocorticoids.[13] In the "patient's perspective" box (below) a patient with giant cell arteritis describes her experience with losing her sight.

A 2005 literature review of outcomes in 2651 patients with giant cell arteritis found that, before the advent of glucocorticoid therapy in the 1950s, some degree of visual loss occurred in about half of patients, and about a fifth had bilateral blindness.[2] Notably, once one eye was affected, about a third of patients progressed to complete blindness. After the introduction of glucocorticoid therapy, visual loss fell to 30% and bilateral blindness to 6%. Only 3% developed visual loss after starting glucocorticoids.[2]

Other studies have shown that prompt treatment improves outcomes. A 1998 Spanish retrospective cohort study of 239 patients with biopsy proved giant cell arteritis found that, when glucocorticoid treatment was started within 24 hours of visual loss, 58% of patients experienced improvement in vision, compared with 6% when treatment was delayed beyond 24 hours.[14] These findings were echoed in a 2015 longitudinal observational cohort study, which compared visual outcomes of 135 suspected giant cell arteritis patients seen via a "fast track pathway" (received treatment and specialist review within one working day of presentation) with a historical cohort of 81 patients seen conventionally. The fast track pathway demonstrated a reduction in permanent visual impairment from 37% to 9% (odds ratio 0.17 (95% CI 0.06 to 0.47), P=0.001).[15] The authors suggest that this is probably due in part to the elimination of complex referral pathways, ultimately resulting in earlier commencement of treatment.

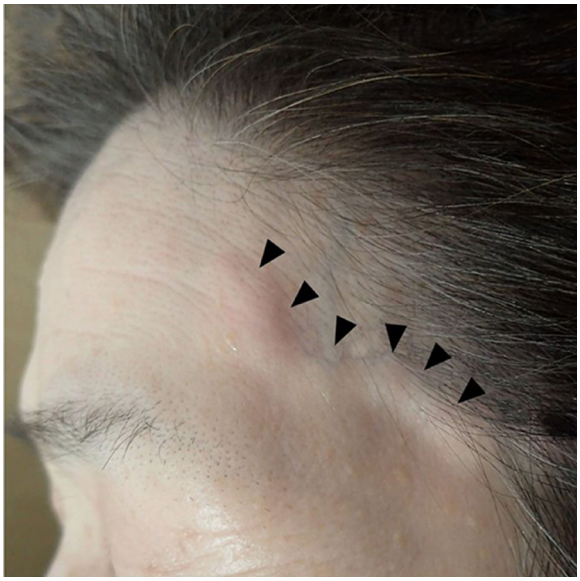
How is it diagnosed?

Giant cell arteritis is diagnosed using a combination of clinical, biochemical, and histological features.

Clinical features

The European Alliance of Associations for Rheumatology (EULAR) updated their guidelines on the diagnosis and treatment of giant cell arteritis in 2018,[3] outlining important diagnostic clinical features and investigations. The box shows selected recommendations from the British Society of Rheumatology, EULAR, and American College of Rheumatology on the key symptoms and signs of giant cell arteritis, investigations, and referral.

No symptoms are specific or pathognomonic for giant cell arteritis, and are therefore of limited use in isolation.



Nodular swelling of the temporal artery (arrowheads) in a 74 year old woman with giant cell arteritis. (Reproduced from Ihoriya H, Nakano Y, Otsuka F. Temporal artery thickening in giant cell arteritis. *BMJ Case Reports CP* 2021;14:e247123)

Based on findings from a 2020 systematic review and meta-analysis of 14 037 patients which analysed the diagnostic value of various symptoms, signs, and laboratory data for giant cell arteritis, only certain features could be used confidently by clinicians to either upgrade or downgrade suspicion of giant cell arteritis.[18] A positive likelihood ratio of more than 2.00 or a negative likelihood ratio of less than 0.5 for these features and a 95% confidence interval not including 1.00 were found to be statistically significant. The three features with the highest positive likelihood ratios were limb claudication, jaw claudication, and temporal artery thickening (see figure), and these should increase clinician suspicion. The three features with the highest negative likelihood ratios were age of ≤70 years, a C reactive protein (CRP) level <25 mg/L, and an erythrocyte sedimentation rate (ESR) <50 mm/h, and so these should decrease clinician suspicion.

Investigations

Where possible, perform ESR, CRP, and full blood count (particularly assessing platelet count) before starting glucocorticoid therapy. However, do not delay treatment pending availability of results where there is a high pretest probability of giant cell arteritis, which is a medical emergency. Plasma viscosity can be used where ESR is unavailable.[9]

Although normal inflammatory markers indicate a low likelihood of disease, a 2012 retrospective observational cohort study of 177 patients who had a positive temporal artery biopsy found that 4% had normal ESR and CRP at diagnosis.[19] Also consider baseline laboratory tests of major organ system function (plasma glucose, renal and liver function tests, calcium and alkaline phosphatase), and screen for any risks of osteoporosis by testing thyroid function and vitamin D levels.[9]

CASE REVISITED

After referral to acute medicine, the patient received 1 g intravenous methylprednisolone for three days. She was also referred to rheumatology for confirmation of diagnosis, further management, and follow-up. On completion of her course of methylprednisolone, she was commenced on a tapering course of oral prednisolone. After 19 days of treatment with steroids, a temporal artery biopsy confirmed the diagnosis of giant cell arteritis, four months after initial symptom onset. The patient has permanent severe visual impairment.

PATIENT'S PERSPECTIVE

Giant cell arteritis has had a devastating impact on my life. A year ago, I could not have imagined my life having changed so drastically. I was an accountant and, in my retirement, used to enjoy using the computer to manage my family's finances and surf the internet, but now I can't see the screen. I used to love travelling, doing my makeup, and watching TV, but I struggle to do any of these things now. My husband is my greatest support, but, having health issues of his own, it has been a difficult adjustment for the both of us. I wish that there was better education for healthcare professionals regarding the diagnosis of giant cell arteritis to prevent other people losing their sight.

The landmark multicentre blinded TABUL study of 381 patients with newly suspected giant cell arteritis compared temporal artery biopsy and ultrasound as diagnostic tests: it found that ultrasound of the temporal and axillary arteries had a sensitivity of 54% (95% CI 48% to 60%) and specificity of 81% (73% to 88%), whereas temporal artery biopsy had a sensitivity of 39% (33% to 46%) and a specificity of 100% (97% to 100%).[20] More recently, a systematic literature review of the use of ultrasound in the diagnosis of giant cell arteritis demonstrated a pooled sensitivity of 88% (82% to 92%) and a specificity of 96% (86% to 99%).[16] Based on these data, European guidelines now recommend consideration of an ultrasound of temporal and axillary arteries as first line imaging in all patients with suspected giant cell arteritis. Furthermore, European guidelines do not recommend performing a biopsy to confirm diagnosis for patients in whom there is a high clinical suspicion of giant cell arteritis and a positive imaging result.[21] In contrast, the American College of Rheumatology expressed a preference for temporal artery biopsy over ultrasound in their 2021 guidelines but clarified that this relates in part to the relative lack of technical expertise in the US with temporal artery ultrasound compared with their European counterparts.[17] This is consistent with Australian and Asian institutions, where ultrasound is less commonly used compared with European centres, and biopsy often remains the reference standard.[22 23]

Further imaging such as magnetic resonance angiography, contrast enhanced computed tomography, and fluorodeoxyglucose positron emission tomography may be used if ultrasound and/or biopsy are unavailable, or if systemic manifestations and limb claudication are present.[9] In resource limited settings, where these investigations may be unavailable, giant cell arteritis remains a clinical diagnosis.

The diagnostic accuracy of vascular ultrasound scan and temporal artery biopsy diminish rapidly after initiation of glucocorticoids. Ultrasound scan of the temporal arteries (and, by protocol, axillary arteries) should ideally be done within one week of starting steroids,[20] and biopsies ideally within two weeks,[24] and UK recommendations suggest within six weeks.[25]

Competing interests: None declared.

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Find the full version with references at doi: 10.1136/bmj-2025-086139

How is it managed?

The British Society for Rheumatology recommends urgent specialist referral via local pathways. If a diagnosis of giant cell arteritis is suspected, high dose glucocorticoid therapy (oral prednisolone 40-60 mg daily) should be commenced,[9] even in cases of late presentation or delayed diagnosis. Referring clinicians, such as primary or emergency care physicians, are recommended to prescribe steroids before specialist referral to prevent treatment delay.[9]

For those presenting with suspected giant cell arteritis and new visual loss (transient or permanent) or double vision, evaluation by an ophthalmologist should be on the same calendar day. These patients should receive intravenous methylprednisolone 500-1000 mg daily for three consecutive days before commencing oral prednisolone therapy as above. If intravenous glucocorticoid therapy is not possible, 60-100 mg oral prednisolone may be given for up to three consecutive days.[9] In the UK, NICE guidelines advise that, depending on the clinical situation, the specialist may advise a single treatment with high dose glucocorticoid in primary care while the patient awaits transfer to ophthalmology.[26]

Input from specialist teams usually focus on suppressing disease activity and tapering the prednisolone over 12 to 18 months. With long term glucocorticoid therapy, strategies to mitigate the associated risks—including adrenal insufficiency, osteoporosis, gastric ucler, diabetes, and cardiovascular disease—should be considered. Patients should be provided with appropriate education regarding sick day rules and steroid cards. In patients who relapse or are at high risk of glucocorticoid toxicity, methotrexate or tocilizumab may be considered.[9]

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We informally interviewed a patient with giant cell arteritis, asking her to reflect on her journey, and she reviewed the final draft of the manuscript. Her story was modelled into our case vignette. We incorporated her reflections on the impact her condition continues to have on her life in the patient's perspective. She wanted to share her story with medical professionals in the hope that it improves understanding of the condition, and so they understand the impact of living with visual impairment.

EDUCATION INTO PRACTICE

- What signs and symptoms do you ask about for patients in whom you suspect giant cell arteritis?
- Think about the last time you diagnosed someone with giant cell arteritis. What was their referral pathway and when did they have treatment initiated?

STATE OF THE ART REVIEW

Antimicrobial use and resistance

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This is a summary of Clinical Review *Antimicrobial use and resistance*. The full version can be read here: https://www.bmj.com/content/391/bmj-2024-082681

CPD READING

0.5 HOURS

Antibiotics facilitate biomedical advances and are relatively cheap, generally safe, and among the most clinically effective drugs ever developed. They patch deficiencies in healthcare systems that are under increasing pressure, bridge periods of diagnostic uncertainty, treat common infections that were historically lethal, and provide a holding function to enable underlying diseases to be identified and treated. Antimicrobial resistance places each of these functions in jeopardy.

An inevitable tension exists between deploying antibiotics empirically versus pursuing diagnostic certainty to maximise therapeutic precision; between treating pathogens residing at the site of infection (for example, the lung) and harming the 10^{11} unassuming bacteria residing in the human gut; and between the rights of an individual to access the best available agent to treat their infection versus the requirement to preserve those same agents as critical societal assets. Balancing these tensions represents a substantial challenge for the delivery of safe and effective healthcare because a completely satisfactory converged solution for any outcome of interest never exists.

In high income countries (HICs), secondary and tertiary care may enable extensive characterisation of multi/extensively drug resistant (MDR/XDR) pathogens, diagnostic driven antibiotic use, and access to new antibiotics. In contrast, antibiotic use in low and middle income countries (LMICs) and in primary care settings throughout the world is constrained by an absence of underpinning laboratory infrastructure, prescriptions directed by presumptive clinical infection rather than a specific microbiological diagnosis, and clinical care delivered using a relatively limited number of generic antibiotics.

WHAT YOU NEED TO KNOW:

- Antimicrobial resistance affects the delivery of safe and effective healthcare. It has attracted a strong political focus but, despite increased political engagement, the global antimicrobial landscape remains imbalanced.
- In high income hospital settings, diagnostics, antimicrobial stewardship, and infection prevention and control are improving. Development and use of new antibiotics is a major focus. By contrast, in low and middle income countries, access to most of these advances is limited.
- In all settings, empirical prescribing of essential antibiotics remains the cornerstone of treatment and conserving their efficacy is critical to effective healthcare.
- Targeted prevention and optimal treatment strategies are needed to mitigate antimicrobial resistance across all settings.

Box 1 | Key antimicrobial resistance challenges—summarised in WHO Priority Pathogen List

Critical
- Carbapenem resistant Enterobacterales
- Third generation cephalosporin resistant Enterobacterales (ESBLs)
- Carbapenem resistant *Acinetobacter baumannii*

High
- Fluoroquinolone resistant *Salmonella typhi*
- Fluoroquinolone resistant *Shigella*
- Vancomycin resistant *Enterococcus faecium*
- Carbapenem resistant *Pseudomonas aeruginosa*
- Fluoroquinolone resistant non-typhoidal *Salmonella*
- Meticillin resistant *Staphylococcus aureus*
- Fluoroquinolone/third generation cephalosporin resistant *Neisseria gonorrhoeae*

Medium
- Macrolide resistant group A *Streptococcus*
- Macrolide resistant *Streptococcus pneumoniae*
- Ampicillin resistant *Haemophilus influenzae*
- Penicillin resistant group B streptococci

ESBL=extended spectrum β-lactamase

Epidemiology

The Global Burden of Disease study reviews pathogen specific antimicrobial resistance worldwide.[4] Recent analyses highlight the high burden of antimicrobial resistance, with an estimated 4.95 million bacterial antimicrobial resistance associated deaths in 2019.[4] Despite antimicrobial resistance being a global phenomenon, the study also highlights the significant regional disparities in its prevalence. Using these estimates, figure 1 (bmj.com) shows differences in global mortality associated with pathogens on the "critical" World Health Organization (WHO) Priority Pathogen List (see "Global policy" below and box 1). The mortality burden of antimicrobial resistance is comparatively higher in LMICs, disproportionately affecting countries with substantial underlying geopolitical instability and poorly developed healthcare systems. The data highlight six pathogens responsible for a combined 3.57 million antimicrobial resistance associated deaths: *Escherichia*

coli, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.[4] For some pathogens, most organism associated deaths are from resistant disease (for example, *A baumannii*, *Enterococcus faecium*), yet the total number of associated deaths may be comparatively low. Conversely, serious bacterial infections caused by pathogens such as *S aureus* and *S pneumoniae* have a high baseline mortality, even in the absence of drug resistance.

Concepts and definitions

A microbiological diagnosis of antimicrobial resistance is established phenotypically (that is, showing a raised minimum inhibitory concentration (MIC), which is the lowest concentration of an antibiotic that prevents microbial growth) and/or genotypically (that is, showing the presence of an underlying genetic mechanism of resistance, such as an extended spectrum β-lactamase (ESBL) gene in Enterobacterales). By contrast, a pharmacodynamic definition of resistance is based on having insufficient drug exposure relative to the MIC. Microbiological definitions of antimicrobial resistance are used for infection prevention and control (IPC) programmes, antimicrobial stewardship, epidemiological studies, and surveillance programmes. Pharmacodynamic principles are used for antibiotic drug development and direct clinical care (for example, infusing β-lactam antibiotics to maximise the fraction of the dosing interval free drug concentration above MIC (*ft*>MIC)). These different constructs of antimicrobial resistance are generally complementary (box 2, see bmj.com).

Global policy

The economic importance of antimicrobial resistance was brought into focus in 2016 by the final report and recommendations of the O'Neill Review on Antimicrobial Resistance, commissioned by the UK prime minister.[6] The estimates for the costs of ignoring antimicrobial resistance in terms of both monetary value and loss of human life were high and a series of recommendations were made, largely focusing on reducing demand for antibiotics. These include improved public awareness, better hygiene and sanitation, minimising use of antibiotics in agriculture, improved surveillance, promotion of rapid diagnostics, and use of vaccines. Additional recommendations include support for people working in infectious diseases, establishing a global innovation fund, improved incentives for antimicrobial drug development, and establishing a global coalition for action. After nearly a decade, modest advances have been made in many of these areas.

The recent United Nations General Assembly (UNGA) 2024 High Level Meeting Political Declaration provides a further framework to tackle antimicrobial resistance and commits to two overarching targets: a reduction in antimicrobial resistance associated mortality of 10% by 2030 (from the 2019 baseline of 4.95 million deaths);

Estimates for the costs of ignoring antimicrobial resistance in terms of both monetary value and loss of human life were high

Box 3 | WHO Essential Medicines List AWaRe Agents (2023)

Access
First or second choice antibiotics—high therapeutic value with relatively limited potential for emergence of resistance

- Amoxicillin (+/− clavulanic acid), amikacin, ampicillin, benzylpenicillin, cefalexin, cefazolin, chloramphenicol, clindamycin, cloxacillin, doxycycline, gentamicin, metronidazole, nitrofurantoin, phenoxymethylpenicillin, spectinomycin, sulfadiazine, tetracycline, trimethoprim (+/− sulfamethoxazole)

Watch
First or second choice antibiotics for specific indications only—emergence of resistance is more common

- Azithromycin, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, chlortetracycline, ciprofloxacin, clarithromycin, erythromycin, imipenem/cilastatin, kanamycin, levofloxavin, meropenem, moxifloxacin, netilmicin, ofloxacin, oxytetracycline, piperacillin-tazobactam, rifabutin, rifampicin, streptomycin, tobramycin, vancomycin

Reserve
"Last resort" antibiotics indicated only in selected cases with underlying multidrug resistant pathogens—targeted stewardship efforts are made to preserve their ongoing effectiveness

- Cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, colistin, fosfomycin (intravenous), linezolid, meropenem-vaborbactam, plazomicin, polymyxin B (intravenous), tedizolid

and a minimum of 70% overall human use to consist of "access" group antibiotics from the WHO AWaRe (Access/Watch/Reserve) system (box 3).[7]

WHO Priority Pathogen List and AWaRe

WHO has published several key documents, including the AWaRe antibiotic book, providing detailed treatment guidance on optimal use of the 41 antibiotics on the Essential Medicines List (EML) (out of the >250 generic antibiotics used in humans) (box 3) and the WHO Priority Pathogen List (PPL) (box 4). Formulated using a multi-criteria decision analysis, the WHO PPL highlights key drug-pathogen combinations of global concern for antimicrobial resistance. Criteria for prioritisation included case fatality ratio, incidence of resistance, non-fatal health burden, 10 year resistance trends, transmissibility, preventability, treatability, and the extent to which the antibacterial pipeline can tackle a resistant pathogen (box 1).[20]

"Push and pull" incentives

"Push and pull" incentives initially envisaged by the DRIVE-AB project within the EU's Innovative Medicines Initiative 1 (IMI-1) programme resulted in the development of reimbursement schemes in Europe (France, Germany, Sweden) and the UK. Push and pull incentives act to combat the commercially unattractive nature of antimicrobial drug development. The push occurs through reducing the costs of development, primarily through public-private partnerships. The pull occurs through fixed annual fees paid to pharmaceutical

companies for valued antibiotics, irrespective of the volume of antibiotic consumed. This encourages the development of agents targeting MDR/XDR pathogens, which would otherwise be conserved as "last line."

Drivers of antimicrobial resistance

Bacteria have an extensive repertoire of resistance mechanisms to counter naturally occurring antibiotics (table 1, bmj.com). These mechanisms have progressively adapted and extended following increasing exposure to modern antibiotics. Bacterial resistance mechanisms are phylogenetically ancient.[2 10] Suboptimal IPC practices promote the transmission of pathogens and/or resistance mechanisms via plasmids or other mobile genetic mechanisms (fig 3, bmj.com). Use of antibiotics promotes the emergence of resistance. Injudicious use encompasses a range of scenarios including the use of antibiotics when not needed (for example, for viral infections); the use of antibiotics to treat diseases that could have been prevented by water, sanitation, and hygiene (WASH) and/or vaccination; inappropriate treatment duration (too short or too long); the use of antibiotics without adequate source control (for example, surgical management, removal of indwelling devices/prosthetic material). Furthermore, the imprecise use of antibiotics (absent or incomplete antimicrobial stewardship programmes, use of antibiotics without a microbiological diagnosis) is a further factor driving resistance. Antimicrobial resistance is a "one health" problem whereby an interaction exists between human, animal, plant, and environmental health. Environmental contamination and veterinary antibiotic use (for example, in companion animals or the food chain) may result in deleterious effects for human health as resistance motifs cross from one domain to another—for example, mcr1 mediated colistin resistance resulting from colistin use in pig farming.[11]

Detection of antimicrobial resistance

Diagnostics

Diagnosis of antimicrobial resistance through the detection of resistance mechanisms described above occurs in only a small subset of patients. Most antibiotics are used empirically, following a clinical diagnosis of an infection that may have an underlying bacterial cause. The choice of empirical antibiotic(s) hinges on plausible pathogens and their likely antimicrobial susceptibility (fig 4, panels 1 and 2).

Community based detection

For a small proportion of patients, detection of a bacterial pathogen may allow inferences to be made about likely antimicrobial resistance, through known intrinsic resistances or propensity of the pathogen for development of antimicrobial resistance over the course of treatment, or from local surveillance data (fig 4, panel 3) However, around 90% of global antibiotic use occurs in the community, where the use of standard culture based diagnostics is neither necessary nor feasible.[107 108] Furthermore, in most common community infections, successful detection of causative pathogens is unlikely. For example, culture of a causative pathogen in community acquired pneumonia occurs in <40%, and although this can be increased to around 60% with extensive diagnostic use in trials, in most clinical settings identification of a causative pathogen is significantly lower.[109] Hence, empirical antibiotic cover based on a clinical diagnosis is recommended for the management of community acquired pneumonia and is a strategy used for most community infections in both LMIC and HIC settings.[110] Advances in diagnostics are unlikely to significantly affect antimicrobial use in these settings, where empirical management is inevitable

Box 4 | International reports, guidance, and policy on antimicrobial resistance (AMR)

- World Health Organization's *Global research priorities for antimicrobial resistance in human health* and *Global research agenda for antimicrobial resistance in human health*.[8 9] These documents describe global research priorities for AMR research
- WHO's *AWaRe classification of antibiotics for evaluation and monitoring of use, 2023*.[10] This document describes the optimal use of antibiotics listed in the WHO Essential Medicines List
- The WHO AWaRe antibiotic book—this provides guidance on the empirical antibiotic choice and regimen for 35 clinical infections for children and adults in primary care and hospital settings[11]
- WHO documents on infection prevention and control and antimicrobial stewardship: *The case for investment and action in infection prevention and control*, *Global report on infection prevention and control 2024*, and *WHO policy guidance on integrated antimicrobial stewardship activities*[12-14]
- Development of national action plans for AMR (see, for example, UK AMR NAP)[15]—this is one of the recommendations of UNGA 2024 as national action plans are implemented in only 68% of countries
- Clinical guidelines for MDR/XDR infections are difficult to compile because of a general lack of high quality clinical trial data for reserve antibiotics.[16] Nevertheless, the ESCMID guidelines for the treatment of infections caused by MDR Gram negative bacilli is a useful and pragmatic document with a planned update in progress at the time of writing.[17] A similar document produced by IDSA, *Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections*, also exists
- WHO global antimicrobial resistance and use surveillance system (GLASS)reports (most recently published in 2022)[18]
- Global AMR R&D hub: Incentivising the development of new antibacterial treatments 2024—a progress report outlining the national action plans and ongoing "push" incentives in G7 nations[19]

AWaRe=Access/Watch/Reserve; ESCMID=European Society of Clinical Microbiology and Infectious Diseases; IDSA=Infectious Diseases Society of America; MDR=multidrug resistant; R&D=research and development; UNGA=United Nations General Assembly; XDR=extensively drug resistant

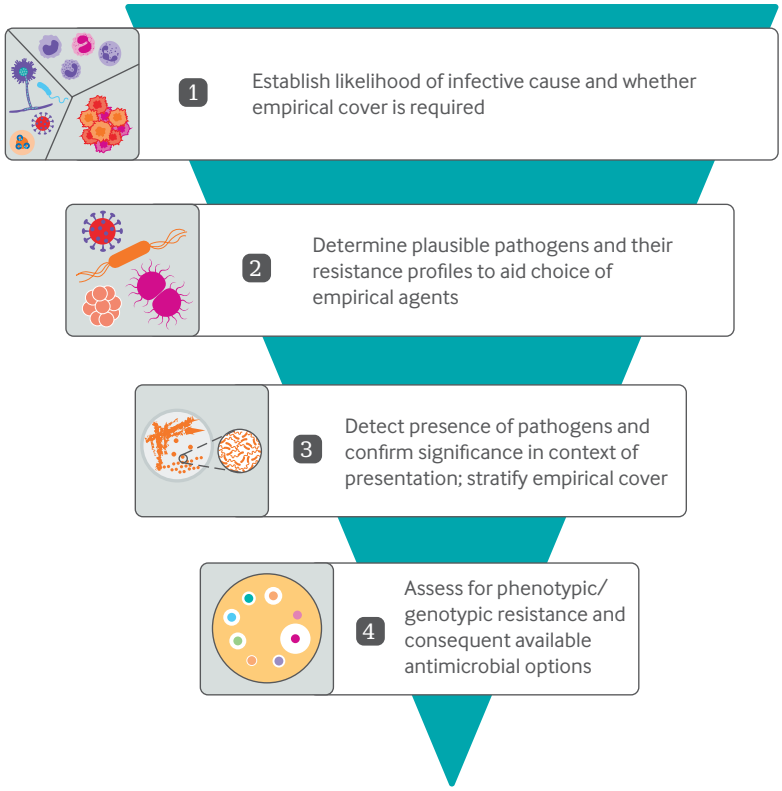

Fig 4 | Conventional diagnostic pathway for antimicrobial resistance, characterised by progressively decreasing proportion of patients reaching each subsequent stage

owing to a range of factors such as cost, time pressure, staff training, and laboratory infrastructure.[111] This highlights the pressing need to maintain the efficacy of antimicrobial agents that are globally accessible and suitable for empirical therapy and can be used widely in community settings.

Hospital based detection

In hospitals, pathogen detection may be more feasible (fig 4, panel 3) and allow antibiotics to be targeted to likely antimicrobial resistance where appropriate. The mainstay of detection uses culture based methods. After a positive culture result, which generally takes 24-48 hours, further phenotypic and genotypic testing for antimicrobial resistance can be undertaken (fig 4, panel 4). Techniques such as matrix assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF MS) are increasingly used in HICs to accelerate bacterial identification,[112] but they are so far not routinely used for detection of antimicrobial resistance.[113 114] Consequently, the definitive detection of antimicrobial resistance (fig 4, panel 4) relies on initial slow culture based methods.

Methods of detection

Assessing for antimicrobial resistance phenotypes traditionally involves culture based in vitro susceptibility testing including disc diffusion, broth microdilution, agar dilution, and E-tests.[115] Specific antimicrobial resistance mechanisms can also be detected through, for example, double disc synergy testing (detection of β-lactamases), the modified Hodge test (detection of carbapenemase production), and other assays.[116] Limitations of these techniques include a lengthy turnaround time, the need for trained staff and a strong laboratory infrastructure, and challenges in identifying antimicrobial resistance genes that are minimally expressed.

Genotypic antimicrobial resistance detection, particularly through nucleic acid amplification tests (NAATs) is increasingly used for microbial identification and detection of antimicrobial resistance motifs. NAATs can detect known antimicrobial resistance genes, including increasingly common cases in which more than one resistance gene is present.

Antimicrobial resistance prevention

Infection prevention and control

The WHO antimicrobial resistance research priorities include the "identification of cost-effective, acceptable and feasible multimodal IPC strategies."[106] Although some recent quasi-experimental studies and randomised controlled trials have assessed the effectiveness of IPC, most examine cost effectiveness overall without an antimicrobial resistance focus, investigate a single pathogen-antibiotic pair (for example, meticillin resistant *Staphylococcus aureus* (MRSA)) without acknowledging wider effects, and/or are conducted exclusively in HICs.[129] Measures such as hand hygiene, targeted screening with decolonisation/isolation, and environmental cleaning may be cost saving/cost effective at reducing healthcare associated infection (HAI) overall, and personal protective equipment shows less benefit.[129] Of all measures, hand hygiene is considered the most effective in reducing HAI.[130] In HICs, IPC alone is unlikely to substantially reduce antimicrobial resistance associated mortality.[131] In LMICs, a 10% increase in adherence to hand hygiene could reduce antimicrobial resistance associated mortality by 4.6%, rising to 7.8% if adherence reaches 80%.[132]

Water, sanitation, and hygiene

WASH measures are considered vital to human health and are part of the United Nations 2030 Sustainable Development Goals. Their role in reducing transmission of antimicrobial resistance, particularly in resource poor and community settings, is highlighted in the WHO antimicrobial resistance research priorities and UNGA 2024.[7 106] WASH also underpins IPC strategies. However, although the evidence is limited, universal WASH coverage in LMICs is estimated to reduce antimicrobial resistance associated mortality by only 4.2%,[132] well below the UNGA 2024 target of 10%.[7]

Vaccination

Vaccination is a key mechanism for tackling antimicrobial resistance in UNGA 2024 and is a WHO antimicrobial resistance research priority.[7 106] Benefits of vaccines may be direct (for example, preventing invasive pneumococcal disease and thereby use of antibiotics)

or indirect (for example, preventing antibiotic use in viral infection). Antiviral vaccines have indirect effects including the prevention of secondary bacterial infection following diseases such as measles or eliminating the need for presumptive antibiotics for a clinical syndrome caused by viral infection (for example, pneumonia).

Even with available vaccines, challenges remain. Efficacy can be variable, particularly in younger age groups.[136] The uptake of available vaccines can vary widely internationally—for example, >95% uptake of the 13-valent pneumococcal conjugate vaccine (PCV-13) in children in Korea and Singapore versus <1% in China and ~10% in Malaysia.[137] Additionally, similar to emergent antimicrobial resistance mechanisms, pathogens can develop pathways to evade vaccine induced immunity. *S pneumoniae* undertakes capsular switching, escaping PCV-13 serotypes. Where uptake is high, PCV-13 serotypes may represent a minority of those in circulation (for example, 37.0% PCV-13 in Korea) with the opposite being true in low uptake regions (for example, 77.2% PCV-13 in Malaysia).[137] However, even with good uptake, PCV-13 serotypes may remain in circulation (for example, 68.7% in Singapore).[137] Notably, antimicrobial resistance in non-vaccine serotypes has increased following the introduction of PCV-13.[137 138]

The complete uptake of vaccines against *S pneumoniae*, *Salmonella typhi*, Group B streptococci (as yet unlicensed), and *H influenzae* B could reduce mortality in the <5 year age group by 9.1%.[132] However, vaccine hesitancy and inequalities in global healthcare limit uptake and therefore derivation of maximum benefit from vaccination.[139]

Antimicrobial stewardship

Antimicrobial stewardship is defined by the UK's National Institute for Health and Care Excellence as "an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness."[140] "Judicious use" of antibiotics depends on the clinical context and is somewhat subjective. Antimicrobial stewardship can include reducing antibiotic consumption (as is recommended in UNGA 2024); improving/refining the choice of antimicrobials to treat predefined target organism(s) while minimising wider effects; and optimising the treatment regimens for chosen antibiotics in terms of dose, schedule, and duration. Antimicrobial stewardship measures may be persuasive (for example, provision of education and feedback to clinicians/patients), structural/systematic (for example, implementation of diagnostic algorithms to guide initiation/selection of antibiotic therapy), enabling (for example, guidelines and antibiotic formularies), or restrictive (for example, control of over-the-counter antibiotic sales or requirements for input from a microbiologist before dispensing of specific antibiotics in hospital settings).[141]

Antimicrobial stewardship interventions can reduce antimicrobial consumption and, in healthcare settings, decrease overall HAI rates. However, evidence for reducing the prevalence of antimicrobial resistance or associated mortality remains limited, particularly in LMICs and community settings.[132 142]

Antimicrobial stewardship interventions can reduce antimicrobial consumption and decrease overall healthcare associated infection rates

Emerging treatments

Non-traditional agents

Despite push and pull initiatives, analyses of global antibiotic pipelines show a lack in both the preclinical and phase 1/2/3 clinical pipelines of small molecule agents with new chemistry exploiting novel microbiological targets that could have the ability to tackle unmet medical needs described in the WHO PPL (box 1).[144] Interest in non-traditional antibiotics is therefore increased, with an increasing proportion (41% in 2023)[145] of such agents in clinical development pipelines. This group includes antibodies, antivirulence agents, bacteriophages and phage derived enzymes, immunomodulators, microbiome modulating agents, and others reviewed elsewhere.[145] Licensed non-traditional agents are limited to three microbiome modulating agents for use in recurrent/refractory *Clostridium difficile* infection.[145] Although the biology that underpins non-traditional therapeutics is often extremely innovative and the overall approach remains attractive, the clinical development pathways are complex. Furthermore, a need often exists for associated expensive diagnostics, making non-traditional agents less suitable for empirical treatment or in resource limited settings.[146 147]

New antibiotics

The development of new antibiotics remains a core component of any strategy to tackle antimicrobial resistance.[7] The requirements for a novel agent are guided by the underlying clinical disease in addition to the potential activity against specific pathogens (fig 5, bmj.com).

As of the most recent WHO pipeline review (2023), 57 traditional antibiotics are in development.[145] Since July 2017, 13 new traditional antibiotics have been approved by a regulatory authority (for example, the US Food and Drug Administration (FDA) or European Medicines Agency (EMA)), of which three belong to a novel antibiotic class. Recently approved compounds and those in active phase 3 studies are discussed in the full version of this article on bmj.com.

Guidelines

Guidelines for the use of novel antibiotics vary considerably internationally, reflecting the very limited evidence base, with most of the new antibiotics in the reserve group. Box 4 describes key policy and clinical guidelines.

Competing interests: See bmj.com.

Patient involvement: No patients were involved in the creation of this article.

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EDITORIAL

Knowledge gaps in coeliac disease

More research and standardisation of care is needed

Coeliac disease is a disorder of acquired loss of immune tolerance to ingested cereal proteins that affects around 1% of the global population.[1] Clinical presentation is highly variable, including gastrointestinal symptoms, extraintestinal manifestations, and asymptomatic disease identified by screening. Performing serological testing on patients while their diet contains gluten is central to the diagnosis. Untreated disease is associated with complications including nutritional deficiency, osteoporosis, infections, and, rarely, malignancy.[2] Nationally and internationally, the screening, diagnostic, and monitoring practices vary considerably for paediatric and adult patients. This heterogeneity, along with "unanswered clinical questions in coeliac disease" raised by Doyle and colleagues' (doi:10.1136/bmj-2024-081353) review in *The BMJ* is a call to address the substantial knowledge gaps that persist. Coordinated, prospective research is needed to address these knowledge gaps, which include: the health and cost effectiveness of mass screening; the optimal role of serological and emerging biomarkers in diagnosis and management; and which drug treatments are effective and how they should be deployed.

Diagnostic considerations

Opinion on "no biopsy" diagnosis continues to vary, which has implications for global standardisation of care and healthcare equity. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American College of Gastroenterology (ACG) endorse no biopsy diagnosis in children with serial markedly raised serum tissue transglutaminase IgA. The American College of Gastroenterology also suggests no biopsy diagnosis for symptomatic adult patients who are unable to undergo upper gastrointestinal endoscopy.[3 4] The European Society for the Study of Coeliac Disease updated guidelines (2025) state that a no biopsy diagnosis is suitable for adults under 45 years of age who have had two separate tissue transglutaminase IgA levels ≥ ten times the upper limit of normal.[5] These guidelines are supported by a meta-analysis of 12 103 participants from 15 countries, wherein an tissue transglutaminase IgA concentration ≥ ten times the upper limit of normal had a specificity of 100% and a positive predictive value of 98% to identify patients with a high pretest probability.[6]

Opinion on 'no biopsy diagnosis' continues to vary

Despite this, most guidelines continue to recommend histological confirmation in most adults, although a successful no biopsy pathway has been adopted in Finland.[4-9] A no biopsy strategy was recommended by the British Society of Gastroenterology during the covid-19 pandemic, which reported cost and time benefits.[10 11] However, variability in assays and upper limits of normal are reported barriers to widespread adoption. In a nationwide UK survey, Alex and colleagues demonstrated substantial inter-laboratory variability in coeliac serology, identifying 12 different transglutaminase IgA assays and wide variation in upper limits of normal (3-30 IU/mL). Upper gastrointestinal endoscopy is not without risks and given the environmental and cost burden, the exploration and widespread adoption of strategies to avoid unnecessary procedures should be considered; and if barriers are identified, the clinician should strive to address them.[14 15]

Screening considerations

Given the debate on serological thresholds, a robust screening programme would have to outline pathways for repeat tests and/or biopsy thresholds.

Another challenge is the inconsistency of international guidance on monitoring progression of the disease. The correlation between symptoms, serology, and mucosal recovery remains unclear.[3-17] Specific thresholds and clinical benefits (reducing villous atrophy and improving disease control) are yet to be determined.[19] Further work is required to position these tests within non-refractory coeliac monitoring.

There is an absence of unified, evidence based guidance for the diagnosis and management of coeliac disease. Prospective, international cohorts, with long term follow-up data, are needed to define serological thresholds and quantify population and individual risk.[9] To minimise unnecessary procedures, "no biopsy" pathways need engagement from clinicians and multidisciplinary teams and investment from healthcare providers. Universal screening might improve equitable diagnosis across diverse populations, although limitations in long term follow-up data and the implications of diagnosing asymptomatic individuals warrants caution. Healthcare providers should strive to resolve these issues—because how they are answered will shape the future delivery of coeliac disease care and improve outcomes of this chronic condition.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.s136

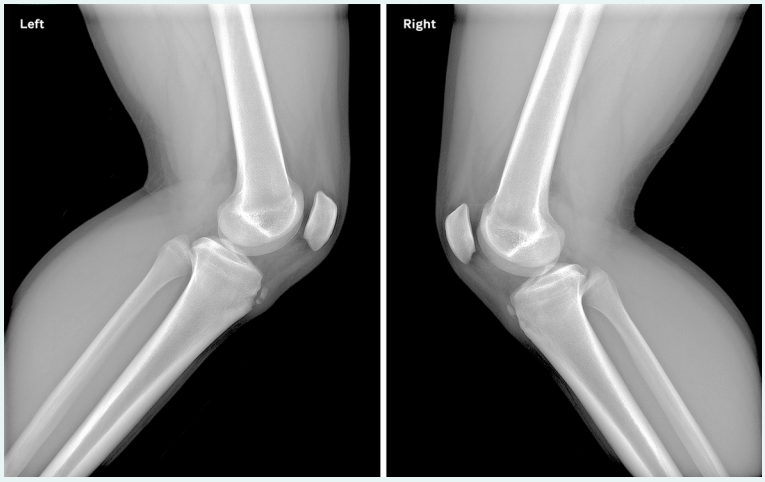
CASE REVIEW

Non-traumatic knee pain in an adolescent boy

A teenage boy presented to the orthopaedic clinic with bilateral knee pain after playing football earlier that day. He reported no trauma or fever, no history of any other joint involvement, or low back pain. He had been a member of the school football team for two years and actively jumped and ran during practices and games. His bilateral knee pain occurred occasionally over the past month, especially after a game, and was relieved by rest. His medical and family histories were unremarkable, with no congenital diseases.

On physical exam, both knees showed mild swelling and noticeable tenderness, with pronounced tibial tubercles. Range of motion was normal. Radiographs revealed bony fragments around the tibial tubercle in both knees with some soft tissue swelling (figure).

1 **What is the most likely diagnosis?**
2 **What is the management?**
3 **What is the prognosis?**



Lateral radiographs of the patient's knees

Submitted by Jiebo Chen, Xueying Zhang, Xiaoxi Li, and Jinzhong Zhao
Parental consent obtained.

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answers

CASE REVIEW **Non-traumatic knee pain in an adolescent boy**

1 What is the most likely diagnosis?

The most likely diagnosis is Osgood-Schlatter disease, or the tibial tubercle osteochondrosis described by Osgood and Schlatter in 1903. The condition is a traction apophysitis of the tibial tubercle, caused by repetitive traction of the patellar tendon on the apophysis of the tibial tubercle, which can be vulnerable to tensile loading before maturation in growing adolescents.

The most likely differential diagnoses in this age group who participate in active sports include tibial tubercle avulsion fracture, Sinding-Larsen-Johansson disease, and patellar tendinopathy. Patients with tibial tubercle avulsion fracture often present with a history of trauma, a sudden onset of symptoms, knee movement limitation, and an irregular fracture line on x ray imaging. Sinding-Larsen-Johansson disease mainly affects the inferior pole of the patella rather than the tibial tubercle. Patellar tendinopathy shows no bony abnormalities on x ray imaging and might show an increased signal in the patellar tendon on MRI.

2 What is the management?

Conservative treatment is the preferred therapy because Osgood-Schlatter disease is conventionally considered to be self-limiting with growth in most cases. Conservative management involves rest, local application of ice, anti-inflammatory drugs, and physical therapy. Bracing or casting the affected knee is generally not recommended. Surgery is rarely indicated for Osgood-Schlatter disease in adolescents, only for severe cases with intolerable symptoms.

3 What is the prognosis?

With accumulating evidence, the long term prognosis of Osgood-Schlatter disease is not as optimistic as previously thought. The traditional belief that Osgood-Schlatter disease follows a benign, non-progressive, self-limiting course has been challenged. Over half of the patients with the condition experienced persistent pain that continued into adulthood.

This case underscores the typical clinical presentation, diagnostic cues, and management of Osgood-Schlatter disease—an overuse injury prevalent in active adolescents.

LEARNING POINTS

- Osgood-Schlatter disease mainly affects active children who participate in jumping and running activities without a history of trauma.
- Key signs of Osgood-Schlatter disease include localised tenderness and swelling at the tibial tubercle, along with characteristic fragments visible on radiography.
- Conservative management might be sufficient in most cases, but targeted strategies are needed to address the potential long term effects of the condition on knee health that persist into adulthood.

PATIENT OUTCOME

See bmj.com.

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0.5 HOURS

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