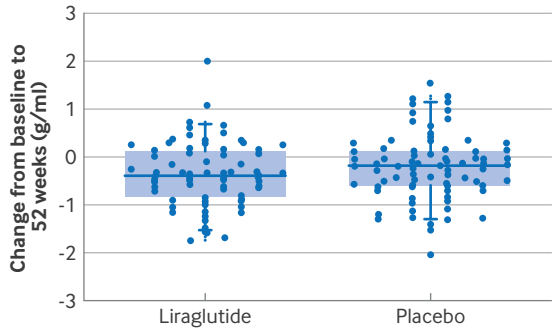
education

RESEARCH REVIEWS Fortnightly round up from the leading medical journals



EDISON P, FEMMINELLA GD, RITCHIE C, ET AL. *NAT MED* 2025 DOI:10.1038/S41591-025-04106-7

Change in cerebral glucose metabolic rate (positron emission tomography (PET) standard uptake value) at 52 weeks between liraglutide and plabebo. Box plot shows the median (centre line) and interquartile range (box limits). Whiskers show 95% confidence intervals

Liraglutide for Alzheimer's disease

It looks as if 2026 is set to be another busy year for glucagon-like peptide-1 (GLP-1) agonists. According to clinicaltrials.gov there are 112 studies involving GLP-1 agonists that are either recruiting or set to start recruiting, across a range of conditions ranging from alcohol use disorder to inflammatory bowel disease. Another potential use for GLP-1 agonists is dementia. The phase 2b ELAD trial assessed the effect of liraglutide in people with mild to moderate Alzheimer's disease without diabetes. No significant difference in the primary outcome, a surrogate outcome of cerebral glucose metabolic rate, was found in the group who received daily injections of liraglutide compared with the placebo group. However, liraglutide was well tolerated and seemed to have a modest effect on cognitive decline over the 12 month study period.

Nature Med doi:10.1038/s41591-025-04106-7

High dose flu vaccine and hospitalisations

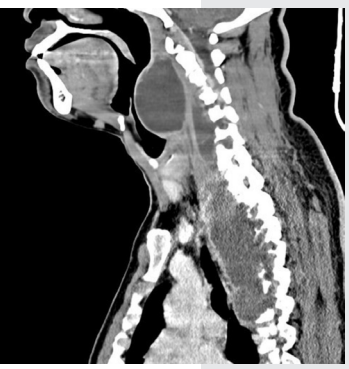
Whenever flu hits the headlines, as it has this winter, attention inevitably turns to the flu vaccine. Might a higher dose be more effective in older adults? A trial set in Denmark randomised adults 65 years of age or older to receive either a high dose or standard dose quadrivalent vaccine. Over three flu seasons they randomised 332 438 participants, and found no clear difference in the primary end point of hospitalisation for flu or pneumonia between the two groups (0.68% in the high dose vaccine group and 0.73% in the standard dose vaccine group).

New Engl J Med doi:10.1056/NEJMoa2509907

Magnesium's fuzzy designs

If there was a prize for a methodological term of the year in 2025 it'd probably go to "causal inference." Journals are now awash with submissions applying new techniques to observational data that try to get closer to establishing cause and effect rather than simply studying associations. When attempting to work out whether treating low magnesium levels in patients on the intensive care unit might improve outcomes, researchers chose a "fuzzy regression discontinuity design." This takes advantage of the fact that having a cut off value between normal and low serum magnesium creates two groups of patients who are likely to be similar in terms of measured and unmeasured confounders but have a marked difference in their chance of receiving treatment—those with a magnesium level just below the cut off will usually receive treatment, whereas patients with levels just above the cut off won't. The fuzzy study found no evidence

CLINICAL PICTURE



Posterior neck pain

A patient in his 30s, who had arrived from Guinea-Bissau nine months earlier, presented to the emergency department with recent onset of odynophagia, dyspnoea, and dysphonia on a background of a posterior neck pain for the past six months. On physical examination, the patient exhibited inspiratory stridor, a bulge in the posterior pharyngeal wall extending to the right piriform sinus, and limited neck mobility. Neurological examination was unremarkable. A computed tomography scan of the neck showed a retropharyngeal abscess and osteolysis of the cervical and thoracic vertebral bodies. Magnetic resonance imaging excluded spinal cord compression.

Empirical antibiotic treatment for deep neck infection (ceftriaxone, clindamycin, and vancomycin) was started and the retropharyngeal abscess was drained transorally under general anaesthesia. He was extubated uneventfully after 48 hours, once a substantial reduction in abscess volume had been confirmed with computed tomography. Microbiological analysis of the pus identified *Mycobacterium tuberculosis* (confirmed by direct microscopy, polymerase chain reaction, and subsequently by culture), *Streptococcus mitis*, *Gemella haemolysans*, and *Veillonella parvula*. Antimicrobial treatment was adjusted accordingly, and the patient completed a prolonged course of ceftriaxone and clindamycin, and 12 months of antituberculosis therapy. After neurosurgical assessment, his neck was stabilised

of an effect of magnesium supplementation on the occurrence of tachyarrhythmia at cut offs ranging from 0.66 mmol/L to 0.82 mmol/L.

JAMA Intern Med doi:10.1001/jamainternmed.2025.6572

Platelet deserts

A platelet desert is a hospital or region that doesn't have access to platelets for transfusion. They arise from a combination of declining donor rates, the short shelf life of liquid platelets (which have to be kept at room temperature), and increased demand from cardiac surgery and oncology services. Cryopreserved platelets offer a potential solution, since they can be stored for up to two years. However, in a double blind randomised control non-inferiority trial set in Australia, dimethyl sulfoxide-cryopreserved platelets were found not to be as effective as liquid platelets when given during cardiac surgery. Results for the primary outcome (post-surgical chest drain bleeding within the first 24 hours following intensive care unit admission) did not reach pre-specified thresholds for non-inferiority. In the cryopreserved platelet arm, 25% of participants received open label platelets in addition to the blinded cryopreserved platelets (compared with just 3.1% in the liquid platelet arm), raising concerns about unmasking caused by higher bleeding rates

in the cryopreserved platelet group. If long life cryopreserved platelets aren't as effective as liquid platelets, could they be better than what's available in platelet deserts? The accompanying editorial doesn't think so, describing cryopreserved platelets as more of a mirage than an oasis.

JAMA doi:10.1001/jama.2025.23355

Under pressure for evidence of shunting

"Small steps, big ventricles" goes the title of an editorial linked to a trial published in the *New England Journal of Medicine*. It describes a condition that nobody seems to want to own, and where many experts remain sceptical about whether it even exists. The big ventricles are those seen in people with normal pressure hydrocephalus; the small steps are the improvements in gait and balance but lack of improvement in cognition or incontinence three months after shunting—an intervention that has been around for decades but lacked a solid evidence base.

New Engl J Med doi:10.1056/NEJMoa2503109

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

Cite this as: *BMJ* 2026;392:r2633

conservatively with a cervical collar for seven months. Following treatment, he had no ongoing symptoms and no neurological deficits once the treatment was complete.

Retropharyngeal abscess in adults is rare and often secondary to direct extension from chronic tuberculosis of the cervical spine (Pott's disease). Early diagnosis and treatment with at least 12 months of antituberculosis therapy, cervical stabilisation (with surgical intervention when indicated), and abscess drainage are essential to prevent life threatening complications.

Francisca Bartolomeu (11757@ulscoimbra.min-saude.pt) Catarina Rato, Otorhinolaryngology Department at ULS Coimbra, Portugal

Patient consent obtained.

Cite this as: *BMJ* 2025;392:e084126

MINERVA From the wider world of research

Screening for testicular cancer

Although testicular cancer is the most common malignancy in young men, a study of Israeli conscripts shows that screening is unlikely to be helpful (*Am J Epidemiol* doi:10.1093/aje/kwaf241). Detecting a single case of cancer required physical examination of 75 000 men, 176 ultrasound investigations, and 112 urology consultations. Most cancers were diagnosed at stage 1, regardless of whether they were detected by screening.

Are humans doomed?

Having read a compelling essay in the *London Review of Books* (https://www.lrb.co.uk/the-paper/v47/n21/david-runciman/are-we-doomed), Minerva is sorry to have to tell you that the answer is yes. The only question is when. As a species, *Homo sapiens* is roughly 300 000 years old. Because it is unlikely that we are at the very beginning or the very end of the human story, we have probably got somewhere between 8000 and 12 000 000 years to go. Mind you, as our projected rate of population growth is only a few decades from going into reverse, even 8000 years might be optimistic.

Antihypertensive treatment in frail patients

A post hoc analysis of a large trial of intensive blood pressure treatment in China found, unsurprisingly, that frail people were more likely to experience adverse events than people who were not frail (*J Am Coll Cardiol* doi:10.1016/j.jacc.2025.08.092). Adverse events, however, were no more common in those receiving intensive treatment (target blood pressure <120 mm Hg) than in those receiving less intensive treatment. What's more, the benefits of intensive treatment in reducing cardiovascular events were as great in frail people as in people who weren't frail. The conclusion is that frailty should not be a barrier to intensive blood pressure control.

Sudden cardiac death

In the United States, rates of sudden cardiac death declined by 2% per year between 1999 and 2018 (*J Am Heart Assoc* doi:10.1161/JAHA.124.040340). The majority of deaths occurred in older people and were linked to coronary artery disease. The fall can largely be attributed to population level improvements in cholesterol levels, blood pressure, and smoking. Better treatment of heart failure and increased use of implantable cardioverter-defibrillator devices may also have helped. Unfortunately, since 2020, rates of sudden cardiac death have surged, perhaps because of a deterioration in access to healthcare since the covid-19 pandemic.

Coffee and atrial fibrillation

Coffee's reputation for causing arrhythmias may be undeserved. Two hundred coffee-drinking adults who had undergone a successful electrical cardioversion for atrial fibrillation or atrial flutter were randomised either to regular caffeinated coffee consumption (at least one cup daily) or abstinence. Over the next 6 months, coffee drinkers were 40% less likely to experience a recurrence of their arrhythmia than the abstainers (*JAMA* doi:10.1001/jama.2025.21056).

Cite this as: *BMJ* 2026;392:r2628

PRACTICE POINTER

Ask an expert: Gout

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This article was adapted from a BMJ Learning module Ask an expert: Gout: https://new-learning.bmj.com/course/10055705

CPD READING
0.5 HOURS

LEARNING MODULE
See learning.bmj.com for linked learning module

Rheumatologist Edward Roddy provides expert answers to GPs' questions on common challenges with managing gout, including treating flares, initiating urate lowering therapy in patients and appropriate target serum urate levels, and counselling patients on the diagnosis and treatment of gout.

WHAT YOU NEED TO KNOW

- Preferred treatments for flares of gout include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroid drugs
- Do not offer NSAIDs to older patients with multiple comorbidities, such as cardiovascular disease and chronic kidney disease
- Consider offering urate lowering therapy early in the course of the disease, and aim for a target serum urate level below 360 µmol/L (6 mg/dL)
- Evidence to indicate that any specific diet prevents flares or lowers serum urate levels is insufficient; therefore advise patients to follow a healthy, balanced diet

BMJ Learning

TEST YOURSELF

You are treating a 62 year old woman for her recurrent flares of gout and tophi with allopurinol. Over a period of four months, you gradually increase the dose of allopurinol. Her serum urate level is lowered successfully to 297 µmol/L. She then experiences a further flare of gout, which affects her first metatarsophalangeal joint.

With regard to this new flare of gout, which one of the following is correct?

a. Treat the flare with colchicine and continue allopurinol during the flare

b. Treat the flare with colchicine and stop allopurinol during the flare

c. The occurrence of a flare suggests that treatment is not working, and you should increase the dose of allopurinol

d. The occurrence of a flare suggests that treatment is not working, and you should switch the allopurinol to febuxostat

e. The occurrence of a flare suggests that treatment is not working, and you should refer the patient to a specialist.

(Answer at end of article)

What do you recommend in terms of management and follow-up for patients with a gout flare?

Most flares should respond quickly to one of the preferred treatments (described below), which are recommended in UK national guidance.[1] In addition, the guidelines recommend applying an ice pack to the affected joint.[1 2]

A non-steroidal anti-inflammatory drug (NSAID)

There is no evidence that any particular NSAID is superior to any other, so offer any immediate release NSAID at full dose (eg, naproxen) guided by your patient's preference, renal function, and comorbidities.[3] Avoid indometacin because of the risk of gastrointestinal, renal, and cardiovascular adverse events.[3-5] Offer gastro protection in addition to a NSAID, for example 20 mg of omeprazole.[3]

Low dose colchicine

Offer colchicine at a dose of 500 µg orally two to four times daily until symptoms are relieved, up to a maximum of 6 mg per course.[6] A randomised trial compared naproxen or colchicine for people with a gout flare and found no difference between the groups in pain intensity for seven days, but adverse events were more common in the colchicine group with the most common one being diarrhoea.[7]

Short course of a corticosteroid drug

A corticosteroid drug is an option for management of a gout flare, although in the UK, this is an off-label use.[1]

- Oral prednisolone is an effective option, for example 30 mg once a day for five days.[3 8]
- You might consider an intra-articular or intramuscular injection of a corticosteroid drug if NSAIDs and colchicine are contraindicated, not tolerated, or ineffective, especially in patients who are older and have multiple comorbidities.

Follow-up

Guidelines from both National Institute for Health and Care Excellence (NICE) and the British Society for Rheumatology recommend reviewing a patient after a gout flare has settled, or four to six weeks later.[1 3] This is to:

- Measure the serum urate level and renal function
- Provide information on how to self-manage and reduce the risk of future flares
- Assess comorbidities including cardiovascular risk factors (eg, obesity, hypertension, hyperlipidaemia, diabetes) and chronic kidney disease

- Assess predisposing lifestyle factors such as excessive alcohol consumption
- Review medications (eg, diuretics)
- Discuss the benefits of long term urate lowering therapy.

Referral criteria

In general, if the diagnosis of gout is uncertain or if treatment is contraindicated, not tolerated, or ineffective, you should refer the patient to a specialist, as outlined in UK national guidance.[1] The most important alternative diagnosis that should not be missed is infection: septic arthritis (box 1) or osteomyelitis. If there is clinical suspicion of infection, then refer the patient as an emergency to a rheumatologist or an orthopaedic surgeon, according to the local care pathway.

Non-infective causes of an acute hot, swollen joint include calcium pyrophosphate crystal deposition and reactive arthritis. Therefore, microscopic examination of synovial fluid that has been aspirated from the affected joint provides an opportunity to confirm a diagnosis of crystal arthritis and differentiate gout from calcium pyrophosphate crystal deposition. The necessary experience and practical skills to perform joint aspiration might not be present in all settings (eg, primary care), and you might need to refer a patient to a specialist for this.

In an older patient with multiple comorbidities, what is the best option to treat a gout flare?

NSAIDs are contraindicated for use in older patients with multiple comorbidities (eg, cardiovascular disease and chronic kidney disease). In accordance with the British National Formulary, in a gout flare, the normal dose of colchicine is 500 µg orally two to four times daily until symptoms are relieved, up to a maximum of 6 mg per course.[6] In an older patient with comorbidities, you can cautiously treat a flare with colchicine, but increase the interval between doses (ie, 500 µg two times daily).[6] Review the drug interactions that potentially increase the toxicity of colchicine (box 2).

Corticosteroid drugs are an effective treatment for a gout flare and provide a valuable treatment option in patients who cannot tolerate, or have contraindications to, NSAIDs and colchicine.

- According to small observational studies, expert consensus, and clinical experience, intra-articular aspiration and injection of a corticosteroid drug are highly effective in a monoarticular gout flare and could be the treatment of choice in patients with a gout flare in a large joint and comorbidity.[3 5] However, there are no randomised controlled trials of intra-articular injection of a corticosteroid drug for a flare of gout, and it is an off-label indication.[13] You should refer a patient to a specialist for this treatment.
- Intramuscular injection of a corticosteroid drug is a useful option in patients with oligoarticular or polyarticular flares.[3]

Box 1 | Distinguishing septic arthritis from a gout flare

Flares of crystal arthritis (either gout or pseudogout) are characterised by sudden onset, severe joint pain that reaches its peak intensity within 12 to 24 hours of onset, joint swelling and erythema, and complete resolution, typically within one to two weeks.[1 4]

If these features are present, and the first metatarsophalangeal joint is affected, then gout is the most likely diagnosis.[9] Onset of septic arthritis is typically less acute.

Traditional markers of infection such as fever and raised white cell count, erythrocyte sedimentation rate, and C reactive protein might be absent or only modestly raised in people with septic arthritis.[10] Conversely, fever might be a feature of a gout flare, and white cell count, erythrocyte sedimentation rate, and C reactive protein might be grossly raised. As a result, traditional markers of infection are not useful to distinguish septic arthritis from gout flares.[11 12]

The only way to definitively distinguish septic arthritis from a gout flare is to aspirate the affected joint before starting antibiotics, and arrange crystal examination, Gram stain, and culture of the aspirated fluid.[9]

- Oral prednisolone is also an option. Four randomised controlled trials of oral prednisolone for a gout flare show comparable pain relief to NSAIDs.[8-16] In these trials, a four or five day course of prednisolone was given at a dose of either 30 mg or 35 mg daily. Following these trials, a clinically credible approach is to offer a short course of prednisolone (eg, 30 mg daily for 5-7 days). In my experience, a rebound gout flare after stopping oral steroid drugs does not appear to be a common problem.

Box 2 | Possible drug interactions that increase the risk of colchicine toxicity[4]

- Amiodarone
- Ciclosporin
- Digoxin
- Diltiazem
- Fibrate drugs
- Antifungal drugs (itraconazole, ketoconazole)
- Macrolide antibiotic drugs
- Protease inhibitor drugs
- Statin drugs
- Verapamil

When should I offer a patient urate lowering therapy to prevent a gout flare?

UK national guidelines recommend that you should offer urate lowering therapy to all patients with gout who have[1]:

- Multiple or troublesome flares
- Chronic kidney disease stages 3 to 5
- Diuretic therapy
- Tophi
- Chronic gouty arthritis.

The British Society of Rheumatology guidelines also recommend urate lowering therapy for patients with[3]:

- Uric acid urolithiasis
- Primary gout starting at a young age
- Evidence of joint damage on radiograph.

Both guidelines recommend making patients aware of the option of urate lowering therapy after their first or subsequent flare.[1 3] In my experience, many people are not offered urate lowering therapy until they have frequent troublesome flares or have developed joint damage or tophi.

With respect to timing, offer urate lowering therapy two to four weeks after a gout flare has settled, but if flares are more frequent, it can be started during a flare.[1] There is growing consensus that you should consider starting urate lowering therapy early in the course of the disease, and discuss this with your patient.[1-4] This is because most patients with gout experience recurrent flares, and imaging studies show chronic crystal deposition both at the time of the first flare, and in hyperuricaemic patients who are yet to have a gout flare.[17-19] Two small placebo controlled randomised trials found that starting allopurinol during a flare first with flare treatment and then with continued colchicine or NSAID prophylaxis, did not increase pain, inflammation, or flare recurrence when assessed at 28 to 30 days.[20 21]

Delaying the start of urate lowering therapy, however, until after the flare has settled and the patient is no longer in pain, allows the patient to better absorb information about their treatment.[4] For example, the patient should know how to treat a further flare, and not to discontinue urate lowering therapy if a flare occurs.[3] Continuing urate lowering therapy once a flare has occurred does not affect the duration or severity of the flare. Furthermore, if it is stopped during a flare, the patient might be reluctant to start it again afterwards because of the perception that the drug has worsened their gout. If urate lowering therapy is restarted, start at a low dose and gradually increase it again.

Patients should not stop the urate lowering drug in the event of a flare

Should urate lowering therapy be used to reach a target serum urate level?

The objective of urate lowering therapy in all patients is to lower serum urate below its physiological saturation threshold in body tissues (the target level). Lowering serum urate to below this level causes existing crystals to dissolve and prevents new crystals from forming. Treating to target stops flares, shrinks tophi so they eventually disappear, and prevents long term joint damage.[22-24] Even once the therapeutic target is achieved, it can take several months for existing monosodium urate crystals to clear, flares to stop, and tophi to reduce in size.

The NICE guideline recommends that you aim for a target serum urate level below 360 µmol/L (6 mg/dL).[1] The guidelines also suggest a lower target serum urate level, below 300 µmol/L (5 mg/dL), for people with gout who:

- Have tophi or chronic gouty arthritis
- Continue to have ongoing frequent flares despite having a serum urate level below 360 µmol/L (6 mg/dL).

Start with a low dose of urate lowering therapy and measure serum urate levels every four weeks to guide dose increases, as tolerated, until the target serum urate level is reached.[1]

UK national guidelines recommend offering either allopurinol or febuxostat as the preferred treatment when starting urate lowering therapy, taking into account the patient's comorbidities and preferences.[1] In patients who have major cardiovascular disease (eg, previous myocardial infarction or stroke, or unstable angina), offer allopurinol as the preferred treatment.

How to manage a flare when starting urate lowering therapy

Warn your patient that they might experience a flare when starting or titrating urate lowering therapy because all urate lowering drugs can cause a flare of gout.[25] Advise patients that such a flare is a "sign of successful treatment" rather than a side effect of the medication. Patients should not stop the urate lowering drug in the event of a flare.

The following might help to reduce the risk of a flare of gout:

- Start urate lowering therapy at a low dose and titrate the dose up slowly[26]
- Consider co-prescribing prophylactic medication, such as colchicine, but be aware of drug interactions (box 2).[1] If colchicine is contraindicated, not tolerated, or ineffective, consider a low dose NSAID, or a low dose oral corticosteroid drug[1]
- As an alternative to prophylaxis, you can prescribe a short course of colchicine, an NSAID, or an oral corticosteroid drug for the patient to keep in reserve in case a flare occurs.[1]

If neither colchicine, NSAIDs, nor corticosteroid drugs are suitable, an interleukin 1 inhibitor could be

considered to prevent gout flares when starting or titrating urate lowering therapy, but this would require referral to a rheumatology service before prescribing.[1]

Do you have any tips on how we can counsel patients in primary care?

All patients with gout should be given a clear verbal explanation of the nature, causes, associations, consequences, and treatment of gout.[1 27] It is helpful to support this with written information, such as a patient information booklet on gout from Arthritis UK.[28] Box 3 outlines examples of key messages I give to patients related to the cause of gout, how it affects people, and how it is treated.

Risks of stigma about alcohol and diet might prevent people from seeking healthcare for gout, so questions about diet and alcohol consumption should be asked sensitively. Although people often assume gout is caused by excessive consumption of alcohol and certain foods such as red meat and seafood, studies show that the risk of gout increases only with high levels of consumption.[29] People with gout who are overweight or obese or drink alcohol excessively should be supported to lose weight and reduce their alcohol consumption, respectively. There is insufficient evidence that any specific diet prevents flares or lowers serum urate levels and people with gout should be advised to follow a healthy, balanced diet.[1]

This is a lot of information to convey in a typical 10 to 15 minute consultation, so it should be reinforced at future appointments.[1] It could be effectively delivered in a clinic led by nurses, as shown by a randomised trial comparing care led by nurses with usual care led by GPs in people with gout.[30] Nurses delivered an individualised package of care over multiple appointments, consisting of holistic assessment, discussion of perceptions of illness, and providing information about gout including its nature, causes, associations, consequences, and treatment options. The nurses shared decision making with the patient, which was combined with gradual escalation of urate lowering therapy to achieve the target level of serum urate. Results at two years showed that with care led by nurses, 95% of participants achieved a target urate level compared with 30% of participants with usual care led by GPs, which was statistically significant (risk ratio 95% *v* 30%, relative risk 3.18, 95% confidence interval 2.42 to 4.18, P<0.001). Patient centred outcomes such as number of flares, tophi, and quality of life were also better with care led by nurses.

Box 3 | Examples of key messages when discussing gout with patients

Cause

- People get gout because the level of urate in their blood is too high, causing urate crystals to form in the cartilage lining the joint. If urate levels remain high, crystals form slowly but continuously, often without causing symptoms
- Urate levels can be high for many reasons including a person's medical conditions, the drugs they take, their genetic make up, and whether they are overweight or obese. Offer the patient an individualised explanation of their personal risk factors for gout
- Gout is often assumed to be caused by drinking too much alcohol or eating too much red meat and seafood, but this is often not true for many people

Effects

- Occasionally, some crystals "spill out" into the joint causing a flare of gout when the joint becomes painful, inflamed, and swollen
- Over many years, these flares can become more frequent and spread to affect other joints
- Lumps of crystals called tophi can form over the joints under the skin and cause damage to the joint cartilage in the joint and bone. This damage to the joint can cause regular day to day pain

Treatment

- Flares can be treated with colchicine, NSAIDs, or corticosteroid drugs
- The aim of treating gout (with drugs such as allopurinol) in the long term is to lower the level of urate below the target level. If the level can be lowered enough and kept low, then new crystals will stop forming and existing crystals will dissolve and eventually disappear altogether. Drugs to lower urate levels usually need to be taken for life
- When there are no crystals left, flares of gout stop, tophi reduce in size (and may eventually disappear), and joint pain due to gout improves
- Starting allopurinol can sometimes set off a gout flare. If this happens, it is not a side effect but a sign that allopurinol is working. The flare has occurred because the urate level is being lowered and crystals are starting to dissolve. The flare can be treated in the same way as any other flare of gout and the allopurinol does not need to be stopped

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r2248

TEST YOURSELF (REVISITED)

A (Treat the flare with colchicine and continue allopurinol during the flare) is the correct answer.

This patient has achieved the therapeutic target serum urate level, indicating that she is taking an appropriate dose of allopurinol. However, even once the therapeutic target is achieved it can take several months for existing monosodium urate crystals to clear, flares to stop, and tophi to reduce in size, although flares will become less frequent. Treat this flare as any other.

Although it is standard advice to delay starting urate lowering therapy until the flare has resolved in order to prevent worsening of the flare, do not stop allopurinol if a flare occurs once urate lowering treatment has already begun; instead, continue at the same dose alongside the treatment for the flare, in this instance with colchicine.[3]

There is no need to switch the allopurinol to febuxostat. UK national guidelines suggests that if people have ongoing symptoms, you can consider referring them to a rheumatologist.

Since she has only had one flare you should be able to manage her in primary care and referral to a specialist is not warranted at present.

STATE OF THE ART REVIEW

Advances in the pathophysiology, diagnosis, and management of coeliac disease

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This is a summary of Clinical Review Advances in the pathophysiology, diagnosis, and management of coeliac disease. The full version can be read here: https://www.bmj.com/content/391/bmj-2024-081353

0.5 HOURS

Coeliac disease is common, affecting about 1% of the general population, and has become increasingly prevalent in recent decades.[1-5] Prevalence of coeliac disease is higher in certain populations, including those with a genetic predisposition,[6] certain autoimmune disorders, or a first degree relative with coeliac disease.[7] Despite its prevalence and long term complications, coeliac disease remains under-diagnosed owing in part to its heterogeneous clinical presentation across the lifespan.[1 4]

Coeliac disease is characterised pathologically by a loss of immune tolerance to ingested cereal proteins, which are commonly referred to as gluten.[11] A strict gluten-free diet is the recommended treatment for coeliac disease, but its therapeutic efficacy is limited by variable adherence rates,[12-14] frequent inadvertent exposure to gluten,[15 16] and psychosocial and economic burdens.[17-19]

This review examines recent advances in our understanding of the epidemiology, pathophysiology, diagnosis, and management of coeliac disease.

Epidemiology

Trends in global prevalence and incidence of coeliac disease

The global prevalence of coeliac disease is estimated to be between 0.7% and 1.5% in the general population.[1-3] A meta-analysis of epidemiological studies found that the global prevalence of coeliac disease as estimated by serological testing alone was 1.4%, whereas the biopsy based prevalence was 0.7%.[3] Prevalence also varies geographically: within Europe and North America, northern latitudes may be associated with higher coeliac disease prevalence than southern latitudes, with particularly high rates in Sweden and Finland.[5 20]

The prevalence and incidence of coeliac disease have been increasing over the past several decades.[3 5 23 24] One meta-analysis of population based studies found that the incidence of coeliac disease has increased by 7.5% per year since the latter half of the 20th century.[23] This trend seems to have continued in the past decade: a population based cohort study in Canada found that the incidence of positive coeliac disease related serologies increased between 2015 and 2020 despite stable testing rates.[24]

Environmental effects

The increasing incidence of coeliac disease suggests that environmental factors are playing a role, but precise environmental effects have not been identified. Birth cohort studies and randomised controlled trials that explored the timing and amount of gluten exposure in early childhood produced mixed results with no strong evidence for a protective effect of specific feeding practices.[6 26-28] Globally, the relation between regional gluten availability and prevalence of coeliac disease has shown mixed associations.[29] Neither duration of breast feeding nor mode of birth reliably predicts the development of coeliac disease.[26 30]

Infections during childhood and adulthood, particularly those of the gastrointestinal tract, may be linked to a higher risk of coeliac disease autoimmunity.[31 32] Exposure to antibiotics has also been associated with development of coeliac disease, but robust data are lacking.[31 33] Alterations in the gut microbiome, which have been shown in children and adults with coeliac disease, have also been hypothesised as a possible trigger for development of coeliac disease, but a causal relation has yet to be established.[34 35]

Genetic risk factors

The risk of coeliac disease is higher in first degree family members of individuals with coeliac disease, presumably owing in part to shared genetic risk factors.[6 36] Human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 haplotypes are the most dominant predisposing genetic risk factors for coeliac disease and are found in nearly all individuals with coeliac disease.[37] Dozens of non-HLA alleles identified through genome-wide association studies have also been associated with increased risk of coeliac disease, which may help to explain the phenotypic variability seen in its presentation.[38 39]

WHAT YOU NEED TO KNOW

- Coeliac disease is an immune mediated disorder characterised by the loss of tolerance to ingested gluten in genetically susceptible individuals
- It remains under-diagnosed owing to its heterogeneous clinical presentation, which includes intestinal and extra-intestinal symptoms in children and adults
- People without symptoms who are in high risk groups, such as those with certain autoimmune conditions or first degree relatives with coeliac disease, should be considered for screening
- A strict gluten-free diet is the current treatment for coeliac disease

Pathophysiology

Coeliac disease is characterised by acquired loss of immune tolerance to cereal proteins and the development of a pro-inflammatory, gluten-specific CD4-positive ($CD4^+$) T cell response. Gluten drives inflammation, but the environmental trigger is enigmatic, may be encountered early in life,[40] and may vary between individuals.

Molecular and genetic basis of coeliac disease susceptibility

HLA alleles that confer genetic susceptibility recognise cereal-derived peptides and are considered necessary but not sufficient for disease development.[37] Mouse models of coeliac disease involve both the introduction of HLA-DQ2 or HLA-DQ8 and additional genetic modifications to potentiate intestinal inflammation.[41] Several overlapping epitopes for HLA-DQ2.2, HLA-DQ2.5, and HLA-DQ8 are contained within α2-gliadin (a protein fragment within gluten), which is rich in proline residues that confer resistance to pepsin and trypsin digestion and rich in glutamine.[42] Selective deamidation of the glutamine residues by tissue transglutaminase-2 and elastase introduces negative charges that increase HLA-DQ2 and HLA-DQ8 binding affinity.[43]

Role of tissue transglutaminase

Much of our understanding of the pathophysiology of coeliac disease (figure) derives from studies of patients with established disease. The multifunctional enzyme tissue transglutaminase-2 plays a central role, as evidenced by the efficacy of the tissue transglutaminase-2 specific inhibitor ZED-1227 in preventing gluten induced duodenal mucosal damage.[46] Most people with coeliac disease produce tissue transglutaminase IgA autoantibodies in a gluten dependent manner.

Gliadin specific $CD4^+$ T cells

Tissue transglutaminase-2 and gliadin specific plasma cells in the lamina propria are the dominant antigen presenting cells in established coeliac disease.[48,49] The antigen presenting cell that initially activates $CD4^+$ T cells when gluten tolerance is first broken has not been identified. Candidates include CD11c-positive, CD103-positive dendritic cells and intestinal epithelial cells.[50,51] Direct antigen presentation by intestinal epithelial cells is an appealing explanation because it implies that tissue transglutaminase-2 from shed enterocytes interacts with gliadin in the lumen where gluten concentrations are maximal.[52] Furthermore, intestinal epithelial cells expressing major histocompatibility complex (MHC) class II molecules have increased expression of CD71,[51] a receptor that has been shown to mediate retrotranscytosis of IgA-gliadin complexes.[47]

Delivery and presentation of immunogenic gluten peptides

Whereas short polypeptides resulting from microbial digestion of gluten may be transported via the paracellular leak pathway,[43] passage of larger gluten peptides necessary to elicit a T cell response likely occurs via transcellular pathways such as CD71 mediated retrotranscytosis,[51] low density lipoprotein receptor related protein 1 mediated endocytosis of gliadin-tissue transglutaminase-2-α2-microglobulin complexes,[47] or persorption of intact gliadin via goblet associated pathways.[53] Once activated, gluten reactive $CD4^+$ T cells produce inflammatory cytokines, including interferon γ, interleukin 21, and interleukin 2. Given the apparent specificity of gluten reactive $CD4^+$ T cells for coeliac disease,[54] cytokine release assays are being developed as a disease biomarker.[55-57]

Role of cytotoxic CD8 positive intraepithelial lymphocytes

Activation of gut homing, gluten reactive $CD4^+$ T cells is a critical event in the pathogenesis of coeliac disease, yet the condition has classically been defined by the $CD8^+$ T cell mediated enteropathy that ensues.[58] Cytotoxic $CD8^+$ T intraepithelial lymphocytes in coeliac disease are characterised by up-regulation of NKG2D and CD94/NKG2C receptors, which interact with MHC class I chain related protein A (MICA) and HLA-E, respectively.[59] These observations support the prevailing view that cytotoxic $CD8^+$ T intraepithelial lymphocytes are licensed to kill in the context of epithelial stress.

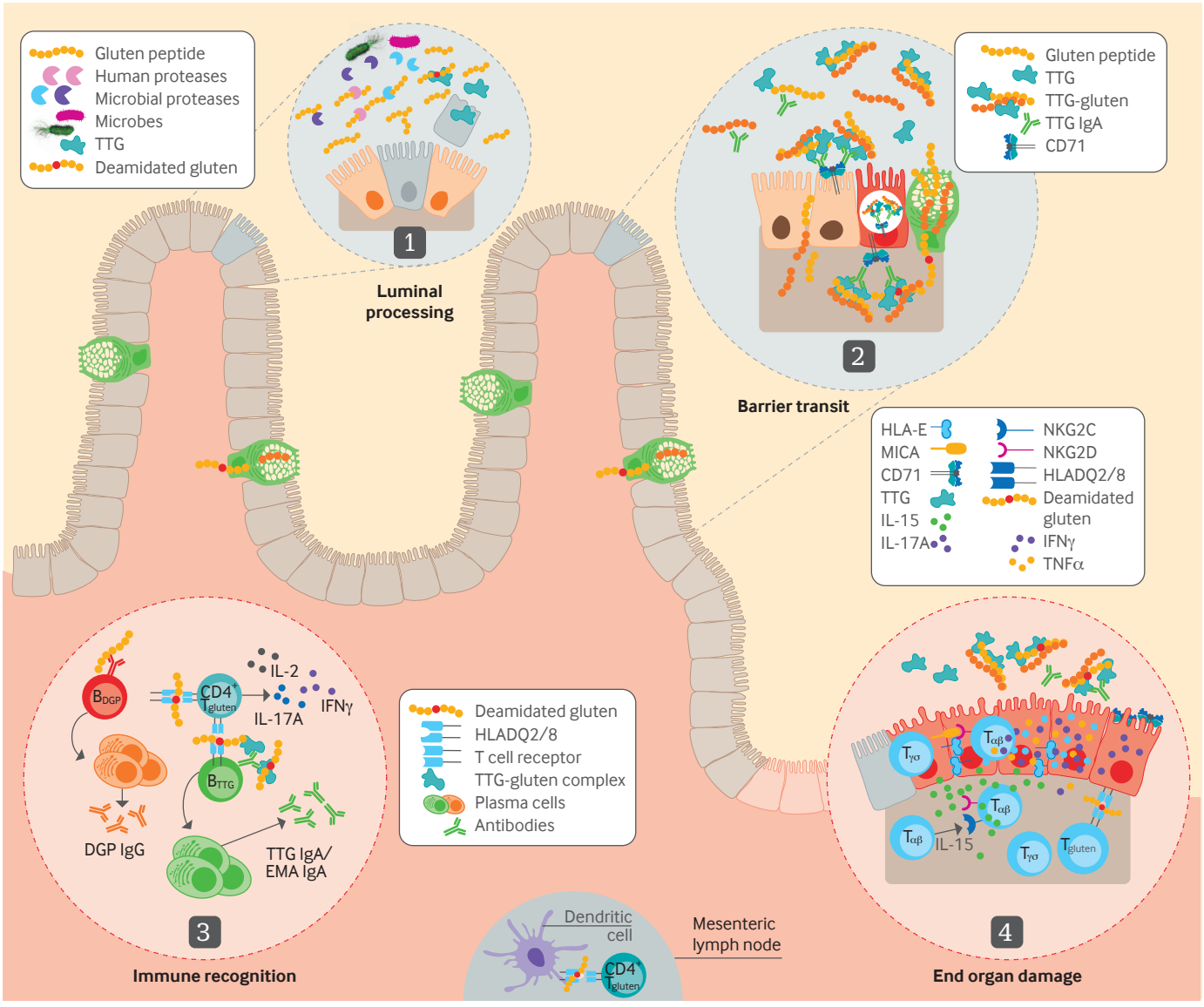
Role of the innate immune system

Innate immune signalling likely has a role in the pathogenesis of coeliac disease and involves a T helper type 1 response. A conserved non-immunogenic α2-gliadin peptide (residues 31-53) activates the innate immune system by a yet-to-be-defined mechanism,[63,64] whereas an immunogenic deamidated α2-gliadin peptide (residues 57-89) activates toll-like receptor 4.[65] Non-gluten proteins (for example, wheat amylase tryptase inhibitors) also have innate immune activity.[66] In this context, viruses and bacteria may act as adjuvants to potentiate the adaptive immune response.

Clinical presentation, diagnosis, and screening

Clinical presentation

Classically, coeliac disease presented with signs and symptoms of malabsorption such as diarrhoea, steatorrhoea, or weight loss/growth failure. Recent evidence suggests that, although being underweight is more common among people with a diagnosis of coeliac disease than the general population, most are of normal weight or overweight at presentation.[67] Furthermore, "non-classical" presentations without symptoms of malabsorption have become more prevalent in all age groups.[68] Non-classical presentations include extra-intestinal symptoms such as fatigue, joint pain, and headaches, as well as gastrointestinal symptoms such as bloating or abdominal pain. Non-classical gastrointestinal symptoms are non-specific to coeliac disease and overlap with disorders of gut-brain interaction.[69,70] Some people report such symptoms after gluten ingestion but do not meet diagnostic criteria for



Pathophysiology of coeliac disease. Ingested protein is digested and post-translationally modified in the lumen by human and microbial enzymes that can increase or decrease toxicity of gluten. Some of these peptides can passively diffuse between epithelial cells, but most are transported via transcellular pathways. Deamidation (eg, by tissue transglutaminase-2 (TTG-2)) greatly increases affinity for HLA-DQ2/DQ8. Sources of TTG include sloughed epithelial cells that leak TTG into the lumen. TTG also binds itself to gluten and can be transcytosed by epithelial cells in a CD71 mediated manner or persorption via goblet associated pathways. Recent studies show that in the presence of interferon-γ, intestinal epithelial cells can express MHCII on basolateral membrane and activate gluten reactive CD4$^+$ T cells directly. Although gluten reactive T cells may be initially activated in the mesenteric lymph nodes, once coeliac disease is established the predominant antigen presenting cell is B lymphocytes in the lamina propria. Antigen presenting cells can endocytose gliadin-TTG-2-α2-microglobulin complexes in a low density lipoprotein receptor related protein 1 dependent manner and present gliadin peptides on HLA-DQ2/DQ8. Epithelial damage is mediated by aβ-T intraepithelial lymphocytes bearing NKG2D and CD94-NKG2C, which are activated in the presence of interleukin 15 and recognise stress induced ligands on epithelial cells, including MICA/MICB, and are not gliadin specific. TNF=tumour necrosis factor. Figure originally created in BioRender. Silvester J. (2025) https://BioRender.com/xzwcm6j

coeliac disease, a condition referred to as non-coeliac gluten sensitivity.[71]

Many extra-intestinal manifestations of coeliac disease should prompt serological screening (table). Dermatitis herpetiformis, characterised by itchy papulovesicular lesions on the legs, arms, and buttocks, is considered a hallmark extra-intestinal manifestation precipitated by exposure to gluten.[72] Oral aphthous stomatitis and tooth enamel defects are also characteristic.[73] Gluten ataxia, an idiopathic sporadic ataxia with positive antigliadin antibodies, can occur even in the absence of duodenal enteropathy.[71]

Many people do not have symptoms of coeliac disease but have a diagnosis made during the investigation of common laboratory abnormalities such as iron deficiency anaemia or elevated aminotransferases. A meta-analysis of epidemiological studies found that more than 1 in 30 adults with iron deficiency anaemia have coeliac disease.[74] Coeliac disease has also been cited as a cause of otherwise unexplained aminotransferase elevation, which may resolve with a gluten-free diet.[75 76]

Diagnostic criteria for coeliac disease

Antibodies to tissue transglutaminase-2 are the first line screening test for coeliac disease, and a small intestinal endoscopic biopsy showing characteristic features of intraepithelial lymphocytosis, crypt hyperplasia, and villus atrophy is considered the gold standard confirmatory test.[58 73 77-81] These findings are manifestations of gluten induced immune activation. Consequently, normal test results cannot exclude coeliac disease in patients on a gluten-free diet.

Serology

Antibodies to tissue transglutaminase-2, specifically tissue transglutaminase IgA and anti-endomysial antibody (EMA), are the essential screening tools for coeliac disease. Both tissue transglutaminase IgA and EMA recognise the same autoantigen, so results are highly correlated.[58 78] In a large international prospective cohort study, tissue transglutaminase IgA had a high sensitivity (98.0%) and specificity (75.0%) for the detection of duodenal villus atrophy in adults with suspected coeliac disease.[83] Tissue transglutaminase IgA antibodies are also highly sensitive and specific in paediatric populations.[84]

Given that development of autoantibodies to tissue transglutaminase-2 is exceedingly rare in people without HLA-DQ2 and/or HLA-DQ8 haplotypes, HLA genotyping may be useful for ruling out coeliac disease in individuals in whom the diagnosis is unclear, including those who have already adopted a gluten-free diet.[86]

Histology

Upper endoscopy with multiple duodenal biopsies (including at least four from the distal duodenum and one to two from the duodenal bulb) is the gold standard diagnostic tool for coeliac disease in all age groups.[73] Sampling of the duodenal bulb in addition to the more distal duodenum increases diagnostic yield and can identify individuals with ultra-short coeliac disease,[88] with positive serologies and villus atrophy confined to the first portion of the duodenum.[89]

Mucosal changes associated with coeliac disease can be classified according to Marsh-Oberhuber criteria, with higher grades corresponding to villus atrophy, crypt hyperplasia, and presence of intraepithelial lymphocytes.[90 91] Complete villus atrophy (Marsh-Oberhuber grade III) has a high specificity for coeliac disease. However, clinicians should rule out other causes of duodenal villus atrophy, including common variable immunodeficiency, infection (for example, tropical sprue, giardia), drug induced changes (for example, angiotensin receptor blockers, especially olmesartan), and inflammatory bowel disease.[82 92]

Alternative confirmatory tests

In 2012 the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) endorsed use of EMA IgA in a second blood sample and permissive HLA genotype as an alternative to biopsy for diagnosis of coeliac disease in children with malabsorptive symptoms and a tissue transglutaminase IgA >10 times the upper limit of normal.[94]

Evidence supporting a serology based diagnosis in adults first surfaced nearly three decades ago[97] and has been validated in more recent prospective cohorts, including the use of DGP IgG rather than EMA as a confirmatory test.[83 98] A recent analysis found that tissue transglutaminase IgA concentrations ≥10 times the upper limit of normal had a positive predictive value of 98% for identifying individuals with coeliac disease, suggesting that serologic diagnosis may have a role in adults at moderate to high risk with a high pre-test probability of coeliac disease.[99]

Associated high risk conditions in which coeliac disease screening is appropriate

Organ system(s)	Disorders
Endocrine	Type 1 diabetes, autoimmune thyroid disease (Hashimoto's thyroiditis and Grave's disease), Sjögren's syndrome
Gastrointestinal	Irritable bowel syndrome, microscopic colitis, inflammatory bowel disease, autoimmune atrophic gastritis
Liver	Autoimmune hepatitis, unexplained liver enzyme elevations
Pancreas and spleen	Hyposplenism or functional asplenia, idiopathic pancreatitis
Neurological	Unexplained ataxia, peripheral neuropathy
Gynaecological	Delayed menarche, premature menopause
Genetic conditions	Down's syndrome, Turner syndrome, Williams syndrome
Miscellaneous	Iron deficiency, dermatitis herpetiformis, IgA nephropathy, IgA deficiency, chronic fatigue syndrome, recurrent aphthous stomatitis, tooth enamel defects

Screening people without symptoms

Serological screening is recommended in certain individuals without symptoms who are at high risk for developing coeliac disease. This includes first degree relatives of patients with coeliac disease, who have approximately seven times the risk of developing coeliac disease as the general population.[58 73 79 100] Screening is also appropriate in people with strongly associated diseases or genetic conditions (see table). In some contexts, the association is strong enough that serological screening can be considered at multiple time points: screening can be considered at two and five years after diagnosis of type 1 diabetes, for instance, or at an increased frequency (for example, every two years) among genetically predisposed children with affected first degree relatives.[36]

Morbidity and mortality in coeliac disease

Morbidity

People with coeliac disease have an increased risk of developing other autoimmune diseases, presumably owing to a shared genetic predisposition and/or immune activation driven by exposure to gluten. The most well established association is among patients with type 1 diabetes, in whom the prevalence of coeliac disease is between 5.1% and 6.0%.[111] Multiple population based studies have shown that coeliac disease is also positively associated with autoimmune thyroid disease, juvenile idiopathic arthritis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease, among other conditions.[112-115]

Coeliac disease is also associated with liver diseases including autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis.[118 119] People with coeliac disease also seem to be at increased risk of fatty liver disease associated with metabolic dysfunction.[75 120]

Coeliac disease is associated with other systemic disease states, although the causal pathway is not clear. For instance, population based studies have shown that individuals with coeliac disease have increased risk of developing and dying from cardiovascular disease.[8 123] Older adults with coeliac disease also have increased rates of end stage renal disease and frailty.[124 125]

Cancer and mortality

A nationwide cohort study found that coeliac disease was associated with an overall increased risk of cancer relative to the general population (hazard ratio 1.11).[9] A strong association exists between coeliac disease and non-Hodgkin's lymphoma, particularly enteropathy associated T cell lymphoma.[9 126 127] In a nationwide case-control cohort study in France, people with coeliac disease were four times more likely to develop non-Hodgkin's lymphoma than matched controls.[127]

People with coeliac disease have an increased risk of overall mortality, driven in large part by malignancy. In a large population based cohort study from Sweden, people with coeliac disease had a small but significant increased risk of mortality relative to controls (hazard ratio 1.21), with increased risk of death from cancer, cardiovascular disease, and respiratory disease.[8]

Dietary treatment

Gluten-free diet

Lifelong avoidance of dietary wheat, barley, and rye—referred to as a gluten-free diet—is the recommended treatment for coeliac disease. Intestinal and extra-intestinal symptoms are expected to improve within two to four weeks of starting a gluten-free diet.[130] Serologies can normalise within the first year of starting a gluten-free diet and often decline significantly within months of starting.[131 132] To provide education about a gluten-free diet, multiple international guidelines recommend evaluation by a dietitian, preferably with expertise in coeliac disease, soon after diagnosis.[73 77 133]

Limitations of gluten-free diet

Adherence to a gluten-free diet varies widely despite best efforts by care givers and patients. In a systematic review of 49 studies of children with coeliac disease, rates of "adequate" adherence ranged from 23% to 98%.[14] Surveys of adults have found similarly high rates of non-adherence.[12 13]

Inadvertent exposure to gluten seems to be common among patients on a gluten-free diet. Among 18 adults with reportedly good adherence to a gluten-free diet, two thirds had detectable amounts of gluten immunogenic peptides in stool or urine over just 10 days of observation[15]; in most exposures, the gluten source could not be identified and was unsuspected.[16] "Gluten-free" food labelling, defined by the Codex Alimentarius Commission as food containing <20 ppm gluten,[135] is critical to gluten-free diet adherence and is supported by evidence that gluten doses above 50 mg/day (which may occur on ingesting sufficient quantities of foods with >20 ppm gluten) can result in intestinal damage in people with coeliac disease.[136]

Although coeliac disease related symptoms generally improve within weeks of starting a gluten-free diet, 50-60% of patients experience persistent symptoms

The difficulty of gluten-free diet adherence can lead to hypervigilance among people with coeliac disease. One cross sectional study of 80 teenagers and adults with coeliac disease found that hypervigilance was associated with significantly lower quality of life scores.[17] The burden of maintaining a gluten-free diet can be particularly difficult and socially isolating for children and adolescents.[18] Specialty gluten-free products are often more expensive than gluten containing equivalents, creating an economic burden for patients with coeliac disease.[19]

Persistent symptoms on gluten-free diet

Although coeliac disease related symptoms generally improve within weeks of starting a gluten-free diet, 50-60% of patients experience persistent symptoms.[130 138] Inadvertent gluten exposure is the most common cause of ongoing symptoms, which manifests as persistent mucosal damage.[139] As such, identifying and eliminating sources of gluten in a gluten-free diet is critical in patients with ongoing symptoms.

Long term management and monitoring

Evaluation of dietary adherence

Given that the most common cause of persistent coeliac disease activity is ongoing gluten ingestion, consistent long term follow-up with a dietitian is paramount.[73 77 133] This enables close monitoring of the nutritional balance of a gluten-free diet, which can be low in essential vitamins and fibre and high in processed or fatty foods.[121 143] Studies have linked gluten-free diets to weight gain and cardiovascular disease.[144 145] Validated patient questionnaires, such as the Biagi Score and the Coeliac Disease Compliance Assessment Test, are useful tools in the evaluation of persistent symptoms of coeliac disease and may be superior to subjective self-reporting in monitoring adherence to a gluten-free diet.[133 146 147]

Serological monitoring

Monitoring serologies is recommended after initiation of a gluten-free diet in patients with coeliac disease.[133] Serologies that remain persistently positive or do not decline after a gluten-free diet is started may suggest ongoing exposure to gluten over time.[131 148] Of note, complete normalisation of serology often takes longer (more than a year) in children with more severe disease at the time of diagnosis.[149] Although tissue transglutaminase IgA is recommended for serological monitoring,[133] recent evidence suggests

that DGP IgA titres may correlate better with recent gluten exposure.[150] Importantly, however, serological monitoring does not reliably predict either symptoms attributed to coeliac disease or persistent mucosal injury.

Role of follow-up endoscopy with biopsy

High quality evidence is lacking on the routine performance of follow-up duodenal biopsy in patients with asymptomatic coeliac disease without concerning clinical features. Recent consensus based guidelines recommend against a routine re-biopsy strategy, but if this is done they advise waiting at least 12-24 months after diagnosis to allow time for mucosal healing on a gluten-free diet.[133]

A primary goal of follow-up endoscopy in patients with coeliac disease is to identify individuals with persistent duodenal villus atrophy. Persistent villus atrophy has been found in 23-53% of patients on follow-up biopsy, and predicting it non-invasively can be difficult because it is not associated with symptoms or coeliac disease specific serologies.[140 151-156]

Persistent villus atrophy on follow-up biopsy may be linked to worse long term outcomes. A large population based cohort of patients with coeliac disease in Sweden found that persistent villus atrophy on follow-up biopsy was associated with an increased risk of developing lymphoproliferative disorders and osteoporotic fractures.[128 156]

Urinary and faecal gluten immunogenic peptides

Measurement of gluten immunogenic peptide (GIP) concentration in the urine or stool is a promising tool for monitoring adherence to a gluten-free diet and detecting inadvertent gluten exposure. Following gluten ingestion, GIPs can be detected in urine for up to 24-48 hours and in stool for up to seven days, and their concentration seems to correlate with the amount of gluten ingested.[158-160] Multiple prospective studies have shown that measurement of GIP, particularly faecal GIP, is more sensitive than standardised questionnaires, food diaries, symptom assessment, and serologies in detecting exposure to gluten in patients with coeliac disease.[16 161 162]

Refractory coeliac disease

Refractory coeliac disease (RCD) is diagnosed in patients with ongoing malabsorptive symptoms and persistent enteropathy on follow-up biopsy despite strict adherence to a gluten-free diet for at least a year.[71] A diagnosis of RCD is rare, being estimated to occur in just 0.3-0.5% of patients with coeliac disease.[164 165] Symptoms such as diarrhoea, nutritional deficiencies, weight loss, anaemia, and hypoalbuminaemia predominate.[166]

Given its rarity and poor prognosis, patients with RCD should be treated at referral centres with expertise in coeliac disease. Corticosteroids, most commonly open capsule budesonide, are the first line treatment.[166]

Emerging therapies

Drug therapies to augment a gluten-free diet are a priority for coeliac disease related research. Although no drug therapy for coeliac disease has yet been approved, some promising therapeutic mechanisms are:

Degradation of intraluminal gluten—Peptidases that degrade intraluminal gluten and prevent the formation of immunogenic gliadin peptides may be able to prevent downstream immune activation from inadvertent gluten exposure. Several have shown promise in early phase clinical trials

Transglutaminase inhibition—Blocking gliadin deamidation with tissue transglutaminase inhibitors, which may reduce immune activation by decreasing availability of modified gluten peptides that bind HLA-DQ2/DQ8, is also being explored

Immune tolerance induction—Several strategies to induce immune tolerance are in clinical trials for coeliac disease and other immune mediated conditions with known driver antigens. For example, TAK-101 is an intravenously delivered nanoparticle containing encapsulated gluten proteins that is taken up by antigen presenting cells in the liver and spleen, thereby reducing presentation and subsequent activation of $CD4^+$ T cells[182]

Tight junction modulators—Drugs that decrease mucosal permeability by modulating tight junctions in the intestinal epithelium have been studied with mixed results

Monoclonal antibodies—Monoclonal antibodies against interleukin 15, a cytokine involved in cytotoxic T cell activation, may decrease intraepithelial lymphocyte expansion after gluten exposure in coeliac disease, but early studies have yet to show attenuation of mucosal injury after a gluten challenge[186]

Other therapeutic strategies—Many other therapeutic strategies are under investigation. For instance, genetically modified gluten may allow patients with coeliac disease to safely consume low immunogenic wheat products.[189] Sequestering agents that bind gluten in the intestinal lumen and prevent uptake in the gut also hold promise.[190] Manipulating the microbiome, which is altered in people with coeliac disease, is another potential therapeutic strategy in the future.

Guidelines

Many European and North American societies have published or endorsed guidelines on the screening, diagnosis, and management of coeliac disease in adults and children.[58 73 77-81 100 133] Most guidelines currently require a biopsy proven diagnosis of coeliac disease in adults, but in children a non-biopsy approach has been endorsed by the European Society for Paediatric Gastroenterology and Nutrition and conditionally by the American College of Gastroenterology.[58 73] Following diagnosis, strict adherence to a gluten-free diet with the support of a dietitian is uniformly recommended.

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WHAT YOUR PATIENT IS THINKING

Joining the dots with peer support

Suzanne Baldwin describes the challenges of advocating for care when experiencing unexplained symptoms

CPD READING
0.5 HOURS

PRIYA SUNDRAM

WHAT YOU NEED TO KNOW

- Patients may suggest that their symptoms are connected. Listen and acknowledge their suggestions, even if the descriptions don't fit a common pattern
- Patients with rare conditions may benefit from specialist groups or communities where they can connect with others
- Peer support groups can provide patients with much wanted information on their conditions; try to acknowledge this in consultations

Following a bout of suspected covid-19 in 2023, I developed a chest infection and began to experience severe breathlessness. I received diagnoses of inducible laryngeal obstruction and interstitial lung disease, was given inhalers, and was sent away with a few shrugged shoulders.

A year later I was admitted to hospital with pneumonia, with oxygen saturation readings of 66%. Fortunately, oxygen and intravenous antibiotics worked quickly. Investigations showed my lungs were operating at about half their expected capacity, and that I had ground glass opacities, inflammation, bronchiectasis, and scarring. I was also experiencing all-over itching, sore cracked skin on my fingers, Raynaud's phenomenon, a sensitive larynx, and several months of dysphonia. On the surface there seemed to be no connection between my symptoms. I began to research them endlessly, despite being advised not to go looking online. The more I learnt, the more I started to suspect they may be connected, as symptoms of an autoimmune disorder.

Forced into the driving seat

I went back to the GP, primarily because of the itching I was experiencing, and shared my suspicion that this could be autoimmune. She listened, and decided to send me for a detailed blood test. I was relieved to be heard, finally, and the results of the test pointed to a diagnosis of anti-synthetase syndrome. During this time I felt I had to take the lead on research and to come up with possibilities to explore. It seemed that everyone I saw was focused on one symptom, but no one was stepping back to look at the bigger picture. I was very fatigued and at times frightened by the breathlessness. I found it difficult to advocate for myself while my physical health was so poor.

The new diagnosis meant I came under the care of a great specialist rheumatology and respiratory team, which was reassuring, but the information they were able to give me on the condition was limited. This meant I still had to do more research online to understand the complexity of the condition—resorting to reading scientific research papers, because the condition I have was only briefly mentioned in an NHS information pack on arthritis. Although I like reading in this level of detail, not everyone would, or could, and what I found was frightening, as my condition is progressive, more severe for some than others, and frequently associated with increased mortality. This made me anxious and low. I was prescribed immunosuppressants and a course of steroids, which came with a lot of unpleasant side effects. I was warned by the team to an extent, but didn't know that my moods, thinking ability, and sleep would become as bad as they did.

> I felt I had to take the lead on research

Finding support

I finally have some psychological and informational support via a global online group for people with anti-synthetase syndrome. It connects the small number of people around the world that have the condition. This has given me a community and an idea of others' experiences and treatment options. It is a source of moral support, although sporadically deaths are announced (usually lung related), which is difficult.

My healthcare team are great and spend time discussing my care with me. I feel, however, that they know somewhat less than I do about the many different aspects of anti-synthetase syndrome. I suspect this is common for rare conditions. I think they recognise this as they previously doubted that my all-over itching was connected to the diagnosis, but when I showed them the many similar experiences of the online community, they listened and proposed an additional immunosuppressant, which does help. I feel the team are working with me now but I wish health professionals would identify and put patients in touch with communities like this, as it has been so helpful for me.

Patient author

Cite this as: *BMJ* 2026;392:r2549

EDUCATION IN PRACTICE

- How can you ensure you are exploring a possible connection between a patient's symptoms?
- Where can you find information on peer support groups or communities for patients with rare conditions?

CASE REVIEW

A new and increasingly common pattern of soft tissue injury

A woman in her 20s presented to the burns centre 28 days after sustaining an injury to the medial aspects of both her thighs. The patient reported one occasion of recreational use of nitrous oxide before developing the wounds. This involved stabilising a nitrous oxide canister between her thighs while inflating balloons with the gas to inhale. She noted that her skin had become red initially but did not perform any first aid. The next day there was blistering of the affected areas which prompted a visit to a local medical walk-in centre, where her wounds were dressed and oral clarithromycin was prescribed for a suspected, but unconfirmed, wound infection. She was referred to our burns centre after the wound failed to improve.

She had no relevant medical history and was not taking any regular drugs. On examination, the patient had necrotic areas to both medial thighs covering a total body surface area of 0.3% (figure). There was no evidence of infection or vascular compromise to her lower limbs. Wound swab cultures grew *Staphylococcus aureus* and *Serratia marcescens* from both thighs.

1 **What is the most likely diagnosis?**
2 **How would you manage this patient?**
3 **What are the potential complications of this condition?**

Submitted by Minh Tri Jonathan Van, Laura Cappuyns, Dilnath Gurusinghe, and Kayvan Shokrollahi
Patient consent obtained.
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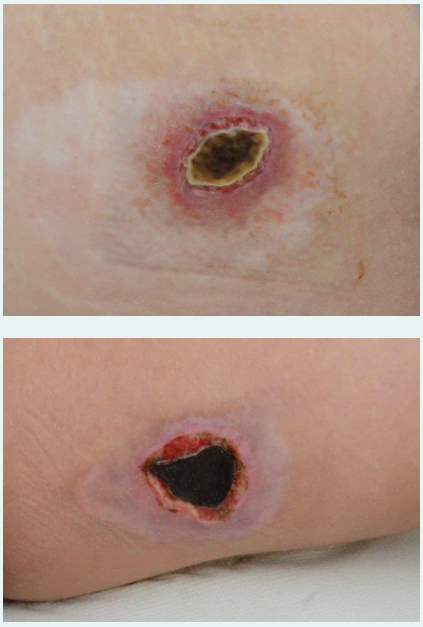

Necrotic wound on bilateral medial thighs

answers

CASE REVIEW **A new and increasingly common pattern of soft tissue injury**

1 What is the most likely diagnosis?

Frostbite injury secondary to contact with a nitrous oxide canister.

Frostbite is defined as a tissue injury sustained when exposed to low ambient temperatures (usually below 0.53°C) resulting in a gradual cellular and vascular injury, tissue ischaemia, and necrosis. The presence of black eschar over the wound bed with concentric areas of active wound healing, the anatomical distribution of the wounds, together with the patient history supports the diagnosis of frostbite injury. The mechanism of injury involved the placement of a nitrous oxide canister between the thighs while inflating balloons with nitrous oxide to inhale for recreational use. The canister can reach temperatures of −40°C during use, which can cause rapid frostbite when the can is in direct contact with skin or through regular clothing.

The incidence of frostbite injuries secondary to contact with nitrous oxide canisters has been increasing in the UK, and legislation has been enacted to limit access to nitrous oxide.

2 How would you manage this patient?

The initial management of frostbite from contact with nitrous oxide canisters during recreational use is similar to the management of conventional frostbite injuries. First aid for frostbite injuries is useful when the presentation is early, which consists of rapid rewarming by immersion of the affected area in water combined with an antiseptic solution (chlorhexidine or povidone iodine) maintained at 37°C to 39°C. Continue rewarming until the affected skin appears purple/red, which might take up to an hour. Rewarming can be painful, and analgesia is recommended.

Maintain body temperature after rewarming and prevent refreezing of the area. Elevate affected areas and avoid constrictive clothing to reduce oedema and maintain peripheral perfusion, respectively. All patients should be referred to a burns service because most injuries are deep and require surgical debridement and reconstruction, typically with skin grafts.

3 What are the potential complications of this condition?

Complications include wound colonisation, invasive infection, need for surgery and skin grafting, and permanent scarring.

PATIENT OUTCOME

See bmj.com.

LEARNING POINTS

- Frostbite secondary to contact with a nitrous oxide canister is uncommon but incidence is increasing in some settings, such as the UK.
- The pattern and mechanism of injury differ from conventional frostbite, but the pathophysiology is similar with vascular injury, tissue ischaemia, and necrosis.
- Management of frostbite injuries requires prompt referral to a specialist burns service because surgery and reconstruction might be required.

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

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