education

RESEARCH REVIEWS Fortnightly round up from the leading medical journals

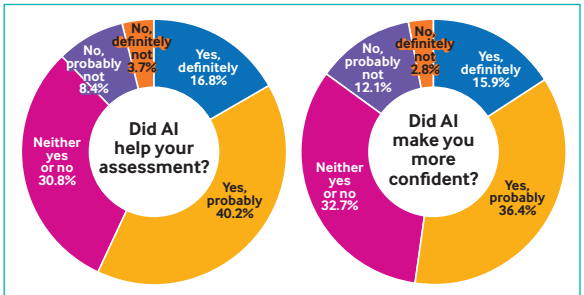
Statin adverse events in trials

The long lists of side effects on summaries of product characteristics (SmPCs) are based mainly on non-randomised and non-blinded studies, which might be subject to bias. The Cholesterol Treatments Trials Collaboration set out to draw up a more reliable list of undesirable effects of statins with a meta analysis of individual participant data from randomised control trials. The analysis of data from more than 100 000 participants and 19 trials found that in addition to the well documented risks of muscle symptoms and diabetes, the only other adverse events from statins were small increased risks of abnormal liver function tests, urinary composition alteration, and oedema. They found no additional risk of cognitive impairment, depression, sleep disturbance, or sexual dysfunction.

Lancet doi:10.1016/S0140-6736(25)01578-8

Another lipid lowering option

Despite the above reassuring findings about statin adverse events, there is still a large group of people who either can't or won't take a statin but who may benefit from lowering their cholesterol. General Practice Quality and Outcomes Framework leads, trawling through lists of patients to add "statin declined" and "statin not tolerated" codes, know this all too well. That's where proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors may start to play a wider role. A phase 3 trial of enlicitide decanoate assessed the effects of the oral PCSK9 inhibitor on low density lipoprotein levels after 24 weeks. It found a 57.1% reduction of levels of low density lipoprotein from baseline in the enlicitide group (95% confidence interval −61.8% to −52.5%), versus just 3% in the placebo group. In contrast to the statin trials, there was no



General cardiologists responses to using AMIE, a large language model-based experimental medical artificial intelligence system

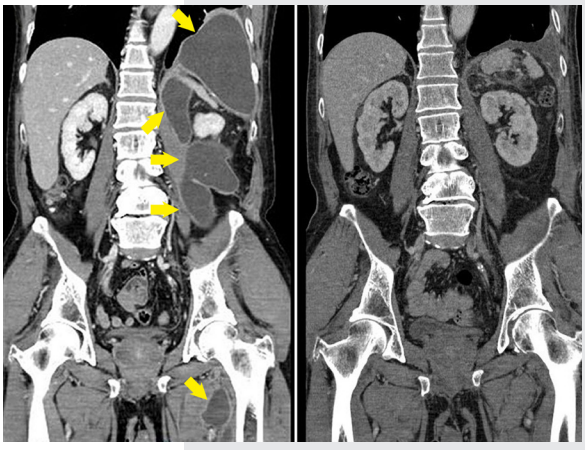
O'SULLIVAN JW, PALEPU A, SAAB K, ET AL. *NAT MED* 2026 DOI:10.1038/S41591-025-04190-9

thanK you aIMee

Trials of large language models that assist with clinical assessment and diagnosis seem careful to stress that they aim to augment the doctor's role, rather than replace it—at least for now. The latest trial is of Google's Articulate Medical Intelligence Explorer (AMIE). Cardiologists were asked to assess patients suspected of having a genetic cardiomyopathy with or without AMIE, an AI assistant that produced an assessment on the basis of clinical details and a text based chat interface. Nine general cardiologists from Stanford assessed 107 patients; they made fewer errors with the help of AMIE and gave generally positive reactions to their experience.

Nat Med doi:10.1038/s41591-025-04190-9

CLINICAL PICTURE



Black pleural effusion

A man in his 60s presented with a six month history of shortness of breath, left sided chest pain, and left thigh swelling. He had chronic pancreatitis related to alcohol use and continued to drink 70 units of alcohol a week.

Physical examination showed reduced breath sounds on the left side and mild tenderness in the left thigh. Laboratory tests showed elevated serum amylase (722 U/L; reference range 44 to 132 U/L) and lipase (1068 U/L; reference range 16 to 51 U/L). Computed tomography imaging showed left sided pleural effusion, cystic lesions extending from the retroperitoneum to the left thigh (arrows in figure, left), and pancreatic calcifications consistent with chronic pancreatitis. Endoscopic retrograde cholangiopancreatography confirmed pancreaticopleural and pancreaticoperitoneal fistulas associated with a pancreatic tail pseudocyst.

Pancreaticopleural fistulas occur in 3-7% of patients with pancreatitis, resulting from pseudocyst rupture or pancreatic duct disruption which allow pancreatic secretions to track through the retroperitoneum to the pleural space.

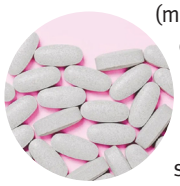
This patient underwent thoracentesis, draining 1.2 L of black pleural fluid with raised levels of amylase (24 280 U/L; reference range <100 U/L) and lipase (78 471 U/L; no

difference in the incidence of adverse events between the enlicitide and placebo groups.

N Engl J Med doi:10.1056/NEJMoa2511002

Semaglutide for heart failure

A secondary analysis of the SOUL randomised controlled trial examined the effect of oral semaglutide on heart failure events in people with type 2 diabetes, atherosclerotic cardiovascular disease/chronic kidney disease, and heart failure. The hazard ratio (HR) for the composite outcome of time to first hospital admission for heart failure, urgent heart failure visit, or cardiovascular death, was 0.78 (95% confidence interval (CI) 0.63 to 0.96) compared with placebo. The improvement in heart failure events due to semaglutide seems to be driven by participants with heart failure with preserved ejection fraction (HR 0.59, 95% CI 0.39 to 0.86); no clear benefit was seen in those with reduced ejection fraction (0.98, 0.7 to 1.38).



JAMA Intern Med doi:10.1001/jamainternmed.2025.7774

Evidence for grief interventions

Prolonged grief disorder (PGD) was added to the World Health Organization's International Classification of Diseases (ICD-11) in 2018. PGD is characterised by severe, intense symptoms of grief that impact on daily living and persist for more than six months (or 12 months in the narrower diagnostic criteria in the 2022 update of *Diagnostic and Statistical Manual of Mental Disorders*, DSM-V). A new systematic review synthesised available randomised control trial evidence on interventions for bereaved people. There are only a few small trials assessing psychotherapeutic interventions in people with PGD, leading to a conclusion that the current strength of evidence for this intervention is low. Stronger evidence (moderate strength of evidence) was found for psychotherapy on grief disorder symptoms and general grieving symptoms.

Ann Intern Med doi:10.7326/ANNALS-24-03679

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

Cite this as: *BMJ* 2026;392:s259

established reference range, abnormal when markedly elevated above serum lipase reference range). Black pleural fluid, caused by haemolysis of blood exposed to pancreatic enzymes, is highly suggestive of a pancreaticopleural fistula. Raised levels of pleural fluid amylase may also indicate malignancy, oesophageal rupture, or uncomplicated pancreatitis.

The cystic lesions and pleural effusion resolved after nasopancreatic drainage of the fluid collections and decompression of the pancreatic duct with stenting to reduce further fluid leakage (figure, right).

Ken Yamamoto; Masayuki Murata (masayuki.murata.097@m.kyushu-u.ac.jp), Kyushu University, Fukuoka, Japan

Patient consent obtained.

Cite this as: *BMJ* 2026;392:e086279

MINERVA From the wider world of research

Social media and adolescent development

The relation between social media use and adolescent wellbeing may not be as simple or linear as many people believe. In a large Australian cohort followed over three years, moderate after-school social media use was associated with better wellbeing than either heavy use or none at all (*JAMA Pediatr* doi:10.1001/jamapediatrics.2025.5619). Although heavy users were more likely to report low wellbeing in early adolescence, non-users had worse outcomes later on. The patterns varied by age and sex.

Paracetamol during pregnancy

Ideas that paracetamol use during pregnancy causes harm to the offspring receive little support from a systematic review of 43 studies (*Lancet Obstet Gynaecol Women's Health* doi:10.1016/S3050-5038(25)00211-0). The review found no evidence that prenatal exposure to paracetamol increased the risk of autism, attention deficit/hyperactivity disorder, or intellectual disability. The strongest data came from sibling-comparison studies that were judged least vulnerable to confounding.

Pregnancy and risk of multiple sclerosis in the offspring

By contrast, it looks as if exposures in pregnancy influence later susceptibility to multiple sclerosis. In a Norwegian cohort of more than 1.3 million births, being born large for gestational age or being exposed to maternal diabetes carried a higher risk of adult-onset multiple sclerosis, whereas being small for gestational age was associated with a lower risk (*JAMA Neurol* doi:10.1001/jamaneurol.2025.5255). Preterm birth, hypertensive disorders of pregnancy, and placental abruption showed no association.

Lymph node metastasis

Neoplastic metastasis to regional lymph nodes is so common that it is easy to forget how paradoxical it is, given that lymph nodes are packed with lymphocytes that are cytotoxic to tumour cells. Part of the explanation may lie in mitochondrial transfer. Experimental work in mice suggests that cancer cells hijack mitochondria from surrounding immune cells, weakening immune function while activating interferon-mediated evasion pathways within the tumour (*Cell Metab* doi:10.1016/j.cmet.2025.12.014).

Carbon dioxide

Five mass extinctions have occurred during Earth's history and, except for the last, which followed an asteroid strike, all were caused by large releases of carbon dioxide into the atmosphere. CO_2 is present only in trace amounts (about 0.04%) in air, but its molecular structure allows it to absorb infrared radiation, making it a primary regulator of planetary temperature. Of course, it is also a primary substrate for photosynthesis, on which almost all life ultimately depends (*New York Review* https://www.nybooks.com/articles/2026/01/15/its-a-gas-the-story-of-co2-mckibben/).

Regulation of journals

Medicine, nursing, and the drug industry are all heavily regulated, and an article in *Nature* asks why academic publishing is an exception (doi:10.1038/d41586-025-04099-w). It argues that independent scrutiny of scientific journals would raise standards for both readers and authors and help restore trust in the scientific literature. Regulations, however, are toothless unless they can be enforced, and Minerva thinks that this might be hard to achieve.

Cite this as: *BMJ* 2026;392:s251

PRACTICE POINTER

Assessment and management of galactorrhoea

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Galactorrhoea is the discharge of milk or milk-like fluid from the breasts that is not associated with childbirth or breastfeeding (non-puerperal lactation).[1] It is a clinical sign rather than a disease entity and can be physiological, pathological, or pharmacological. It is reported to occur in around 20-25% of all women at some point in their lives.[2] Galactorrhoea most commonly affects premenopausal women, but it can occur in people of both sexes.[3] Prevalence in men and in postmenopausal women is less well defined and often suggests underlying pathology. Here, we outline an approach for the assessment and management of patients presenting to primary care with galactorrhoea.

0.5 HOURS

See learning.bmj.com for linked learning module

What are the key hormonal regulators of lactation?

The main hormones involved in lactation are prolactin, oestrogen, progesterone, and oxytocin (table 1).[4 5] Prolactin acts on the breast to stimulate milk production. When prolactin is elevated outside of pregnancy or breastfeeding, it can result in galactorrhoea (figure). Hypothalamic dopamine inhibits lactation by binding to dopamine 2 receptors expressed on anterior pituitary lactotrophs, to suppress prolactin release.

Thyrotropin releasing hormone (TRH), which is increased secondary to low levels of thyroid hormones (free T3 and T4) also promotes prolactin release, accounting for the association between primary hypothyroidism and hyperprolactinaemia (figure).[6]

WHAT YOU NEED TO KNOW

- In premenopausal women, without amenorrhoea, who have normal prolactin, around 30% of galactorrhoea cases are idiopathic; in men and postmenopausal women, galactorrhoea usually indicates underlying pathology
- Measure serum prolactin in all premenopausal women with a negative pregnancy test, and all men and postmenopausal women
- Consider specialist referral to an endocrinologist for galactorrhoea associated with unexplained hyperprolactinaemia, hypogonadism/menstrual disturbance, neurological features, less common presentations (ie, men or postmenopausal women), troublesome galactorrhoea with normal prolactin levels, or any diagnostic uncertainty
- Unilateral, blood stained or serous discharge might suggest underlying malignancy; consider whether suspected cancer referral is indicated

What causes galactorrhoea?

Galactorrhoea can be categorised as hyperprolactinaemic galactorrhoea or normoprolactinaemic galactorrhoea (table 2),[7 8] but estimates of the proportion of galactorrhoea attributable to each cause are limited, owing to the heterogeneous populations in the available studies.

In non-puerperal premenopausal women, galactorrhoea may be physiological, with observational data suggesting that in women without amenorrhoea, who have normal prolactin levels, around 30% of cases are idiopathic.[3] In contrast, galactorrhoea in men and postmenopausal women is less common and generally indicative of underlying pathology.

Hyperprolactinaemia is the most common cause of galactorrhoea, with up to 80% of women with non-puerperal hyperprolactinaemia experiencing galactorrhoea.[9] In men, galactorrhoea is much less frequently observed with elevated prolactin levels, owing to the lack of breast tissue development, lower oestrogen levels, and the inhibitory effects of androgens.

Hyperprolactinaemia has been reported in approximately 40% of cases of primary hypothyroidism.[6] However, galactorrhoea occurring as a result of hyperprolactinaemia in this context is uncommon.

Pathological causes of hyperprolactinaemic galactorrhoea (table 2) include hypothalamic and pituitary causes, and non-pituitary causes (fig 1). Growth hormone excess (acromegaly) may cause galactorrhoea owing to hyperprolactinaemia from prolactin co-secretion, pituitary stalk compression, or the lactogenic effect of growth hormone.

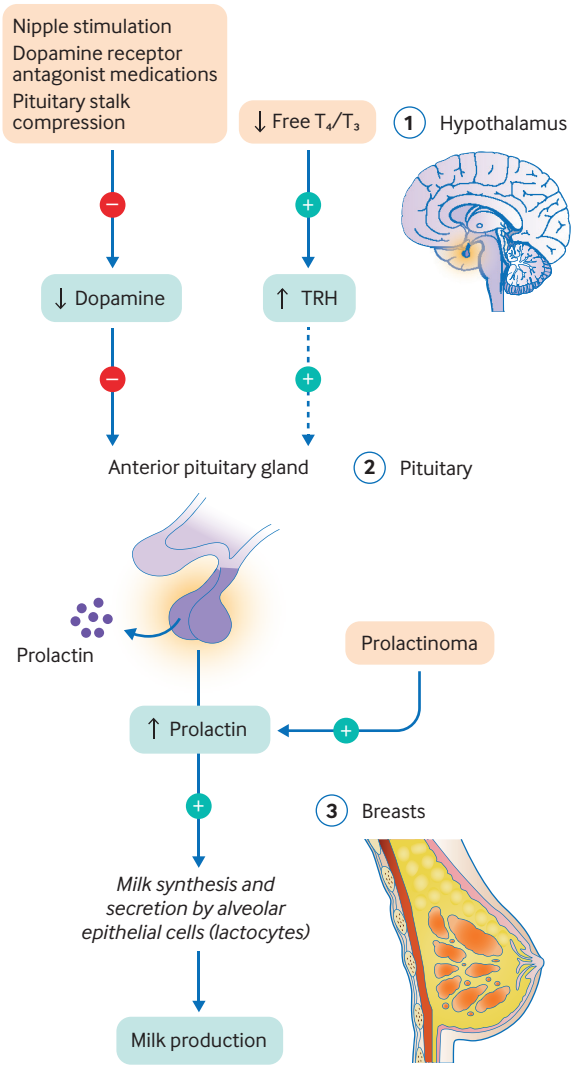
Antipsychotic agents are the most common cause of medication induced hyperprolactinaemia (fig 1).[7] Where possible, serum prolactin should be measured before commencing medications that can increase prolactin levels, to establish a baseline value.[11]

How do I assess someone with galactorrhoea?

Galactorrhoea is typically milky in appearance. If persistent and/or spontaneous (occurring without nipple stimulation), galactorrhoea is more likely to indicate a non-physiological underlying cause.

Table 1 | Key hormonal regulators of lactation

Hormone	Site of synthesis	Function	Stimulator(s)	Inhibitor(s)
Prolactin	Anterior pituitary (lactotroph cells)	Stimulates mammary alveolar formation and differentiation in pregnancy (in conjunction with oestrogen and progesterone). Promotes milk production by mammary alveolar epithelial cells (lactocytes)	Suckling (via suppression of hypothalamic dopamine). Thyrotropin releasing hormone (TRH)	Hypothalamic dopamine
Oestrogen and progesterone	Placenta (during pregnancy)	Stimulates mammary alveolar formation and differentiation in pregnancy (in conjunction with prolactin)	Placental production (during pregnancy)	Withdrawal of progesterone at delivery of placenta, removing inhibition of lactation
Oxytocin	Hypothalamus (paraventricular and supraoptic nuclei). Released into circulation by posterior pituitary	Triggers milk ejection during breastfeeding	Nipple stimulation/suckling Emotional and sensory cues related to breastfeeding	Absence of suckling stimulus. Stress/anxiety



Schematic diagram illustrating the common causes of galactorrhoea. The green + symbol indicates stimulatory actions; the red – symbol represents inhibitory actions. The dotted arrow from TRH (thyrotropin releasing hormone) to prolactin reflects its relatively minor role in causing galactorrhoea

Galactorrhoea is usually bilateral, but it can be unilateral and generally involves multiple ducts. Unilateral galactorrhoea may indicate a local breast cause rather than a systemic hormonal cause. If serum prolactin is normal, unilateral discharge could be caused by intraductal papilloma, ductal carcinoma in situ, Paget's disease of breast, or ductal ectasia. Refer urgently for suspected cancer.[1 13]

In women who have been pregnant, consider galactorrhoea if breast discharge occurs more than one year after either pregnancy has ended or breastfeeding has stopped.[1]

What should I ask about in the history?

- Assess the duration and characteristics of the discharge, including colour.
- Determine whether the discharge is unilateral or bilateral.
- Clarify whether the discharge occurs spontaneously or only with expression (including any nipple stimulation). For premenopausal women, ask about the date of the last menstrual period, most recent pregnancy, and cessation of breastfeeding. Milk discharge during pregnancy and breastfeeding and up to one year after is considered physiological lactation.[1]
- When considering causes, inquire about
  - Medications (prescribed, over the counter, and illicit—table 2), with particular attention to whether the onset of galactorrhoea coincides with drug initiation. Antipsychotic medications cause the greatest elevations in serum prolactin, with risperidone, amisulpride, and first generation antipsychotics such as haloperidol, particularly associated with this side effect. Hyperprolactinaemia typically emerges within 14 days and peaks 1-2 months after treatment initiation.[11] Consistent with this, depending on the antipsychotic agent, galactorrhoea typically appears with a median onset of 20 days (range 7-75 days) after starting treatment[14]
  - Headaches, visual disturbance, and features of pituitary hormone deficiencies which could suggest a pituitary tumour
  - Fatigue, constipation, weight gain, cold intolerance, and low mood which could be symptoms of hypothyroidism
  - In women, ask about oligomenorrhoea and amenorrhoea, and in men, ask about erectile dysfunction and reduced libido. These features are suggestive of hyperprolactinaemia causing secondary hypogonadism, with sex hormone deficiency.

What should I look for on examination?

Although prolactin can rise in response to nipple stimulation, data from prospective studies show that routine breast and nipple examination do not acutely alter serum prolactin levels.[15 16] During breast examination, including examination of regional lymph nodes, observe for spontaneous galactorrhoea. If there is serous or blood stained nipple discharge, consider

Table 2 | Categorisation and causes of galactorrhoea[7 8]

Category	Causes	Typical serum prolactin value
Hyperprolactinaemic galactorrhoea		
Physiological	Nipple stimulation (including during sexual activity and intensive exercise) Stress	Acute venepuncture stress: <47 µg/L (<1000 mIU/L)
Pharmacological	Dopamine receptor antagonists (metoclopramide, domperidone) Neuroleptics (chlorpromazine, haloperidol, prochlorperazine, risperidone, sulpiride, thioridazine) Antidepressants (tricyclics, selective serotonin re-uptake inhibitors, monoamine oxidase inhibitors) Cardiovascular drugs (digoxin, methyldopa, reserpine, spironolactone, verapamil) H_2 receptor antagonists (cimetidine) Oestrogens Illicit drugs (cannabis, cocaine, opiates)	Medication induced hyperprolactinaemia: 25-100 µg/L (500-2000 mIU/L), but can exceed 200 µg/L (~8760 mIU/L) with metoclopramide, risperidone, and phenothiazines
Pathological (hypothalamic-pituitary causes)	Prolactinoma GH and mixed GH secreting tumours Hypothalamic/pituitary tumours distorting the pituitary stalk (eg, craniopharyngioma, meningioma) Infiltration (eg, lymphocytic hypophysitis, granulomatous disorders) Trauma to the pituitary stalk (eg, head injury, surgery, radiotherapy)	Prolactinomas: Microprolactinomas: 100 µg/L (~2000 mIU/L) Macroprolactinomas: >1415 µg/L (~30 000 mIU/L) Compression of the pituitary stalk from non-functioning pituitary adenomas impairing transport of hypothalamic dopamine to anterior pituitary lactotrophs (<94 µg/L, <2000 mIU/L)
Pathological (non-pituitary causes)	Hypothyroidism Chronic renal failure Severe liver disease Chest wall lesions (trauma, herpes zoster, nipple piercings, burns, surgery)	Usually mild-to-moderate elevations and typically <100 µg/L (<2000 mIU/L)
Idiopathic hyperprolactinaemia		
Normoprolactinaemic galactorrhoea		
Previous transient hyperprolactinaemia from one of the above physiological, pharmacological, or chest wall causes that has since resolved or is resolving		
Idiopathic galactorrhoea		

Serum prolactin reference ranges: women 4.7-25.9 µg/L (100-550 mIU/L), men 3.3-18.9 µg/L (70-400 mIU/L). Variation in reference ranges may occur between laboratories.
Hyperprolactinaemic galactorrhoea=galactorrhoea that occurs when serum prolactin levels are elevated above the reference range.
Normoprolactinaemic galactorrhoea=galactorrhoea that occurs with serum prolactin levels within the reference range.
Idiopathic hyperprolactinaemia=prolactin levels elevated above the reference range and physiological, pharmacological, and pathological causes have been excluded. This may include microprolactinomas that are too small to be detected on magnetic resonance imaging.
Idiopathic galactorrhoea=prolactin levels within the reference range and other causes excluded.

an underlying breast disorder and refer urgently for suspected cancer. In accordance with other published clinical opinion, we recommend against attempting to express galactorrhoea during the examination, although the patient may be asked to attempt to elicit the discharge themselves if they feel comfortable doing so.[1 17]

Examine for visual field defects to confrontation in all patients presenting with galactorrhoea. Unitemporal or bitemporal hemianopia suggests optic chiasm compression from a pituitary lesion.[18] Formal visual field testing in secondary care is warranted when visual field defects are detected on clinical examination, or a pituitary mass is seen on imaging which is touching or compressing the optic chiasm.

Look for features suggestive of growth hormone excess such as frontal bossing (prominent and protruding forehead), prognathism (jaw protrusion), and interdental separation, macroglossia (enlarged tongue), as well as enlarged hands and feet.[19]

How should I investigate someone with galactorrhoea?

Recommended initial laboratory evaluation for individuals presenting with galactorrhoea in primary care should include testing for pregnancy, serum prolactin, and thyroid, renal, and liver profiles.

Pregnancy test (for all premenopausal women)

During pregnancy, serum prolactin levels rise approximately 10-fold, reaching concentrations of 150 to 300 µg/L (3200 to 6400 mIU/L) by term.[20] Elevated prolactin levels during pregnancy can lead to breast milk production, which is a normal physiological response. If there are no features to suggest mass effect from a pituitary tumour (ie, the key pathological differential in galactorrhoea, as pituitary adenomas are the most common cause of pathological hyperprolactinaemia and the principal diagnosis requiring exclusion; see above), a positive pregnancy test requires no further evaluation for galactorrhoea.

> The degree of prolactin elevation can help to identify the underlying cause

Serum prolactin

Consider this for all premenopausal women with a negative pregnancy test, and all men and postmenopausal women. The degree of prolactin elevation can help to identify the underlying cause. While medication induced hyperprolactinaemia is typically associated with serum prolactin levels ranging from 25 to 100 µg/L, certain drugs can cause levels to exceed 200 µg/L (table 2).[7] In the context of prolactinomas, prolactin levels generally correlate with tumour size (table 2). Non-functioning adenomas can cause hyperprolactinaemia by distorting the pituitary stalk, thereby interrupting transport of hypothalamic dopamine to the anterior pituitary, and a prolactin level >94 µg/L (>2000 mIU/L) is rarely encountered.[21]

A single sample is usually sufficient, which can be measured at any time of day. A level above the upper limit of the reference range confirms hyperprolactinaemia, provided that the sample was obtained without excessive venepuncture stress (box 1, bmj.com).[7]

Box 2 | When to consider specialist referral to endocrinology

We recommend that GPs consider referral for these scenarios, with the timing of review determined by specialist triage in secondary care:

- Unexplained hyperprolactinaemia after excluding pregnancy, medication induced causes, and primary hypothyroidism
- Hypogonadism/menstrual disturbance
- Male or postmenopausal galactorrhoea
- Headache, visual field defects, or other neurological symptoms
- Suspected medication induced hyperprolactinaemia, where the causative drug cannot be stopped, or when the onset of galactorrhoea does not align with treatment initiation
- Troublesome galactorrhoea with normal prolactin levels, when a trial of dopamine receptor agonist therapy is being considered
- Difficulty interpreting prolactin results (eg, possible stress induced elevations, macroprolactin)

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Via The Pituitary Foundation UK, we collaborated with a patient co-author who experienced galactorrhoea owing to a prolactinoma. She provided opinions and comments on the draft manuscript, emphasising the importance of listening to patient concerns, as well as the need for greater awareness (among both the public and healthcare professionals) about galactorrhoea as a presenting symptom of prolactinoma. In response, we emphasised patient centred, conservative strategies suitable for use in primary care when evaluating and managing galactorrhoea.

EDUCATION INTO PRACTICE

- What advice would you offer to a patient with galactorrhoea but normal serum prolactin levels?
- When would you refer a patient with galactorrhoea to a specialist?

Serum thyroid, renal, and liver profiles

Consider testing thyroid, renal, and liver function for all individuals with confirmed hyperprolactinaemia. Primary hypothyroidism, renal insufficiency, and liver failure are recognised causes of hyperprolactinaemia. However, the extent to which hyperprolactinaemia secondary to renal insufficiency and liver failure is likely to cause galactorrhoea is less well defined.

When should I consider referral?

If a physiological, pharmacological, or pathological cause for raised prolactin is not identified, seek advice from or consider referral to endocrinology (box 2). Further investigations in secondary care might include formal visual field examination, pituitary magnetic resonance imaging (MRI), and/or blood pituitary hormone profile.

Pituitary MRI is recommended for patients with confirmed pathological hyperprolactinaemia when there is suspicion of a prolactinoma or another pituitary mass causing hyperprolactinaemia.[7 8] If a pituitary lesion is identified on imaging, additional pituitary testing may be needed to detect co-secretion of other pituitary hormones (especially GH), and for pituitary hormone deficiencies related to tumour mass effect, including insulin-like growth factor-1, 9 am cortisol, luteinising hormone, follicle stimulating hormone, testosterone (men), and oestradiol (women).

How is galactorrhoea managed?

Conservative management

Advise the patient to:

- Wear loose fitting clothing
- Use breast pads (which also aid in absorbing discharge)
- Avoid excessive self-examination and nipple stimulation.

Treat the underlying cause where possible

- Galactorrhoea in individuals with primary hypothyroidism causing hyperprolactinaemia is reversible with levothyroxine replacement and normalisation of thyroid function.[8]
- For medication induced hyperprolactinaemia causing galactorrhoea, the Endocrine Society recommends a trial of discontinuing the suspected medication for three days or switching to an alternative agent, followed by repeat measurement of serum prolactin levels.[7]
  - If the medication cannot be stopped and/or the onset of galactorrhoea does not align with treatment initiation, refer to endocrinology for consideration of a pituitary MRI to differentiate medication induced hyperprolactinaemia from a pituitary or hypothalamic lesion.
  - Discuss any modification (reduction to a lower tolerated dose, discontinuation, or substitution) of psychiatric medication with the prescribing clinician before making changes.

Causes for which referral is recommended

Idiopathic galactorrhoea

In individuals with galactorrhoea and normal prolactin levels, after exclusion of other potential causes, a trial of dopamine receptor agonist therapy may be considered if symptoms are bothersome. Dopamine receptor agonist initiation and monitoring usually require input from an endocrinologist.

Prolactinoma

Dopamine receptor agonist therapy is the first line treatment for most patients with prolactinomas and is highly effective in improving hyperprolactinaemia and galactorrhoea and decreasing size of prolactinomas.[8] Results from cumulative studies show that dopamine receptor agonists result in resolution of galactorrhoea in 33-100% (median 86%) of patients with prolactinomas.[7] Cabergoline is the dopamine receptor agonist of choice, although bromocriptine is also licensed for this indication.[8] Common side effects of dopamine receptor agonists include gastrointestinal discomfort, nausea, vomiting, and mild dizziness, which typically improve with time.[26] These drugs can also lead to mood changes or impulse control disorders, even in patients without a psychiatric history.[27 28]

Competing interests: None declared.

Cite this as: *BMJ* 2026;392:e086122

Find the full version with references at doi: 10.1136/bmj-2025-086122

STATE OF THE ART REVIEW

Medical management of inflammatory bowel diseases

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This is a summary of Clinical Review Medical management of inflammatory bowel diseases. The full version can be read here:https://www.bmj.com/content/391/bmj-2025-079050

Inflammatory bowel diseases (IBD), comprising Crohn's disease and ulcerative colitis, are relapsing-remitting, immune mediated disorders of the gastrointestinal tract. Inflammation in ulcerative colitis is typically limited to the colonic mucosa, whereas Crohn's disease is a transmural inflammation that can affect the entire gastrointestinal tract, from mouth to anus. The term IBD-U (IBD unclassified) is used when endoscopic, histological, and radiological findings do not distinguish between ulcerative colitis and Crohn's disease. Meanwhile, the term indeterminate colitis is used when ulcerative colitis and Crohn's disease cannot be differentiated based on the pathology of a resected colon.[1]

Genome-wide association studies have identified over 300 single nucleotide polymorphisms associated with IBD susceptibility. Advances in understanding have expanded our knowledge of the complex interplay between mucosal immunity, intestinal microbiota, and host metabolism. These advances have translated into a dramatic increase in therapeutic options, with biological and small molecule treatments intercepting and abrogating the immune inflammatory cascade (figure). Wider appreciation of potential "disconnect" between symptoms and objective measures of disease activity, and evidence that uncontrolled inflammation may lead to progressive intestinal injury, irreversible bowel damage, and adverse events have redefined our treatment goals. Therefore, incorporating patient reported outcomes along with objective measures and "treat to target" (the target being mucosal healing) strategies—as outlined by Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE II), Selecting End Points for Disease Modification Trials, and International Organization for the Study of Inflammatory Bowel Diseases consensus statements—is the current standard of care.[2] We review the latest evidence on IBD diagnosis, staging, and management.

CPD READING
0.5 HOURS

WHAT YOU NEED TO KNOW

- Modern treatment goals for inflammatory bowel diseases (IBD) have shifted from controlling symptoms to achieving remission, as defined by patient reported outcomes and objective measures, associated with improved long term prognosis and quality of life.
- The therapeutic landscape now includes a broad array of options, including conventional agents, biological agents, biosimilars, and small molecules.
- Multidisciplinary care, risk stratification, and individualised treatment selection (considering disease phenotype, severity, comorbidities, and patient preferences) are now central to optimal IBD management.

Epidemiology

The global burden of IBD is increasing, with an estimated worldwide prevalence of 6.8 million in 2017 and an age standardised prevalence of 84.3 per 100 000 people.[3 4]

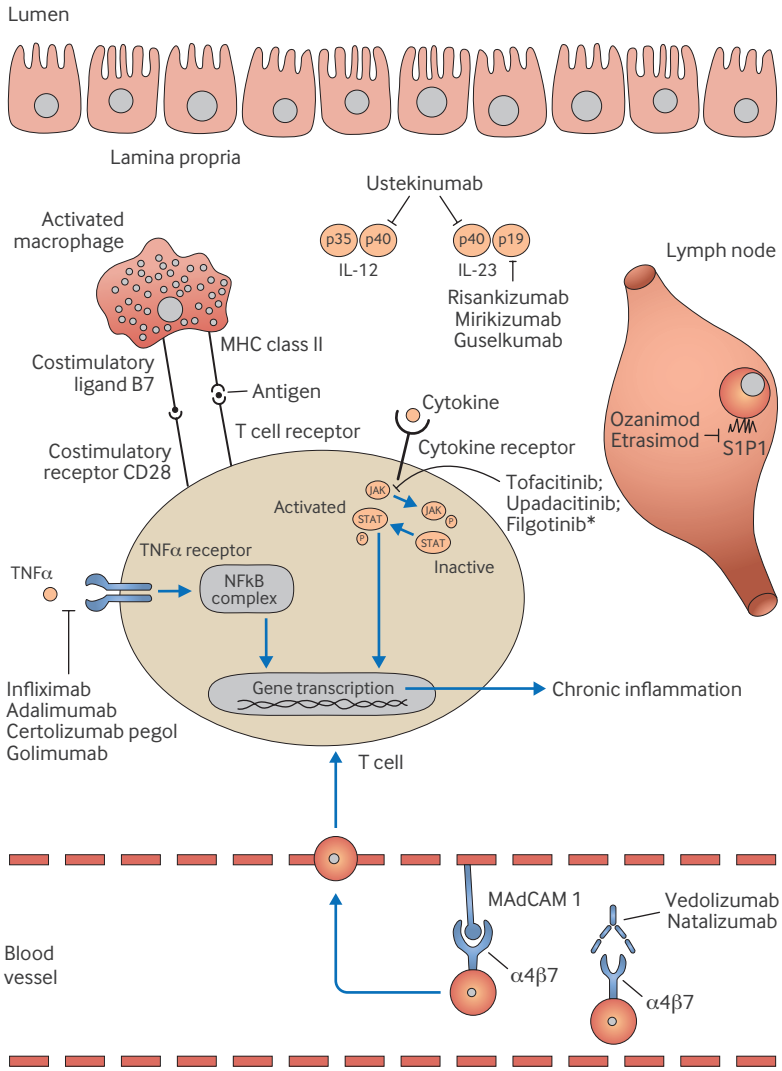
Presenting symptoms

Crohn's disease typically presents with abdominal pain or diarrhoea, or both, while ulcerative colitis presents with diarrhoea, urgency, and haematochezia. Fatigue, anaemia, fever, nausea or vomiting, weight loss, urgency, and extraintestinal manifestations of IBD are also presenting symptoms in adults.[7] Early diagnosis and treatment are important and can help mitigate risk of disease related complications. Delay in IBD diagnosis is common, from lags in seeking medical attention to eventual referral to a specialist for a diagnosis.[8] Faecal calprotectin to distinguish IBD from irritable bowel syndrome and the judicious use of imaging and high index of suspicion in the appropriate setting by primary and urgent care providers are critical for early diagnosis.[9 10] Endoscopy is central to confirming and classifying disease.[11 12] Pathways with checklists have been proposed to enable earlier IBD diagnosis in the emergency department, in primary care, and gastroenterology settings.[13]

Current treatment paradigm

Symptoms do not reliably correlate with objective measures of disease activity and uncontrolled inflammation may lead to progressive intestinal injury and irreversible bowel damage with negative outcomes.[14] Risk stratification is based on a cumulative assessment of disease phenotype, behaviour, and established risk factors .[14-17 19] The current paradigm is to treat beyond symptoms, addressing inflammatory activity early and effectively before irreversible intestinal damage and disability occur.[2 20 21] This treatment concept, which was developed by the STRIDE committee,[2] implies identifying a predefined goal for which treatment is started and optimised, with regular monitoring until the goal is achieved, in consultation with the patient and in the context of the patient's individual needs.[22]

The STRIDE II consensus incorporated short term, intermediate term, and long term goals.



Pathophysiology of inflammatory bowel diseases. For full description see bmj.com

Short term—clinical response

- Crohn's disease: ≤50% in patient reported outcomes of stool frequency and abdominal pain.
- Ulcerative colitis: ≤50% in rectal bleeding and stool frequency.

Intermediate term—clinical remission

- Crohn's disease: abdominal pain score ≤1 and stool frequency score ≤3, or Harvey Bradshaw index <5.
- Ulcerative colitis: rectal bleeding=0 and stool frequency=0 or partial Mayo score (<3 and no score >1), and normalisation of biomarkers (C reactive protein (CRP) less than upper limit of normal for assay, typically <5 mg/L, and faecal calprotectin <150-200 mg/g).

Long term—endoscopic healing

- Crohn's disease: SES-CD (simple endoscopic score for Crohn's disease) ≤3 points or absence of ulcerations (eg, SES-CD ulceration subscores=0).
- Ulcerative colitis: Mayo endoscopic subscore=0 or UCEIS (ulcerative colitis endoscopic index of severity) ≤1 point, normalised quality of life, and absence of disability.[2]

Medical treatment

5-Aminosalicylates and sulfasalazine

Oral 5-aminosalicylates (5-ASAs) and sulfasalazine are effective at inducing remission of mild to moderate active ulcerative colitis and maintaining remission.[43-45] In patients with active Crohn's disease, 5-ASAs are no more effective than placebo for induction or maintenance of remission, and achieving mucosal healing.[46 47] Therefore, guidelines recommend against the use of 5-ASAs in Crohn's disease.[19 46-49] Sulfasalazine, in contrast, has shown some efficacy in Crohn's disease with colonic involvement and can help with concomitant arthralgias. When used, sulfasalazine should be given with folic acid.[16 43]

In ulcerative colitis, once daily dosing is as effective as divided dose regimens.[50] More severe disease should be treated with maximum doses until remission is achieved, and subsequent dose reduction to ≥1.5 g/day to maintain remission.[51] Combining oral and topical mesalazine to induce remission for active disease beyond the recto-sigmoid junction may have superior efficacy to treatment with oral mesalazine alone.[52 53] Combination treatment is protective against proximal extension of mucosal inflammation in ulcerative proctitis. Patients who are allergic to aspirin may not tolerate 5-ASA agents. Side effects reported with 5-ASAs include rash, fever, diarrhoea, worsening of colitis flare, pancreatitis, myocarditis, and nephritis. For patients with ulcerative proctitis, 5-ASA suppositories are well tolerated and effective for inducing remission and maintaining remission.[16 45] Nightly tacrolimus suppository or steroid suppository or enema can be used for proctitis refractory to topical mesalazine.[16 45]

Sulfasalazine is associated with adverse effects, including headache, nausea, dyspepsia, anorexia, fever, rash, arthralgias, haemolysis, neutropenia, reversible sperm abnormalities, and hypersensitivity reactions involving the colon (exacerbation of colitis), lungs, liver, nerves, or pancreas. Intolerances are mainly linked to high sulfapyridine serum levels and allergy to the sulfa component. Most patients who are intolerant or allergic to sulfasalazine can tolerate 5-ASA agents.[55 56]

Corticosteroids

Corticosteroids are effective for inducing remission in active ulcerative colitis and Crohn's disease, but not for maintaining remission.[57-61] These drugs have numerous side effects and are associated with increased mortality in patients with IBD, making a compelling case for avoiding steroids when possible and using effective treatments to induce and maintain steroid-free remission.[62 63]

In patients with mild to moderate active ulcerative colitis, colonic release corticosteroid budesonide multimatrix system may be used for eight weeks.[66]

Immune modulators

Thiopurines

The thiopurines azathioprine and 6-mercaptopurine are purine derivatives that are incorporated into DNA and

inhibit DNA synthesis. Azathioprine is metabolised in vivo to 6-mercaptopurine, and its biological effects are identical to those of 6-mercaptopurine. These drugs are effective steroid sparing agents for maintaining remission in moderate to severely active ulcerative colitis, but evidence for maintaining remission in Crohn's disease is of low quality.[69 70]

About 10% of patients will have intermediate thiopurine methyltransferase activity, and for these patients, half the usual dose of 6-mercaptopurine or azathioprine is used because regular doses lead to neutropenia. One in 300 patients is estimated to be deficient in thiopurine methyltransferase and thiopurines should not be used to treat such patients. During thiopurine treatment, blood counts, electrolytes, and liver chemistry should be checked at least at weeks 2, 4, 8, and 12, and then at least every three months. These tests should be repeated two weeks after any dose increase.[49]

Thiopurines increase the risk of lymphoproliferative disorders by 5.3-fold (95% confidence interval 2.01 to 13.90, P<0.001), especially non-Hodgkin's lymphoma, although with a low prevalence at 0.2%.[75] Male sex, older age, and longer disease duration conferred the highest risk. Combination treatment (with anti-TNF) increases the risk of lymphoma compared with using either treatment alone.[76 77] Longer duration of thiopurine exposure is associated with increased lymphoma risk, with a marked reversal of risk when treatment is stopped.

Thiopurines also increase the risk of non-melanoma skin cancer, which, upon discontinuation, decreases, but not to baseline.[80-82] Therefore, patients treated with azathioprine or 6-mercaptopurine should have a total body examination by a dermatologist every year.[80-82] The risks of cancer and infection increase with age, and generally, thiopurines should be avoided in patients older than 60 years.

Methotrexate

Methotrexate is a dihydrofolate reductase inhibitor with anti-inflammatory and immunosuppressive effects. It is administered intramuscularly, subcutaneously, or orally at weekly doses of 15-25 mg in patients with Crohn's disease. Side effects include headache, nausea, pneumonitis, and abnormal liver transaminases.[88 89] Methotrexate is typically used as a steroid sparing immunomodulator for patients with Crohn's disease or to avoid the risk of hepatosplenic T cell lymphoma in younger male patients receiving a combination of antitumour necrosis factors (anti-TNF) and thiopurine, and to decrease immunogenicity to anti-TNF agents.[90] Methotrexate is not effective in inducing or maintaining remission in ulcerative colitis.[91-94] Methotrexate is teratogenic and therefore contraindicated in pregnancy. Folic acid 1 mg daily or 5 mg weekly, 48 hours before receiving methotrexate, should be prescribed for patients along with periodic monitoring of complete blood count and liver function tests.

PATIENT PERSPECTIVE AND PRIORITIES

- The risk of disease progression and complications can far outweigh side effects from advanced treatments for inflammatory bowel disease (IBD). Many patients are unaware that there is a "life after IBD," and remission can give people their life back. Many are more scared of the drugs than of the disease itself.
- Emphasise that shared decision making is a two way street and that patients are partners in their own care. Some patients can be afraid to speak up at their appointments and then come to a support group to ask questions.
- Treat the patient holistically; patients with IBD are more than their diagnosis and disease. Patient wellbeing is more than drug management, and both physicians and patients may need to remind themselves of this.
- Address mental health. Ask patients how they are doing emotionally with this disease. Time is short, but patients really need their doctors to ask. If accessible, refer to a gastrointestinal psychologist if patient is willing to see one.
- Consider SOGI (sexual orientation and gender identity) and even the role of race, ethnicity, and culture in IBD care while trying not to stereotype or bring in implicit biases.
- Address diet and refer to a gastrointestinal IBD dietitian.
- Do not be afraid to ask about sex and intimacy or pregnancy.
- Even if parents or loved ones are in the room, politely ask them to leave in order to discuss personal issues with the patient.
- Do not be afraid to mention surgery early. Patients need to be prepared emotionally for this possibility.
- At times, a second opinion is needed, especially when surgery and escalation of treatments are considered.

Ciclosporin

Ciclosporin is a cyclic 11 amino acid peptide, widely used as an immunosuppressant in organ transplantation for its selective effect on T lymphocyte mediated immune responses. Intravenous ciclosporin A may be used in severe, steroid refractory ulcerative colitis with short term benefit, although most patients will experience relapsing disease and require colectomy unless bridged to a thiopurine or vedolizumab (or another advanced treatment).[95-98] Side effects include hypertension, paraesthesia, nausea or vomiting, hirsutism, infection, and renal dysfunction.

Biological treatments

Biological agents are antibodies targeting specific molecules involved in immune regulation. These treatments have transformed IBD care since the approval of the first biological agent in 1998. They are approved for induction and maintenance of disease. Some biological treatments are approved for ulcerative colitis and Crohn's disease.

Anti-TNFα antibodies

Infliximab is a chimeric monoclonal antibody targeting TNFα, a proinflammatory molecule that triggers and perpetuates gut inflammation in IBD.[57] Adalimumab, a fully humanised anti-TNFα antibody, is approved for Crohn's disease and ulcerative colitis.[100-102 128] Certolizumab pegol is a humanised anti-TNFα antibody FAB fragment that has been pegylated and is approved for use in Crohn's disease.[103 104] Golimumab, another fully humanised anti-TNFα agent, is approved for use in ulcerative colitis.[105 129]

Anti-TNFα treatment may reactivate quiescent tuberculosis and so all patients should be assessed with purified protein derivative skin testing or QuantiFERON gold before receiving any anti-TNFα treatment (or any advanced treatment).[84 130-133] Anti-TNFα treatment could also increase the risk of fungal infections, including histoplasmosis and *Pneumocystis jirovecii*.

Anti-integrin antibodies

Natalizumab is a humanised antibody that targets α-4 integrin and prevents memory T cells from migrating into the gut and brain.[135 136] Approved for multiple sclerosis and Crohn's disease in the US, it was temporarily withdrawn from the market after reports of progressive multifocal leucoencephalopathy, and then reintroduced in 2008 for Crohn's disease with a safety monitoring programme.[106 137]

Vedolizumab, which blocks α4β7 and selectively inhibits trafficking of memory T cells to the gastrointestinal tract, is approved for use in ulcerative colitis and Crohn's disease.[107 108 138] Because vedolizumab is gut specific, there is no increased risk of serious infections or malignancy.[76 139]

Anti-interleukin 12 and 23 antibodies

Ustekinumab is a monoclonal antibody against the p40 subunit shared by interleukin (IL)-12 and IL-23.[140] Ustekinumab has not been associated with any increased risk of malignancy, but may increase the risk of infections.[141]

Anti-interleukin 23 antibodies

Risankizumab, mirikizumab, and guselkumab are monoclonal antibodies against the p19 subunit of the IL-23 cytokine and so specific for inhibiting only IL-23.[142] Anti-IL-23 based treatments have not been associated with increased risk of cancer or serious infections.[145 146]

Biosimilars

Biosimilars have been shown to be similar to the originator product in terms of safety and efficacy, and reduce costs.[147 148] Recent randomised controlled trials have shown that several switches among biosimilars do not affect efficacy or immunogenicity.[148 149] Antibodies to one product will cross react with its biosimilars. Therapeutic drug monitoring assays are the same for the biosimilar to the originator drug. Therefore, if a patient loses response to or develops an antibody to a biosimilar, the originator product or another biosimilar cannot be substituted.

Small molecules

Janus kinase inhibitor

Tofacitinib is the first oral Janus kinase (JAK) inhibitor approved for ulcerative colitis.[114 150] JAKs (JAK1, JAK2, JAK3, and TYK2) are important signal transducers from cytokine receptors through the JAK-STAT signalling pathway. Tofacitinib is a pan JAK inhibitor and results in suppression of STAT1 dependent genes.[150] Adverse effects include immunosuppression with increased risks of infection, including zoster and malignancy.[151]

The current paradigm is to treat beyond symptoms

Upadacitinib is a selective oral JAK1 inhibitor approved for ulcerative colitis and Crohn's disease.[115 116] Filgotinib, another JAK1 selective inhibitor, is approved in the UK for ulcerative colitis, but not in the US.

S1P receptor modulation

S1P receptor modulators are a class of drugs that target sphingosine-1-phosphate (S1P) receptors (S1P1-5), particularly S1P1, to modulate lymphocyte trafficking. Ozanimod is an oral small molecule that works through S1P1,5 receptor modulation, trapping circulating T lymphocytes in lymph nodes. Ozanimod is approved for ulcerative colitis.[117 158] Etrasimod, another oral S1P1,4,5 receptor modulator, is approved for ulcerative colitis and has also shown efficacy in ulcerative proctitis.[118] Contraindications to S1P modulators include transient ischaemic attack or stroke within six months, severe untreated sleep apnoea, monoaminoxidase inhibitor use, and macular disease (macular degeneration, oedema, uveitis).[159] Fundoscopic exam, full blood count, liver function tests, tuberculosis screening, HBV status, and electrocardiography are recommended before starting treatment.[159] These agents work best in patients with ulcerative colitis who are naive to biological medicines, and if response is achieved, it is durable over several years.

Diet treatment

Patients with IBD should be encouraged to adhere to a diet that is low in ultra-processed foods, low in salt and sugar, and rich in fresh fruits and vegetables.[160] In a small, six week, randomised controlled trial of patients with Crohn's disease and mild to moderate symptoms, a Mediterranean diet was not inferior to a specific carbohydrate diet at achieving symptomatic remission (92 *v* 99; P=0.77), faecal calprotectin response (13 *v* 23; P=0.83), and CRP response (28 *v* 37; P=0.68).[161] The Mediterranean diet was shown to improve quality of life, improve biomarkers, and reduce disease activity, even in patients with ulcerative colitis.[162]

Treatment approach by phenotype

Mild Crohn's disease

Approximately 20-30% of patients with Crohn's disease have a mild disease course defined as having mild endoscopic activity (SES-CD 3-6), tolerating a diet, and an uncomplicated course.[15 165] In mild Crohn's disease, it may be appropriate to only monitor symptoms and objective markers.[166] Patients should be counselled on avoiding tobacco and non-steroidal anti-inflammatory drugs, and eating a Mediterranean diet. Low dose aspirin can be used as otherwise clinically indicated. 5-ASAs are ineffective and should not be used in Crohn's disease, whereas sulfasalazine may have a modest role in Crohn's colitis and ileocolitis.[46] Biological agents and other medical therapeutic options should be reserved for when there is risk of disease progression or for those at risk of disease complications.[167]

Moderate to severe Crohn's disease

Moderate to severe Crohn's disease is defined as corticosteroid dependence or refractoriness, presence of deep or large ulcers on endoscopy with more severe endoscopic disease activity scores (SES-CD >6), and risk factors.[168] Patients with shorter disease duration (≤18 months) have higher rates of clinical remission on biological agents.[169] For patients likely to have an aggressive disease course, early use of effective treatment (within one to two years of diagnosis) has been shown to lead to better outcomes, including lower rates of surgery, hospital admission, and disability.

Current treatment choices will largely be driven by patient factors (such as comorbidities, pregnancy related considerations, mode of administration), disease factors, and presence of extraintestinal manifestations.

Perianal Crohn's disease

Perianal Crohn's disease affects 25-35% of patients with Crohn's disease and may even present before luminal inflammation. A multidisciplinary approach between specialised IBD colorectal surgeons, radiologists, and gastroenterologists is key to effective management. Different classifications exist to categorise perianal Crohn's disease, and they consider whether the fistula is simple or complex, disease severity, outcomes, and goals of treatment.[184-186]

Evaluation of patients includes a colonoscopy for mucosal assessment, along with detailed examination of the fistula with magnetic resonance imaging of the pelvis or an exam under anaesthesia by a colorectal surgeon. A rectal endoscopic ultrasound may be needed to better characterise the fistula.[187]

Perianal abscesses should be drained and antibiotics commenced. Antibiotics have shown efficacy in perianal fistulising Crohn's disease even without an abscess, especially in conjunction with immunomodulator or advanced treatments.[188-190] American Gastroenterological Association guidelines recommend using antibiotics with biological agents over a biological drug alone for inducing fistula remission.[19]

After control of infection, the goal of treatment is mucosal (rectal) healing. Anti-TNFα treatment, primarily infliximab, in combination with a thiopurine in patients with perianal Crohn's disease, currently has the best evidence for fistula healing.[59 60]

Mild ulcerative colitis

Patients with mild ulcerative colitis have mild symptoms (less than four bowel movements each day, intermittent rectal bleeding, and mild urgency), normal haemoglobin, normal to mild increase in CRP, mildly raised faecal calprotectin >150-200 µg/g, and endoscopic Mayo score of 1.[16] The mainstay of treatment is 5-ASA (mesalazine), which can be given orally, topically, or typically in combination, for inducing and maintaining remission.

Competing interests: See bmj.com.

Cite this as: *BMJ* 2025;391:e079050

Find the full version with references at doi: 10.1136/bmj-2025-079050

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS MANUSCRIPT

Four patients or patient advocates (Elizabeth Richardson, Tina Aswani Omprakash, Rocio Castrillon, and Rola Ajib) with inflammatory bowel disease reviewed the manuscript, gave constructive feedback, and provided the patient perspectives and priorities box.

Moderate to severe ulcerative colitis

Moderate to severe ulcerative colitis is defined as more than six bowel movements each day, frequent blood in the stool, urgency, anaemia, raised erythrocyte sedimentation rate and CRP, increased faecal calprotectin >200 µg/g, and endoscopic Mayo score ≥2.[16] Treatment choice and sequencing are determined by disease activity and severity, presence of extraintestinal manifestations, comorbidities, life events such as pregnancy, and safety considerations.[17]

Mesalazine (5-ASA), preferably a combination of oral and topical preparations, may be used in recently diagnosed moderately active ulcerative colitis, with careful monitoring of clinical and biochemical parameters and ultimately mucosal healing.[51 54 207 208]

Infliximab is the most widely used first line biological agent, often combined with an immunomodulator, to treat patients with moderate to severe ulcerative colitis.[16 18 99 210]

Acute severe ulcerative colitis

Acute severe ulcerative colitis is conventionally defined by the presence of at least six bloody stools a day, with at least one of: temperature ≥37.8ºC, haemoglobin <10.5 g/dL, erythrocyte sedimentation rate >30 mm/h, CRP >30 mg/dL, and a pulse rate of ≥90 beats/min.[45 49 216 219]

Initial management hinges on a careful history and exclusion of differential diagnoses, baseline laboratory and stool tests, and optimisation of the fluid, electrolyte, and nutritional status.[45 49 220 221] Patients may continue an oral diet unless surgery is imminent.[222] Infliximab or ciclosporin are commonly given as rescue treatment and emerging data support using a JAK inhibitor (tofacitinib or upadacitinib).[223] Proctocolectomy has a definite role in medically refractory acute severe ulcerative colitis or when medical salvage treatment is contraindicated because of massive haemorrhage, toxic megacolon, or colonic perforation.

Guidelines

Guidelines were reviewed from the American College of Gastroenterology, the American Gastroenterological Association, the American Society of Gastrointestinal Endoscopy, the British Society of Gastroenterology, the International Organization for the Study of IBD, and the European Crohn's and Colitis Organisation. Overall, the guidelines are congruent in prioritising early identification of IBD, early treatment, risk stratification, and the treat-to-target approach. Certain drugs are not available in Europe and vice versa in the US. In this review, emphasis was placed on the more recent guidelines when making recommendations.

Race is not a biological category: healthcare must challenge this misconception

Institutional racism in healthcare has received increased coverage in recent years, including in *The BMJ*'s special issues in 2020 and 2025. Yet the harmful misconception that race is a biological category rather than a shifting social construct remains entrenched in the public consciousness, including among healthcare staff. As trusted experts, healthcare professionals should lead on dismantling this misconception that leads to poor medical care and patient harm.

For example, the misuse of race in clinical equations can lead to prediction error and missed diagnoses. Race based treatment recommendations are still made despite studies showing that drug responses do not reliably vary by race. There are also egregious racial inequities found in pain treatment, resulting from implicit assumptions about biological differences in pain tolerance in racialised patients.

Scientific racism

The consensus within modern genetics, that there is no biological basis for race, is not taught in schools or in the canonical medical curriculum. I only came across it as a postdoctoral researcher in a biology department. I didn't fully grasp its importance until I began lecturing on a new module on scientific racism, covering how evolutionary theory was historically co-opted to support ideas of race and eugenics that justified colonialism.

In teaching this topic, I've come across many resources explaining these findings in depth—but there are some key points that everyone working in healthcare should know.

Firstly, and most importantly: the physical differences associated with race and ethnicity (eg, skin colour, hair texture, eyelid shape) are not representative of overall genetic difference between people. Racial or ethnic identity—where ethnicity is often used interchangeably with race—is therefore a poor predictor of a patient's genetic disease susceptibility or drug response.

Secondly, genetic variation exists on a gradient. Human genomes do not fall naturally into clusters. Any way of categorising humans into groups genetically will require arbitrary cut-off points or gene selections.

Approach every patient as an individual

Thirdly, there is more human genetic variation found within populations than between populations: most genetic variants are present within all human groups. Classifying a patient according to their continent of birth will therefore tell you little about their individual genetic make up.

Finally, because of all this, the most plausible biological mechanism by which a person's "race" could make them more or less prone to any health condition is through racism itself. Genetic differences that have been historically linked to race, like sickle cell disease, lactase persistence, or even skin pigmentation, are in fact local adaptations, cutting across traditional racial or continental lines. In most cases these adaptations evolved independently in different populations that share relevant cultural or environmental conditions.

Social determinants of disease that correlate with socially defined racial categories are, however, very real. Health is well known to be affected by differential rates of healthcare access, toxin exposure, poverty, incarceration, and other socioenvironmental factors linked to structural racism. These inequalities are given relatively little attention and funding. A biological conception of race has given those in power license to dismiss the need for structural change to tackle health inequalities. If this false narrative were to finally be dispelled, the urgency of confronting social problems would be harder to ignore.

Some positive change is already under way. Race free versions of the glomerular filtration rate equation have recently been adopted as standard in both the US and UK. Misleading references to biological race have been removed from at least one prominent medical textbook. Evolutionary geneticist Joseph L Graves Jr, author of books on medical racism, has lectured on this topic at over 70 medical departments across the US and some in the UK.

Reject racial generalisations

To systematically root out misconceptions about race, our best approach is by using curriculum reform. Medical education needs complete revision to remove its over-reliance on racial and ethnic stereotypes and replace this with personalised, evidenced based approaches to medical testing, diagnosis, and care.

Those of us involved in medical training can influence change in what students and trainees are taught and tested on. Free resources are available to help. With the current political climate in the US stymying what progress has been made there, we in the UK must lead on this, particularly as a former colonial power that was instrumental in proliferating racist ideology.

Patient data collection also needs to be reformed. Given that racialisation is a social determinant of health, race and ethnicity data are important for equalities monitoring, but this has not been made sufficiently clear to patients or clinicians. Standardising the language on medical websites, leaflets, and forms to clarify that data collection is for monitoring rather than racial profiling or treatment decisions, and better guidance for clinicians about this, would help.

Changes to the medical curriculum and to official guidance from institutions must be implemented, but that can take time. One thing that any healthcare professional can act on today is to consciously reject discredited racial generalisations and approach every patient as an individual.

Jasmeen Kanwal, project officer, University of Edinburgh

Cite this as: *BMJ* 2026;392:s150

CPD READING
0.5 HOURS

Linking my chronic pain with trauma

Keeping an open mind about factors contributing to chronic pain can help patients to explore what approaches might work for them, writes Barbara Holtzman

At age 29, with a desire to get stronger and feel more alive, I took up intermittent jogging. After two days, my knee swelled and the pain forced me to stop. Even with prescription strength ibuprofen from my doctor, I needed a knee brace to walk a block or two. Fearful of the pain, I stopped running.

The stiffness and pain in my knee lingered for many years—sometimes a mild ache and sometimes more debilitating. Over time, I started having pain in other parts of my body as well, including my back, hip, neck, and shoulder. I had multiple x rays, magnetic resonance imaging scans, and laboratory tests. My doctors found mild, and eventually moderate osteoarthritis in my joints, but nothing autoimmune related such as rheumatoid arthritis or Lyme disease. No one could figure out why I felt and moved like the tin man from *The Wizard of Oz*.

I consulted many practitioners over the following years. I tried to manage my symptoms with yoga, monthly chiropractic adjustments, frequent referrals to physical therapy for flare-ups, my knee brace, and consistently high doses of ibuprofen—which caused serious digestive side effects, forcing me to cut back the dose. I removed sugar and wheat from my diet which reduced the level of pain temporarily, but it always returned.

Connecting mind and body

The first time I experienced complete and total relief from the pain in my body was after an exceptionally effective massage. As I lay there savouring a deep, exquisite release, a thought crossed my mind: "How long will this last?" Almost immediately, I felt a muscle tighten. Another negative thought brought another tightening, and the ease and sense of wellbeing I had just experienced disappeared. I had read about the mind-body connection, but this was the first time I felt it so viscerally.

PRIYA SUNDRAM

WHAT YOU NEED TO KNOW

- In some people, a history of trauma may be contributing to their experience of chronic pain.
- Consider inviting patients with chronic pain to become curious about their symptoms. Do flare-ups coincide with increased stress? Does fear of the pain increase it? Is there anything that helps?

I dived into research, investigating the link between mind and body, and how a perceived lack of safety dysregulates the nervous system. Based on this research, I began to suspect that, during childhood, my brain might have developed protective strategies to cope with feeling unsafe. While my mind had dissociated from overwhelming emotional pain, my body had remembered and stored it all. I had talked *about* my trauma history in therapy, but it was a shock to realise that my body had been feeling the emotions I had been too scared to feel. It was also a relief because now that I understood my pattern, I could change it. Interestingly, I noticed that the automatic protective reaction of tightening against the pain actually increased the sensations. Additionally, my habitual strategy of racing to figure out what was wrong and how to fix it created an obsessive loop, which not only exhausted me but actually increased the pain.

EDUCATION INTO PRACTICE

- How might you support a patient who is experiencing chronic pain?
- Are you aware of local or online peer support networks they might try?

Addressing the cause, not just the symptom

Trauma informed, somatically based, therapies gave me the tools I needed. Body based trauma healing altered the loop of pain reaction by enabling me to expand my tolerance so I could actually feel–not fight–my feelings. An online support group encouraged me to become curious about my painful sensations, instead of tightening against them or avoiding them. I learnt how to allow my muscles to relax enough to reveal the memories and emotions my body had been suppressing.

My chronic pain started when I was 29. Now 72, I no longer identify as having chronic pain. Now, when pain is triggered, I listen to my body for what it needs. I have learnt to be with the sensations and feel compassion for myself. I am no longer afraid of my bodily sensations and do not create secondary pain from guarding against the sensations; even if some discomfort remains, I feel more at ease.

Most of the healing treatments I found helpful were discovered on my own. I wish my doctors had spoken to me about the link between trauma and chronic pain so they could have guided me in my healing journey. It is my hope that by understanding my experience, doctors will keep an open mind when exploring the factors that contribute to chronic pain.

Patient author

Cite this as: *BMJ* 2026;392:s59

CASE REVIEW

Young man with rectal bleeding

A man in his late teens presented with a six month history of painless bright red blood in his stool and on wiping. He also reported subjective, non-specific weight loss over the same period. The patient had a history of constipation from the age of 5 and used osmotic laxatives and timed toileting during his school years. However, when he left school, these routines stopped and he noted that the sensation of the need to defecate had reduced.

Routine blood tests including full blood count, electrolytes, and inflammatory markers were unremarkable, and he was initially managed for suspected haemorrhoids with a high fibre diet, increased fluid intake, and supplemental stool softeners. When his symptoms did not improve, he was referred for a surgical opinion.

Digital rectal examination revealed a soft lobular lesion which was mobile and not tethered to the underlying musculature, confirmed by colonoscopy. Colonoscopy showed no other pathology (including inflammatory bowel disease) and biopsies were performed.

1 What are the differential diagnoses?

2 What is the most likely diagnosis?

3 What is the management of this condition?

Submitted by David Mackrill and Lauren Neill

Patient consent obtained.

Cite this as: *BMJ* 2026;392:e087498

answers

CASE REVIEW **Young man with rectal bleeding**

1 What are the differential diagnoses?

Differential diagnoses for the rectal bleeding and mass include rectal adenocarcinoma, benign soft tissue tumours (leiomyoma and lipoma), polyps (adenomatous, juvenile, Peutz-Jegher's syndrome), solitary rectal ulcer syndrome), and lymphoma. All such lesions can look very similar macroscopically and formal histopathology is required to differentiate them. Inflammatory bowel disease is an important differential diagnosis to consider in a young patient like this, as Crohn's disease could potentially present with a palpable abscess or fistulating disease. Rectal adenocarcinoma is unusual in a patient this young. Although rectal cancer or other mass lesions might have bleeding as the only symptom, disordered defecation symptoms are not uncommon with these conditions.

2 What is the most likely diagnosis?

Solitary rectal ulcer syndrome (SRUS), which has developed as a result of dyssynergic defecation.

Dyssynergic defecation occurs when there is dysfunction of the pelvic floor muscles that leads to difficulty defecating. This might be due to toilet habits (eg, delaying passing stool, straining), eating disorders, neurological disorders (eg, Parkinson's disease), or psychological distress.

SRUS has a documented incidence of 1 in 100 000/year. It is caused by a hypertonic and/or dyssynergic pelvic floor, which requires patients to exert high rectal pressures for defecation to overcome the increased pelvic floor muscle tone. These high pressures result in mucosal ischaemia and sheer forces that cause the SRUS lesions. Despite the name, most cases of SRUS do not manifest as a solitary ulcer. Many lesions are polypoid and commonly occur anteriorly and within 10 cm of the anal verge. Common presentations of SRUS include painless rectal bleeding, constipation, excessive straining, tenesmus, and passing mucus.

Clinical examination is important for diagnosis of SRUS. Colonoscopy, which can include biopsies, is the optimal investigation for rectal blood loss and should be considered in any patient with rectal bleeding who hasn't had this investigation previously, even in young adults. A flexible sigmoidoscopy may be considered as an alternative, but it can miss more proximal pathology including concurrent terminal ileal disease (which is seen in Crohn's disease).

Anorectal physiology testing (including transanal ultrasound, manometry, and nerve conduction studies) can provide additional information in functional defecation disorders. However, no guidelines currently exist to inform their use.

3 What is the management of this condition?

Cases are treated with dedicated pelvic floor physiotherapy, patient education, and behaviour modification. Pelvic floor physiotherapy (including biofeedback) to assess and address the defecatory disorder may be used to correct dyssynergia. Dietary changes (such as increasing fibre intake) and bulk laxatives can also be beneficial. Most patients will make a full recovery, defined as resolution of symptoms, by using these interventions. Early recognition and treatment of dyssynergic defecation has the potential to prevent complications such as SRUS and rectal prolapse.

More severe cases, where the above measures have been ineffective or there is rectal prolapse, may require surgical intervention.

LEARNING POINTS

- Defecation disorders can occur as a result of pelvic floor dysfunction.
- Diagnosis of dyssynergic defection and SRUS is aided by the clinical presentation, colonoscopy, and anorectal physiology testing.
- SRUS is an uncommon rectal disorder caused by a hypertonic and/or dyssynergic pelvic floor that leads to difficulties with defecation.

PATIENT OUTCOME

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