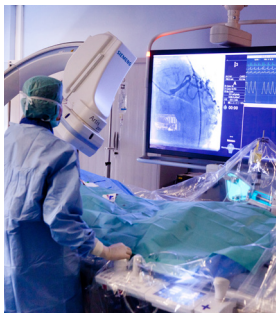
education

RESEARCH REVIEWS Fortnightly round up from the leading medical journals

Acute coronary syndrome in older adults

In older adults presenting with acute coronary syndrome (ACS), no difference in mortality was found in those who received early invasive treatment compared with conservative management, in a new systematic review and meta analysis. Investigators reviewed trials of people presenting with ACS over the age of 70, and defined early invasive treatment as receiving coronary angiography, coronary revascularisation with percutaneous coronary intervention, or coronary artery bypass grafting within 72 hours. Conservative management was guideline-directed medical therapy with invasive treatment in specific situations (eg, ongoing ischaemia or recurrent myocardial infarction). The average age of participants was 82.6 years and 46% were women. The 22%



reduction in risk of recurrent myocardial infarction with early invasive treatment (95% confidence interval 0.67-0.91) was offset by a 60% higher risk of major bleeding (1.01-2.53).

JAMA Intern Med doi:10.1001/jamainternmed.2025.2058

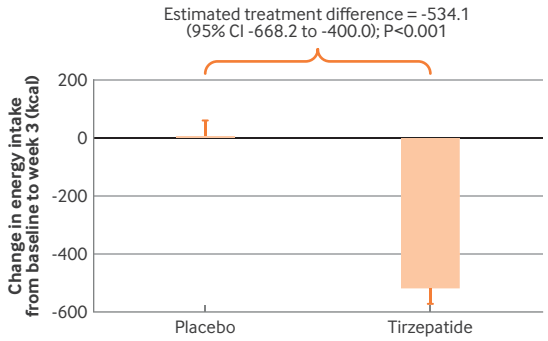
Monthly jabs to turn the tide?

A monthly weight loss injection could be a more convenient and sustainable option than weekly tirzepatide or semaglutide. Maridebart cafraglutide (MariTide for short), is a long-acting peptide-antibody conjugate that includes GLP-1 receptor agonist effects, and can be given monthly, but is it as effective? A phase II study with 592 participants found that MariTide led to weight reduction in people with obesity of between 12.3%-16.2% depending on the dose after 52 weeks,

Ingestive behaviour with tirzepatide

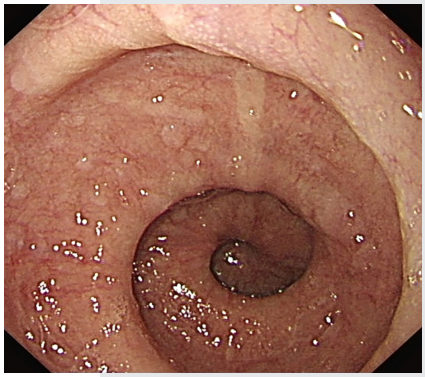
Talk to anyone who takes tirzepatide—or get sucked into any tirzepatide social media algorithm—and you'll hear people say how they no longer feel hungry or get persistent, intrusive thoughts about eating (known as "food noise"). It's surprising, then, to hear that the underlying mechanisms for weight reduction with tirzepatide "are unknown," according to a study in *Nature Medicine*. The small trial measured participants' energy intake at an all-you-can-eat meal three weeks after starting tirzepatide or placebo, and found that those taking tirzepatide consumed over 500 kcal less than those in the placebo group (figure). The authors conclude that their findings "suggest tirzepatide reduces food intake, potentially by impacting ingestive behavior."

Nature doi:10.1038/s41591-025-03774-9



Change in energy intake from baseline to week three in placebo and tirzepatide groups

MARTIN CK, ET AL. *NAT MED* 2025 DOI:10.1038/S41591-025-03774-9



CLINICAL PICTURE

Spiralling appearance of the oesophagus

This man in his early 70s with type 2 diabetes mellitus presented with a one year history of intermittent dysphagia and regurgitation of both liquids and solids, retrosternal pain, and 4 kg weight loss.

Barium swallow showed irregular oesophageal dilation. Oesophago-gastro-duodenoscopy showed a spiralling appearance, with spastic contractions of the lower oesophagus, and the gastro-oesophageal junction continuously closed during gas insufflation. The diagnosis of type III (spastic) achalasia was confirmed by high resolution oesophageal manometry, which demonstrated the lack of coordinated peristalsis and impaired relaxation of the lower oesophageal sphincter (LES).

Type III achalasia is a rare form of achalasia characterised by premature oesophageal contractions, affecting the mid and distal oesophagus and leading to symptoms such as

compared to 2.5% with placebo. HbA1c reductions of between 1.2-1.6 percentage points were found in those with obesity and diabetes, paving the way for phase III trials.

N Engl J Med doi:10.1056/NEJMoa2504214

Sponge on a string for Barrett's oesophagus

One way to reduce the need for repeat endoscopy for people with Barrett's oesophagus is to use a capsule sponge. Patients swallow a capsule that is attached to some surgical string; inside the stomach the outer coating dissolves to release a sponge; pulling the string brings the sponge back up, taking a sample of cells from the oesophagus along the way. A real world evaluation of 910 patients with Barrett's oesophagus concluded that people in low-risk groups can be managed with a nurse-led capsule sponge service.

Lancet doi:10.1016/S0140-6736(25)01021-9

Diabetes deprescribing

Deprescribing in older people with type 2 diabetes can be a hard sell, particularly for the many patients who have put up with a substantial treatment burden for many years on medical advice that they need to get their sugars down. Priming patients for deprescribing discussions before the consultation, known as patient activation, could help. One of the first controlled trials of deprescribing in type 2 diabetes recruited people with type 2 diabetes over the age of 75 taking insulin or a sulphonylurea, and a glycated haemoglobin (HbA1c) of 8% or lower. The patient activation arm involved giving the patient a one page handout before the consultation, including an explanation of the balance of benefits and risks of tight glycaemic control and questions designed to get them thinking about their values and preferences. When coupled with "physician academic detailing" (a 45 minute teaching session), patient activation led to more deprescribing than physician academic detailing and a healthy lifestyle handout for patients (15.8% *v* 9%).

JAMA Intern Med doi:10.1001/jamainternmed.2025.2015

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

Cite this as: *BMJ* 2025;390:r1365

dysphagia, chest pain, and weight loss. The diagnosis is confirmed through high resolution oesophageal manometry, showing premature contractions and LES dysfunction.

This patient declined surgical myotomy and was treated with oral calcium channel blockers with limited symptomatic relief. He was advised to eat smaller, more frequent meals and avoid eating too quickly to improve his oral intake.

Dan Liu; Zhi Hu (huzxwk@swmu.edu.cn), The Affiliated Hospital of Southwest Medical University, China

Patient consent obtained.

Cite this as: *BMJ* 2025;390:e081229

MINERVA From the wider world of research

Cancer screening

Almost everyone believes that cancer screening is a good thing because it leads to early detection of malignancy and better outcomes for people who screen positive. An essay in the *New Yorker* explains why almost everyone is wrong (https://www.newyorker.com/magazine/2025/06/23/the-catch-in-catching-cancer-early). It's worth reading even by doctors who think they understand lead time bias, predictive values and Bayesian probability. Muir Gray and colleagues (*BMJ* 2008 doi:10.1136/bmj.39470.643218.94) were right nearly 20 years ago when they wrote: All screening programmes do harm; some do good as well, and, of these, some do more good than harm at reasonable cost.

Novelty in science

Scientific papers often boast about the novelty of their findings. But novelty doesn't necessarily imply usefulness or importance. By contrast, investigations that replicate previous work can be valuable without being novel. In an attempt to measure novelty and find out whether it matters, an open competition to devise and validate indicators of scientific novelty in academic papers is running until November (*Nature* https://www.nature.com/articles/d41586-025-01882-7go.nature.com/3hhsdp3).

Sweetened beverages

Sugar sweetened beverages are diabetogenic, obesogenic, and, according to many experts, harmful to health. Nevertheless, one disease they don't seem to cause is dementia. Longitudinal data on 11 000 older people taking part in US cohort studies in which sweetened beverage consumption had been assessed by food frequency questionnaires showed no association between higher consumption and a subsequent diagnosis of any type of dementia (*JAMA Psych* doi:10.1001/jamapsychiatry.2025.1230).

Postoperative outcomes

Follow-up of two million patients who underwent major surgery in the United States finds that those who were operated on by female surgeons experienced slightly lower rates of complications, readmission, and death (*JAMA Surg* doi:10.1001/jamasurg.2025.0866). These better outcomes were only seen in female patients treated by female surgeons. Where male patients were concerned, outcomes weren't affected by the gender of the surgeon.

Atrial fibrillation

An analysis of a primary care electronic database compared 34 000 adults with atrial fibrillation with 91 000 without atrial fibrillation (*Heart* doi:10.1136/heartjnl-2024-324618). Hardly surprisingly, the commonest health conditions associated with atrial fibrillation were cardiovascular, with cardiomyopathy and heart failure at the top of the list. Several non-cardiac conditions also showed statistically significant associations, but only pleural effusion and oesophageal malignancy carried a high risk.

Placebos

Compared with modern high technology medicine, which tends to deliver small benefits at exorbitant costs, placebos are cheap, free of adverse effects, and a seriously underused and under-researched resource. Numerous anecdotes testify to the power of belief and expectation on otherwise intractable symptoms. Indeed, the fact that doctors place so much faith in the outcomes of placebo controlled trials is a tacit acknowledgment of the power of the placebo effect (*New York Rev* https://www.nybooks.com/articles/2025/06/26/what-do-you-expect-the-power-of-placebos/).

Cite this as: *BMJ* 2025;390:r1360

Aspirin

Marc George,[1] Sama ElSayed,[1] Cormac Magee,[2] Marie Elsya Speechly-Dick[3]

Full author details on bmj.com

Correspondence to: M George marc.george@ucl.ac.uk

Practical Prescribing is a series produced in conjunction with the *Drug and Therapeutics Bulletin* to highlight important issues for prescribers to consider and prompts for shared decision making between prescribers, patients, and their carers. Targeted at all medical and non-medical prescribers, particularly doctors in training, the series covers medicines commonly prescribed in primary and secondary care.

Advisers to this series are Fraz Mir, consultant physician at Addenbrooke's Hospital, Cambridge, and David Phizackerley, deputy editor of *Drug and Therapeutics Bulletin*.

CPD READING

0.5 HOURS

A 68 year old woman presents to her general practitioner with central chest pain on exertion, which she has been experiencing for several months. The pain radiates to her neck, is associated with shortness of breath, and is relieved by rest. She has a 10 year history of hypertension and type 2 diabetes and is taking metformin, amlodipine, and atorvastatin. Examination is unremarkable. Your working diagnosis is stable angina, and you refer her for an outpatient cardiology assessment. You are considering prescribing aspirin for suspected ischaemic heart disease while she waits for specialist review.

WHAT YOU NEED TO KNOW

- Aspirin has multiple indications, including secondary prevention of coronary, cerebrovascular, and peripheral vascular disease; treatment of acute coronary syndromes and ischaemic stroke; prevention of pre-eclampsia; and colorectal cancer in Lynch syndrome, as well as pain, migraine, and pyrexia
- Consider starting aspirin for a clinical diagnosis of stable angina while awaiting a formal cardiology assessment
- Before prescribing aspirin, screen for gastrointestinal symptoms, assess risk of gastrointestinal bleeding, and consider co-prescribing a proton pump inhibitor
- Enteric coated aspirin does not reduce the risk of gastrointestinal side effects and is therefore not recommended

How often is aspirin prescribed and how does it work?

Aspirin (acetylsalicylic acid) is one the most commonly used drugs worldwide.[1] In England, over 1.6 million prescriptions for low dose aspirin are issued in primary care a month.[2] This is likely an underestimate as it is also available widely over the counter. However, internationally, particularly in low and middle income countries, aspirin is underused in the secondary prevention of cardiovascular disease.[3]

The mechanism of action of aspirin (figure) was first elucidated by John Vane in 1971.[1] It has multiple indications in adult patients but is not licensed for use in children under the age of 16 years due to the risk of Reye's syndrome.

Secondary prevention of coronary artery disease and stroke

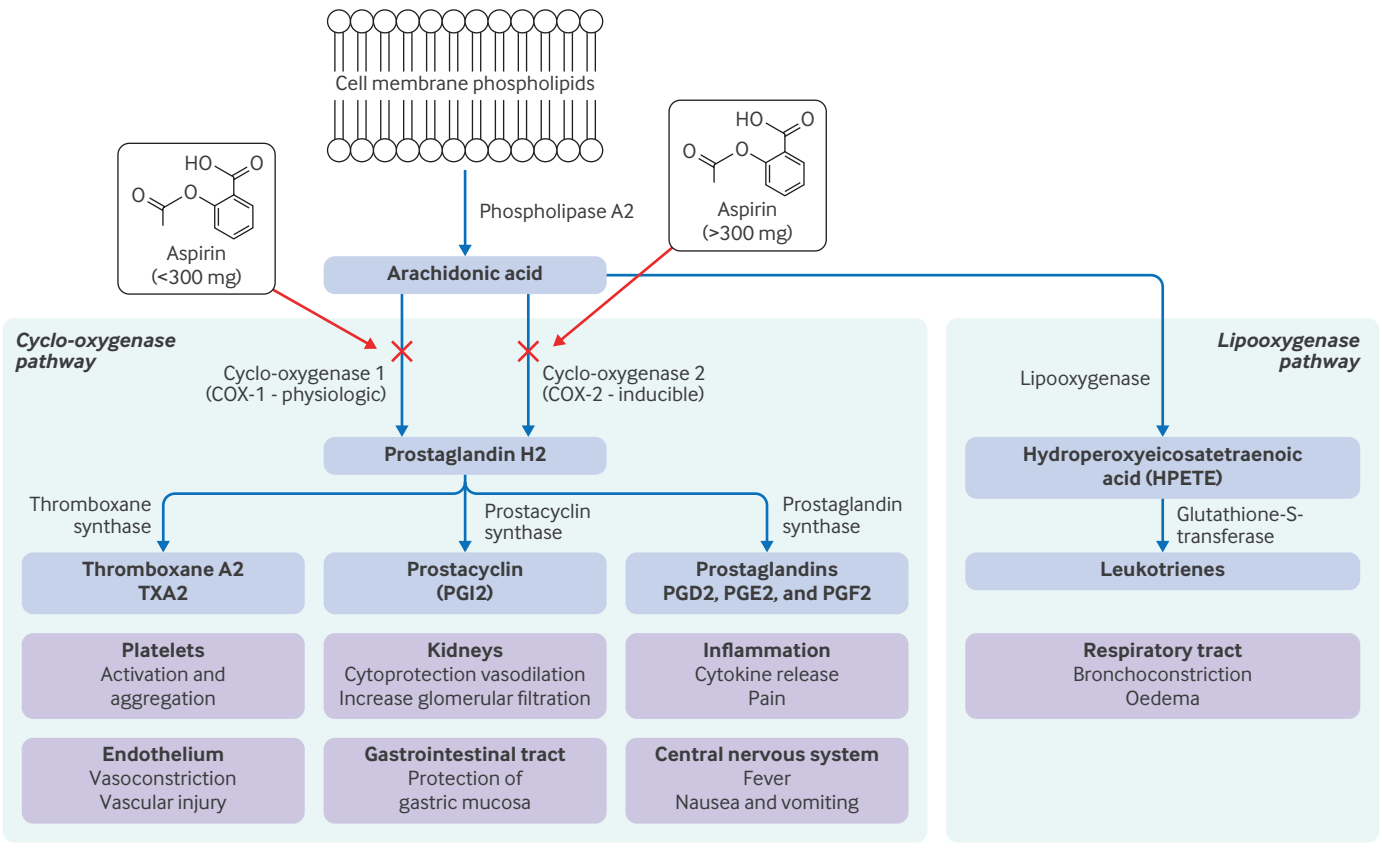
At low dose (<300 mg), aspirin exerts an antiplatelet effect by irreversibly inhibiting cyclo-oxygenase 1 (COX-1) within platelets, blocking the formation of thromboxane A2 from arachidonic acid.[1]

Low dose aspirin is most commonly prescribed for the secondary prevention of cardiovascular disease, where platelet activation and aggregation plays a major role in the pathogenesis of acute cardiovascular events.[7] In high risk patients with coronary artery disease (defined by NICE as patients aged ≥65 years or with atherosclerosis in ≥2 vascular territories or with ≥2 risk factors) it may be used alongside low dose rivaroxaban. When considering this combination, the potential benefit must be weighed against the increased risk of bleeding and the patient involved in shared decision making.[8] However, aspirin is no longer recommended for the primary prevention of coronary artery disease[9] because, in this population, the bleeding risk outweighs the cardiovascular benefits.[10]

In patients with peripheral vascular and cerebrovascular disease, clopidogrel is the antiplatelet of choice for secondary prevention. However, if clopidogrel is not tolerated aspirin may be used instead in the secondary prevention of stroke. In this context, clinical guidelines recommend its use in combination with modified-release dipyridamole.[11] Although this combination reduces risk of future stroke more than aspirin monotherapy, its use is limited by increased side effects and is not commonly used in current practice.[12] If clopidogrel is not tolerated in the secondary prevention of peripheral vascular disease, aspirin may be used, and its combination with low dose rivaroxaban should be considered in high risk patients.[8]

It is also prescribed as part of the treatment of acute coronary syndromes and ischaemic stroke (initial dose(s) 300 mg).[13]

In our example case above, if aspirin is not contraindicated, it should be considered if stable angina is likely before confirmatory diagnostic testing with computed tomography coronary angiography or further specialist investigations, such as non-invasive functional testing and invasive angiography.[17]



Mechanism of action of aspirin. At low dose (<300 mg) aspirin exerts its antiplatelet effect by irreversibly inhibiting cyclo-oxygenase 1 (COX-1) within platelets, blocking the formation of thromboxane A2 from arachidonic acid. Thromboxane A2 increases aggregation by upregulating expression of the platelet cell membrane glycoprotein complex GP IIb/IIIa, which binds circulating fibrin.[4] Higher doses of aspirin (>300 mg) also block COX-2, resulting in reduced prostaglandin production which mediates its analgesic and antipyretic effects. (Adapted from Rolnik et al "Prevention of preeclampsia with aspirin"[5])

Pre-eclampsia and pregnancy

In pre-eclampsia, data suggest that suboptimal trophoblastic invasion leads to inflammation, endothelial damage, and platelet activation, resulting in thrombotic events and placental infarcts. Therefore, it was hypothesised that aspirin would exert a protective effect by reducing platelet aggregation and thereby improving placental health.[5]

Clinical trials investigating the role of aspirin in preventing pre-eclampsia began in the 1980s,[18] but, because of heterogeneity across studies, it took until the 2010s for the treatment to be recommended in international guidelines.[19] Subsequent high quality studies such as the Aspirin for Evidence-Based Preeclampsia Prevention trial have provided further evidence of benefit.[20] Therefore, aspirin should be offered to women at high risk of pre-eclampsia,[21] and current UK guidelines recommend 75-150 mg of aspirin from 12 weeks.

Analgesia and pyrexia

Higher doses of aspirin (>300 mg) are required to block COX-2 and reduce prostaglandin production, which mediates its analgesic and anti-pyrexial properties. Cochrane systematic reviews and meta-analyses have found that aspirin analgesia is effective for tension-type headache[22] and postoperative pain,[23] but less so for acute pain.[24] It has an established evidence base in the management of acute migraine.

Aspirin's antipyrexial effects have been used for many years[1] and have been demonstrated in a randomised controlled trial in the context of upper respiratory tract infections, where its effect was similar to that of paracetamol.[26]

Lynch syndrome

There is increasing evidence that aspirin use may reduce the risk of and improve survival in certain cancers by showing several protective mechanisms, including reducing proliferation, angiogenesis, and metastatic spread.[27]

In the UK its use is recommended in national guidelines to reduce the risk of colorectal cancer in patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer).[28 29] However, use in the general population is limited by the increased bleeding risk.[29]

In patients with Lynch syndrome, who have an approximately 50% lifetime risk of developing colorectal cancer, the risk:benefit ratio is improved with aspirin. This has been demonstrated in several trials, most notably the CAPP2 trial.[16] Current guidelines recommend the 600 mg dose,[28] but results from the recently published CAPP3 trial demonstrated that aspirin 100 mg was non-inferior to 600 mg daily.[30]

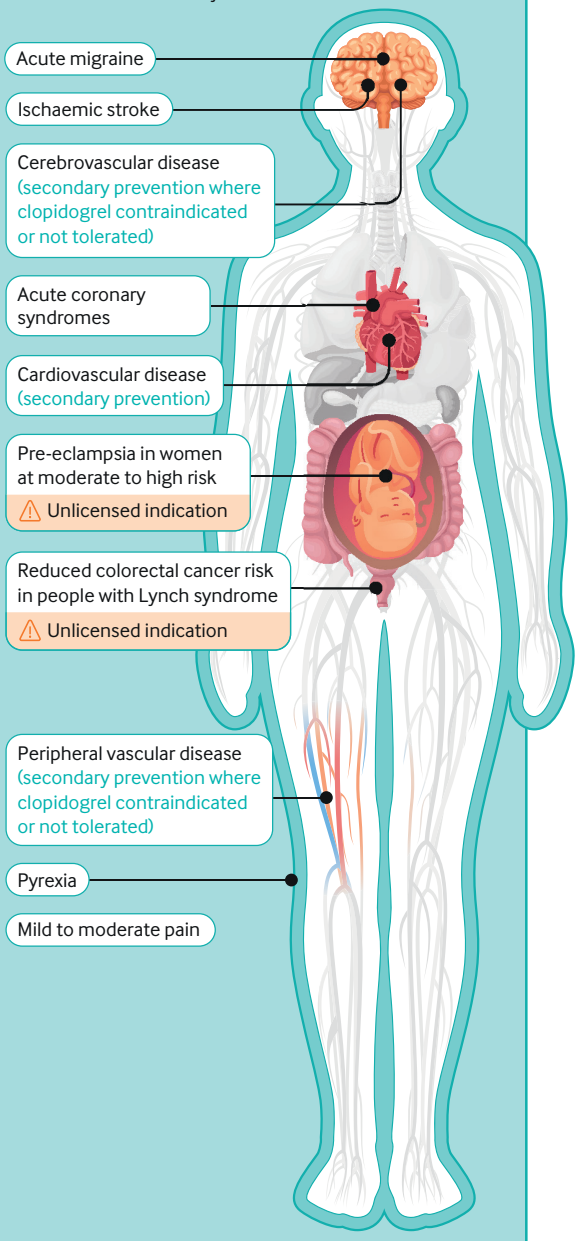
thebmj Visual summary

Prescribing considerations: Aspirin

Aspirin (acetylsalicylic acid) is one of the most commonly used drugs worldwide. This graphic summarises the main indications for aspirin, as well as some important considerations when prescribing it.

Indications

UK prescribing guidelines from the British National Formulary (BNF)



- Acute migraine
- Ischaemic stroke
- Cerebrovascular disease (secondary prevention where clopidogrel contraindicated or not tolerated)
- Acute coronary syndromes
- Cardiovascular disease (secondary prevention)
- Pre-eclampsia in women at moderate to high risk
  - ⚠ Unlicensed indication
- Reduced colorectal cancer risk in people with Lynch syndrome
  - ⚠ Unlicensed indication
- Peripheral vascular disease (secondary prevention where clopidogrel contraindicated or not tolerated)
- Pyrexia
- Mild to moderate pain

What should I monitor?

In advance of starting:

- Full blood count, specifically for anaemia
- Renal function
- Liver function

Once patient is established on aspirin:

Minimum of annual blood tests. More frequent if initial tests were abnormal or patient develops new symptoms

- Full blood count
- Renal function

Important adverse effects

- Dyspepsia
- Increased risk of bleeding and anaemia
- Hypersensitivity: asthma attack, angioedema, urticaria and rhinitis

Important interactions

British National Formulary:
Lists 196 interactions, of which 140 are classed as severe

Most common concerns:

- Increased bleeding risk
- Nephrotoxicity

Check possible interactions in your local database

Discuss the risks and mitigating measures with the patient

Avoid if

- Aged <16 years, unless specifically indicated (such as Kawasaki disease)
- Avoid high dose aspirin (>300 mg per day) in pregnancy after 30 weeks
- Breast feeding
- Previous hypersensitivity reaction to aspirin or an NSAID (given cross reactivity)
- Severe renal and liver impairment

Caution if

If needed for secondary prevention of cardiovascular disease, **discuss with specialist**

- Mild-to-moderate renal and liver impairment
- Asthma
- Anaemia or high bleeding risk
- Thyrotoxicosis
- Previous peptic ulcer
- G6PD deficiency
- History of gout

thebmj Read the full article online https://bit.ly/bmj-asp

See more visual summaries http://www.bmj.com/infographics

What should I discuss with patients before starting treatment?

Aspirin is available over the counter, in a range of doses and in combination formulations, such as with paracetamol and caffeine. Therefore, establish whether the patient has had aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) before and for what indication. If they have taken one before, ask why they took it, what effects it had, and whether they experienced any adverse effects.

For patients who require aspirin for cardiovascular indications, understanding the patient's individual cardiovascular risk is an important starting point and can help frame the discussion. While many cardiovascular disease risk calculators are designed for use in the setting of primary prevention, there are also dedicated risk calculators freely available for use in secondary prevention, such as "SMART" from the European Society of Cardiology phone application[31] and "REACH" available online.[32]

For patients being advised to take aspirin for the secondary prevention of cardiovascular disease, the medication is for risk reduction and does not usually affect symptoms, which may lead to reduced adherence.[33] As in our case study, commencing aspirin may not lead to a resolution of angina. Encourage patients to take their medication by giving clear information about the benefits, which can be supplemented by directing patients to online resources such as the British Heart Foundation.

When they are clinically indicated, offer first-line anti-anginal therapies such as beta blockers and calcium channel blockers in primary care.[17] Support patients to acknowledge and address modifiable cardiovascular risk factors, including diabetes, smoking, diet, and exercise. This may include advice given during the initial consultation and continued signposting to self-help resources.[13 15]

Patients often ask if they can take over the counter medications in addition to aspirin. While there are no additional risks associated with paracetamol, caution against the regular use of NSAIDs because of the increased risk of side effects including gastrointestinal bleeding.[34] Also, caution against taking prescribed aspirin together with over-the counter aspirin preparations unless it is for its additional analgesic properties, such as for migraine.

What are the important adverse effects to discuss?

Common side effects include dyspepsia and increased risk of bleeding, and these require special consideration.[6] Uncommon side effects include consequences of severe bleeding, such as gastrointestinal and intracranial haemorrhage and menorrhagia. Aspirin hypersensitivity reactions may also occur, especially in high risk individuals.

Dyspepsia and gastrointestinal bleeding

Aspirin can have multiple adverse effects on the upper gastrointestinal tract, ranging from dyspepsia to peptic and duodenal ulceration and gastrointestinal bleeding. Observational data from a French nationwide survey including 986 patients aged over 50 taking low dose aspirin suggest that about 15% of patients report upper gastrointestinal symptoms.[35] The principal mechanism is thought to relate to aspirin's inhibition of COX-1 and the depletion of protective gastric mucosal prostaglandins, although other mechanisms have been proposed.[36]

Older patients are particularly at risk of developing anaemia due to occult bleeding while being treated with long term, low dose aspirin.

When counselling patients about starting long term low dose aspirin, enquire about current upper gastrointestinal symptoms, such as dyspepsia and reflux. If these are present, ask whether the patient has any additional "alarm" symptoms, including unexplained appetite loss and weight loss. Also ask if they have a history of, or additional risk factors for, gastrointestinal bleeding, including a history of gastroduodenal ulcers, use of medications that increase the risk of bleeding (such as other antiplatelets, anticoagulants, NSAIDs, corticosteroids) and age >75 years.[9] If the patient has dyspepsia with alarm symptoms or additional bleeding risk factors, offer the patient a proton-pump inhibitor for gastroprotection.[9] Those with alarm symptoms should also be referred via cancer pathways for urgent endoscopy and review.

Usually, aspirin can be continued unless dyspepsia symptoms are not well controlled or if recommended to stop by a specialist while undergoing investigation for alarm symptoms. If aspirin is discontinued, consider switching to an alternative antiplatelet such as clopidogrel.

Other bleeding

One meta-analysis suggests that aspirin use in the secondary prevention of vascular disease marginally increases the risk of haemorrhagic stroke compared with control, with an absolute increase of 0.11% (0.65% *v* 0.54%), however, this did not reach statistical significance.[15] In patients with a history of major intracerebral bleeding, specialist input should be sought before commencing aspirin.

Aspirin hypersensitivity and allergy

Aspirin use can result in hypersensitivity reactions—including rhino-conjunctivitis, bronchospasm, urticaria, angioedema, and anaphylaxis—which are thought to be as a result of COX inhibition. In sensitive individuals, this reduces levels of the anti-inflammatory prostaglandin E2 while increasing the synthesis of leucotrienes, tilting the balance in favour of inflammation.[40] Patients may also have type I and IV hypersensitivity reactions. There is notable cross-sensitivity with other NSAIDs; therefore, aspirin is contra-indicated in patients in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.[6]

Internationally, particularly in low and middle income countries, aspirin is underused in the secondary prevention of cardiovascular disease

Although reactions can be idiosyncratic with a population prevalence of ~0.6%, it is much higher in patients with atopy, especially allergic rhinitis and asthma.[41] Therefore, use with caution in this population.

Other cautions

In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, aspirin can rarely precipitate haemolysis,[44 45] and so this cohort should be monitored carefully. Low dose aspirin reduces uric acid excretion and can increase the risk of gout,[46] so in patients with gout consider alternative treatments such as clopidogrel.[47] High dose aspirin can increase free thyroid hormone levels by displacing them from transthyretin,[48] so caution is recommended in patients with hyperthyroidism.

What to consider when prescribing?

Aspirin is available as a standard, dispersible tablet and as a gastro-resistant (enteric coated) one. However, enteric coated aspirin has not been shown to reduce the risk of gastrointestinal side effects[49] and is therefore not recommended.[6] Aspirin is also available as a suppository, which may be of use when the patient is unable to swallow safely (such as patients who have acute stroke). These are available in 150 and 300 mg formulations.[6]

When considering aspirin, it is important to establish whether the patient is already being treated with another antiplatelet or anticoagulant for a different indication. Outside the treatment of acute or recurrent cardiovascular events, the addition of aspirin in these circumstances is not usually required.

In acute coronary syndromes (with or without percutaneous coronary intervention), aspirin is usually given alongside a second antiplatelet agent for one year, before de-escalating back to aspirin monotherapy. If the patient also requires anticoagulation after acute myocardial infarction (such as for atrial fibrillation), several factors (including bleeding, thromboembolic, and cardiovascular risks) as well as patient wishes should guide duration of triple (dual antiplatelet + anticoagulation) or dual (single antiplatelet + anticoagulation) therapy.[50] In high risk patients with coronary and peripheral vascular disease, the combination of aspirin and low dose rivaroxaban can be considered for long term secondary prevention.[8]

Interactions

Aspirin can interact with a wide range of medications, with increased bleeding risk and nephrotoxicity being the most common concerns. For example, co-administration of a selective serotonin reuptake inhibitor with aspirin after myocardial infarction can increase the risk of bleeding.[51] Check possible interactions in your local database and discuss the risks and mitigating measures with the patient. In the UK, the interaction checker in the *British National Formulary* can be used.[34]

Pregnancy and breastfeeding

In pregnancy, low dose aspirin (75-150 mg) is generally considered safe with no associated increased risk of congenital heart defects or other developmental abnormalities.[5] However, high dose aspirin (≥300 mg) in pregnancy should be avoided after 30 weeks because of multiple risks to the fetus.

As aspirin can pass into breast milk, it should be avoided by women who are breast feeding because of the risk of Reye's syndrome in the infant.[6] Reye's syndrome is a rare paediatric illness with high mortality characterised by a rapidly progressive acute encephalopathy with hepatic dysfunction. A strong association with aspirin administration led to recommendations against its use in children under the age of 16 years unless specifically indicated (such as for Kawasaki disease).[52]

EDUCATION INTO PRACTICE

- Think about the last time you prescribed aspirin for a patient with cardiovascular disease. Did you calculate their individual risk and discuss with them the anticipated reduction associated with aspirin use?
- How often do you ask about risk factors for gastrointestinal bleeding before prescribing aspirin long term?

What should I monitor during the course of the prescription?

In advance of starting aspirin, check the patient's full blood count, assessing specifically for anaemia. Also check renal and hepatic function; the *British National Formulary* recommends caution in patients with mild to moderate renal and hepatic impairment and to avoid in severe impairment.[6] However, if needed for the secondary prevention of cardiovascular disease, low dose aspirin should be considered with input from a specialist to help guide decision making.

Once a patient has been established on aspirin, we recommend a minimum of annual bloods to monitor the full blood count, renal function, and electrolytes. If initial bloods were abnormal or the patient develops new symptoms, more frequent monitoring may be required.

How long should treatment continue?

In the context of secondary prevention of cardiovascular disease, aspirin should be continued long term, whereas in pre-eclampsia it is stopped at the birth of the baby.

Review the prescription in the context of new side effects, conditions which increase bleeding risk (such a severe hypertension), and new diagnoses requiring different antiplatelets or anticoagulants. In the UK, these are summarised in the STOPP criteria in the *British National Formulary*.[6] Review prescriptions in patients who are severely frail, where benefits are less certain and risks are increased.[37] Reviews in primary care should happen at least annually once the patient is stable. If the initial indication for aspirin is unclear, consider stopping it.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patients were involved in the creation of this article.

Competing interests: See bmj.com.

Cite this as: *BMJ* 2025;390:e081606

Find the full version with references at doi: 10.1136/bmj-2024-081606

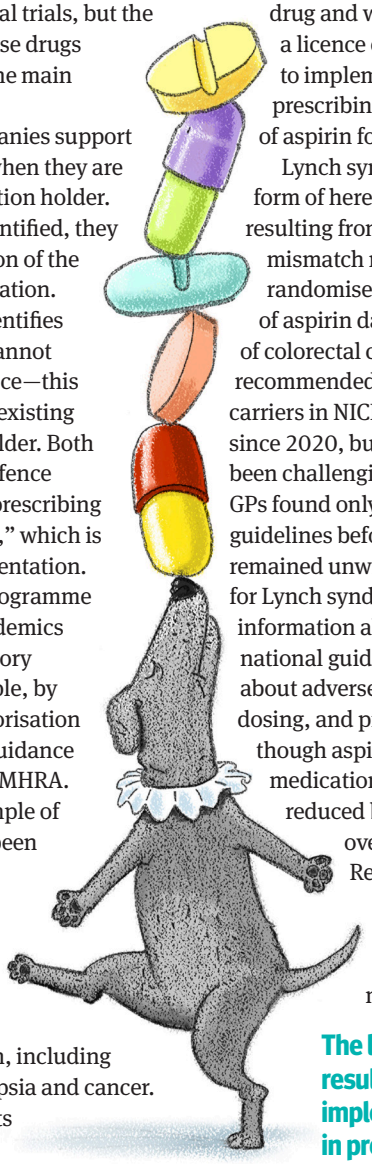
OPINION Ruth Langley and colleagues

Suspending the NHS medicines repurposing programme in England is a missed opportunity

Drug repurposing involves finding new indications for established medicines. New indications are a win for patients, manufacturers, and healthcare systems, and deserve government and academic support. It is therefore disappointing that the NHS medicines repurposing programme in England—a multiagency initiative set up in 2021—was suspended in April 2025. The explanation offered was that opportunities for repurposing were fewer than anticipated. We contend that this is not the key issue. There are many potential candidates, and academic funders are willing to invest in clinical trials, but the final step of bringing these drugs into routine practice is the main challenge.

Pharmaceutical companies support research on medicines when they are the marketing authorisation holder. If a new indication is identified, they can apply for an extension of the licence for the new indication. If an academic group identifies a new indication, they cannot apply to extend the licence—this can only be done by the existing market authorisation holder. Both the GMC and medical defence unions caution against prescribing medications "off-licence," which is then a barrier to implementation. The NHS repurposing programme provided support to academics in navigating the regulatory environment—for example, by identifying market authorisation holders and providing guidance on interactions with the MHRA.

Aspirin is a good example of a drug that has already been repurposed from anti-inflammatory agent to cardiovascular agent. In a linked *BMJ* Education article George and colleagues note new uses for aspirin, including prevention of pre-eclampsia and cancer. Anti-inflammatory effects are achieved with doses of 300-600 mg four times a day, mediated through cyclo-oxygenase 2 (COX-2) inhibition in systemic tissues, whereas other indications exploit the antiplatelet effect of low dose aspirin (75-300 mg) once daily and the irreversible acetylation of COX-1 in platelets. The new indications described are based on information in the *British National Formulary* and National Institute for Health and Care Excellence (NICE) guidelines and not on licence extensions. This reflects that the new indications were identified by academic research groups and that there is little financial incentive for an existing marketing authorisation holder to extend a licence if the product is already a generic drug and widely available. The lack of a licence extension results in barriers to implementation and hesitation in prescribing, as exemplified by the case of aspirin for Lynch syndrome.



MALCOLM WILLETT

Lynch syndrome is the commonest form of hereditary cancer syndrome resulting from mutations in DNA mismatch repair genes. The CAPP2 randomised trial showed that 600 mg of aspirin daily halved the incidence of colorectal cancer. Aspirin has been recommended for Lynch syndrome gene carriers in NICE guidelines (NG151) since 2020, but implementation has been challenging. A survey of 672 British GPs found only 17% were aware of the guidelines before the survey and 20% remained unwilling to prescribe aspirin for Lynch syndrome despite receiving information about the trial results and national guidance. GPs cited concerns about adverse events, uncertainty about dosing, and prescribing off-label, even though aspirin is an over-the-counter medication and adverse events can be reduced by relatively simple measures overseen in primary care. Recent confirmatory data from the CaPP3 trial showed that aspirin 75-100 mg daily is non-inferior to aspirin 600 mg daily in preventing Lynch syndrome cancers with significantly fewer serious adverse events.

The lack of a licence extension results in barriers to implementation and hesitation in prescribing

A similar issue is anticipated for aspirin use after a colorectal cancer diagnosis in selected patients. Recent trial results have shown that patients with colorectal cancer whose tumours harbour mutations in the PIK3CA gene and associated pathway showed a 50% relative reduction in the risk of developing metastases with aspirin. Although this has already been incorporated into US National Comprehensive Cancer Network guidelines, there is no pharmaceutical company poised to extend the licence. Therefore, it is unclear how widely this will be implemented in clinical practice.

Effects of the repurposing programme

The NHS repurposing programme had its first successful licence extension in November 2023. Academic research had identified that anastrozole was effective in preventing breast cancer as well as treating established disease, but it was not licensed for this indication and some practitioners were unwilling to prescribe it as a preventive agent.

Drug repurposing is not a quick or cheap approach, but rather an opportunity where one aspect of drug development, the phase I assessment confirming the drug can be safely used in humans, has been completed. Further mechanistic studies and trials will be needed to establish the new indication. Drug repurposing takes time, as exemplified by the 32-year Lynch syndrome cancer prevention programme. While including a new indication in clinical guidelines or for a commissioning group to support prescribing for the new indication is welcome, until all stakeholders come together to tackle the issue of drug repurposing there will still be barriers to implementation.

Ruth E Langley, oncologist, University College London, UK

Gemma Vilahur, cardiovascular researcher, Research Institute Sant Pau (IR SANT PAU), Barcelona, Spain

Mairead Mackenzie, patient representative, Trustee, Independent Cancer Patient Voices, UK

John Burn, geneticist, Newcastle University Translational and Clinical Research Institute, Newcastle upon Tyne, UK

Cite this as: *BMJ* 2025;390:r1309

STATE OF THE ART REVIEW

Advances in the management of hepatitis B

Ruma Rajbhandari,[1 2] Vy H Nguyen,[2] Abigail Knoble,[2] Gregory Fricker,[1 2] Raymond T Chung[1 2]

[1]Liver Center, Massachusetts General Hospital, MA, USA
[2]Harvard Medical School, Boston, MA, USA

Correspondence to: R T Chung chung.raymond@mgh.harvard.edu

This is a summary of Clinical Review Advances in the management of hepatitis B. The full version can be read here: https://www.bmj.com/content/389/bmj-2024-079579

CPD READING
0.5 HOURS

Hepatitis B remains a major public health threat.[1] Despite the availability of an effective vaccine and antiviral therapies, hepatitis B continues to cause substantial morbidity and mortality worldwide owing to persistent underdiagnosis, variable treatment uptake, and the challenge of achieving a functional cure.[1]

Epidemiology

Chronic hepatitis B is a leading cause of liver disease, including cirrhosis and hepatocellular carcinoma, and contributes to about 1.1 million deaths annually.[2] The highest prevalence of hepatitis B is found in sub-Saharan Africa, East Asia, and the Pacific Islands, where more than 5% of the population is chronically infected, compared with less than 1% in North America and western Europe.[3] However, hepatitis B virus infection remains severely underdiagnosed, with only 30 million (10%) people aware of their hepatitis B virus infection and less than 10% of those eligible receiving treatment.[1] Furthermore, as the global population ages, the increasing prevalence of comorbidities, such as cardiovascular disease, renal impairment, and metabolic disorders, seems to collectively exacerbate the clinical course of hepatitis B virus infection and leads to poorer overall outcomes.[4]

WHAT YOU NEED TO KNOW

- Hepatitis B virus infection remains a pervasive global health challenge, affecting an estimated 254 million people worldwide.
- Substantial progress has been made in the screening, prevention, and management of hepatitis B virus infection. An effective and safe vaccine has enabled the implementation of universal vaccination programs in many countries
- Advances in antiviral therapy have also reduced the risk of disease progression and hepatocellular carcinoma among people already infected with hepatitis B virus. However, low disease awareness and social and structural barriers to care continue to exacerbate inequalities in disease burden across geographical regions

Transmission of hepatitis B virus from mother to child is the primary route of infection in high prevalence areas.[3] Without appropriate prophylaxis, up to 90% of infants born to mothers with hepatitis B virus will develop chronic infection.[5] The introduction of universal infant vaccination programs can be highly successful, as evidenced by the dramatic decrease in prevalence from 10% to less than 1% among children in Taiwan after the implementation of a national universal hepatitis B virus vaccination program, along with corresponding decreases in childhood hepatocellular carcinoma.[6] Hepatitis D virus affects 5% of people who have chronic infection with hepatitis B virus. Hepatitis D virus requires hepatitis B virus for its replication, and this combined infection is considered to be the most severe form of chronic viral hepatitis owing to more rapid progression toward cirrhosis and hepatocellular carcinoma.[12 13]

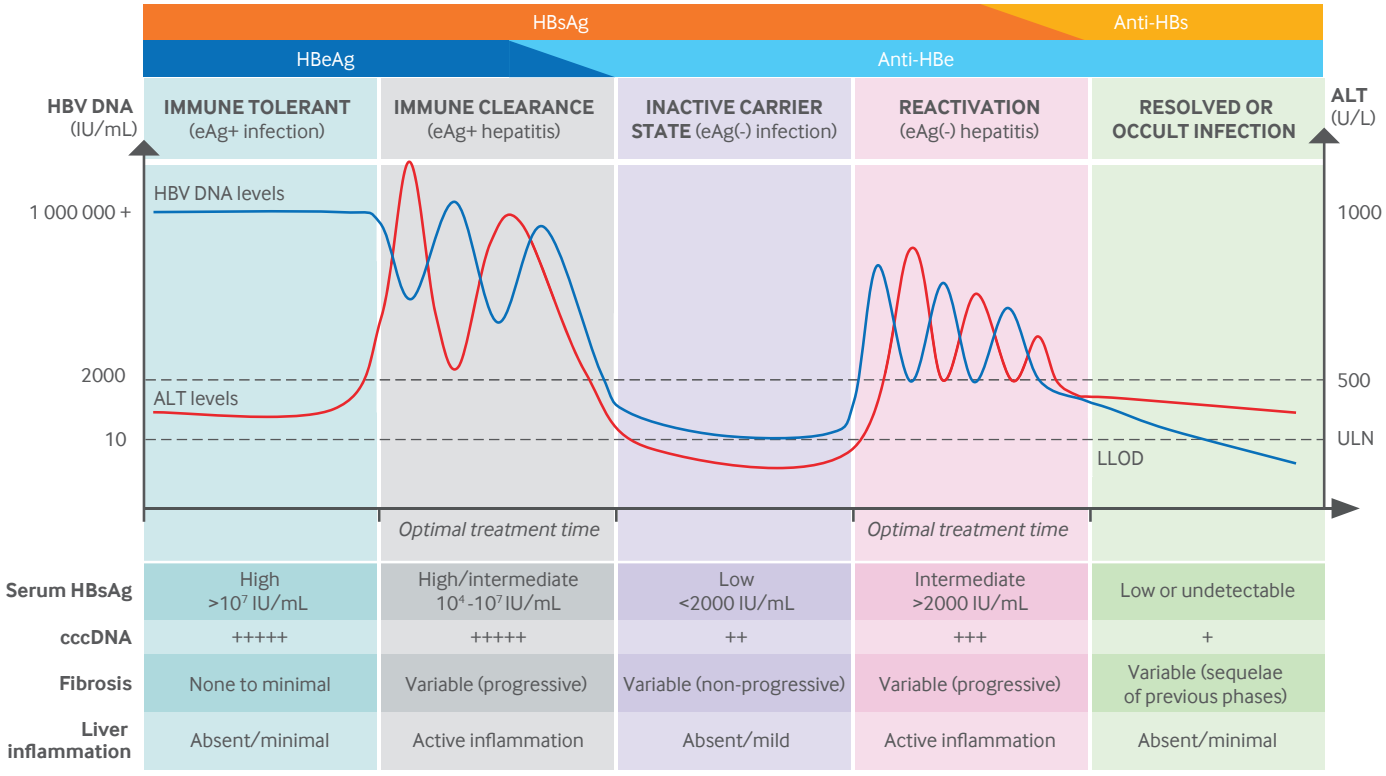
Immunology

Antibodies against hepatitis B virus surface antigens (HBsAg) are the cornerstone of immunity following infection or vaccination and a key marker of protective immunity in clinical practice. However, the continuous presence of viral antigens in chronic hepatitis B infection can lead to diminished ability of the immune system to recognise and mount an effective response to the virus. Both central and peripheral immune tolerance, clinically defined as HBeAg positive, DNA ≥20 000 IU/mL, and no significant immune response, may be abetted by the immunomodulatory effects of hepatitis B e antigen (HBeAg) and HBsAg.[23]

Chronic hepatitis B frequently results in persistent hepatic inflammation, which in turn leads to fibrosis, cirrhosis, and hepatocellular carcinoma. This chronic inflammatory state is primarily driven by cytotoxic CD8 positive T cells that while attempting to eliminate infected cells also cause significant damage to hepatocytes. Over time, the deposition of reparative extracellular matrix components results in hepatic fibrosis and can culminate in cirrhosis. Although the pathogenesis of hepatitis B virus related hepatocellular carcinoma is multifactorial, cirrhosis is a major risk factor. The repeated cycles of hepatocyte injury and repair create an environment conducive to genetic and epigenetic alterations and malignant transformation.[24]

Prevention

Universal infant vaccination, with the timely administration of the birth dose followed by a complete vaccine series, remains the cornerstone of prevention, particularly in high endemic regions where vertical transmission is predominant.[6] In areas with low prevalence, horizontal



Natural evolution and phases of chronic hepatitis B from e antigen positive infection to resolved or occult infection phase. ALT=alanine aminotransferase; cccDNA=covalently closed circular DNA; eAg(-)=e antigen negative; eAg+=e antigen positive; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; LLOD=lowest levels of detection; ULN=upper limit of normal

transmission, especially via sexual contact and unsafe injection practices, is more common.[3] Moreover, immigration from high endemic regions has altered incidence trends in many low prevalence countries, contributing to an increased burden of hepatitis B among immigrant communities.[5] Consequently, tailored screening and vaccination initiatives, along with broader public health education and safe medical practices, are essential.[1 12]

Clinical presentation and natural history

Acute hepatitis B virus infection

Acute hepatitis B virus infection typically manifests clinically following the new horizontal acquisition of infection in adults with mature immune systems. Although symptomatic hepatitis (with icterus in 30%) is the rule in acute hepatitis B, the infection is self-limited and resolves spontaneously in more than 90% of cases, likely a reflection of a brisk T cell mediated response.[25-27] In rare instances, the exuberance of this response may result in potentially life threatening acute liver failure. Reactivation of hepatitis B virus can also present with an acute hepatitis-like picture.[25]

Phases of chronic hepatitis B virus infection

When HBsAg has persisted beyond six months without spontaneous clearance and seroconversion, it has moved into a chronic phase. Chronic hepatitis B has a complicated natural history with four identified phases, classified by HBeAg status. These include chronic e antigen positive infection (immune tolerant), e antigen positive hepatitis, e antigen negative infection (inactive carrier), and e antigen negative hepatitis (figure).[28]

e antigen positive infection (immune tolerant)

Chronic e antigen positive infection is characterised by high hepatitis B virus DNA (usually >1 million IU/mL) and normal alanine aminotransferase concentrations with minimal liver inflammation as the virus is not cytopathic. This phase is thought to occur most frequently in people who are infected perinatally and reflects limited recognition of viral antigen by host CD8 T cells.[29]

e antigen positive hepatitis (immune active)

e antigen positive hepatitis is marked by engagement of an active T cell response and characteristically elevated alanine transaminase concentrations with active necro-inflammation and often progressive liver disease[29]. Hepatitis B virus DNA concentrations typically exceed 20 000 IU/mL.

e antigen negative infection (inactive carrier)

Once a successful T cell response has been evoked, e antigen seroconversion may ensue, and this brings about a quiescent phase of e antigen negative infection. Hepatitis B virus DNA concentrations are low to undetectable, alanine aminotransferase concentrations are normal, and disease is typically stabilised with minimal necro-inflammatory activity and fibrosis.[29]

e antigen negative hepatitis (HBeAg negative immune active)

After e antigen seroconversion, a subset of patients

Summary of screening recommendations for hepatitis B virus infection.[11-32]

High risk groups	WHO 2015, 2017, and 2024	CDC 2023	AASLD 2018	APASL 2015
Household or sexual contacts of people with HBV	✓	✓	✓	✓
People with HIV	✓	✓	✓	✓
People who inject drugs	✓	✓	✓	✓
Men who have sex with men	✓	✓	✓	✓
People who are incarcerated	✓	✓	✓	✓
Blood and organ donors	✓	✓	✓	✓
Migrants from endemic countries	✓	✓	✓	
All adults aged ≥18 once in their lifetime		✓		
All pregnant people and infants born to people with positive HBsAg	✓	✓	✓	✓
People with STIs or multiple sex partners	✓	✓	✓	✓
People with HCV infection, including those about to start DAAs	✓	✓	✓	✓
People with elevated liver enzymes	✓		✓	
People needing immunosuppressive therapy or who have chronic liver disease	✓	✓	✓	✓
Healthcare workers	✓	✓	✓	✓
Travelers to high HBV prevalence countries			✓	
Unvaccinated people aged 19-59 with diabetes			✓	
Sex workers, transgender people, or certain indigenous people	✓		✓	

AASLD=American Association for the Study of Liver Diseases; APASL=Asian Pacific Association for the Study of the Liver; CDC=Centers for Disease Control and Prevention; DAA=direct acting antiviral; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; STI=sexually transmitted infection; WHO=World Health Organization.

may enter a phase of infection called e antigen negative chronic hepatitis B, characterised by the absence of HBeAg, presence of anti-HBe, and fluctuating hepatitis B virus DNA concentrations (usually >2000 IU/mL) and usually elevated alanine aminotransferase concentrations reflective of hepatic inflammation and injury. e antigen negative hepatitis can be as progressive as e antigen positive hepatitis. Patients with untreated e antigen negative hepatitis have a high risk of progression to cirrhosis.[29]

Occult hepatitis B virus infection

Occult hepatitis B virus infection (OBI) is defined as the presence of hepatitis B virus DNA in the liver and/or hepatitis B virus DNA in the blood of people who test negative for HBsAg. OBI is linked with the risk of viral reactivation in patients receiving cancer chemotherapy or other immunosuppression, transmission of hepatitis B virus to blood or organ transplant recipients, and even the development of hepatocellular carcinoma in patients with chronic hepatitis C or other liver disease. Antiviral therapy is not routinely recommended for patients with OBI except in those undergoing therapy with agents that pose a risk for triggering hepatitis B virus reactivation.[30]

Screening, diagnosis, and staging

Screening guidelines

All major screening guidelines currently recommend identifying and screening people with increased risk for hepatitis B virus infection (table). The American Association for the Study of Liver Diseases (AASLD) 2018 guideline additionally recommends screening people born in endemic regions with ≥2% HBsAg prevalence.[29] More recently, the US Centers for Disease Control and Prevention 2023 guidelines recommend a one-time screening for all adults aged ≥18, regardless of risk factors.[31]

Hepatitis B virus reactivation

Patients with chronic or previous hepatitis B virus infection receiving immunosuppressive or immunomodulatory therapies are at risk of hepatitis B virus reactivation, which could lead to hepatitis flares. Rituximab and anti-CD20 regimens, as well as intensive preparative regimens for stem cell transplantation, have the highest risk of provoking reactivation.

Diagnosis and staging

Serological tests and their relevance to immune phases of chronic disease

The diagnosis of chronic hepatitis B requires a persistently positive HBsAg for more than six months. Further evaluation should include a complete history and physical examination to assess for signs of cirrhosis, alcohol and metabolic risk factors, and family history of hepatocellular carcinoma. Laboratory tests should include assessment of liver disease activity and function (full blood count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, albumin, international normalised ratio), markers of hepatitis B virus replication (HBeAg/anti-HBe, hepatitis B virus DNA quantification), tests for co-infection with hepatitis C virus, hepatitis D virus, and HIV, and assessment of hepatitis A virus immunity to determine the need for vaccination. Patients should be educated on measures to prevent transmission and prevent further liver damage (for example, limiting alcohol intake and medications or supplements that could be hepatotoxic, optimising weight) and the importance of long term monitoring, particularly surveillance for hepatocellular carcinoma. Patients older than 40 years, with cirrhosis, or with a family history of hepatocellular carcinoma should undergo ultrasonography and serum α-fetoprotein testing every six months.[29]

Non-invasive imaging modalities to stage hepatitis B virus liver disease

Assessment of liver fibrosis is important to guide treatment and predict prognosis in chronic hepatitis B. In the past, invasive liver biopsy was the only available modality for assessment of liver fibrosis. Over the past decade, elastography has emerged as a first line choice for non-invasive assessment of fibrosis. It measures liver stiffness (a proxy for fibrosis) and can be accomplished using vibration controlled transient elastography (VCTE), ultrasound shear wave elastography (SWE), or magnetic resonance imaging plus slow frequency vibration elastography.[46-48] Both VCTE and SWE can be used to distinguish cirrhosis from non-cirrhotic liver fibrosis with high accuracy but are susceptible to confounding from hepatic necro-inflammation, steatosis, and abnormal aminotransferases, thereby limiting their use in differentiating between mild and moderate fibrosis or in differentiating between stages of fibrosis.[46]

Rationale and goals of treatment

The goals of treatment for chronic hepatitis B are to prevent progression to cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma. Drugs approved for treatment of chronic hepatitis B include pegylated interferon (peginterferon) and oral nucleotide (or nucleoside) analogues; each has been shown to be effective in achieving these goals.[49] Peginterferon is an antiviral cytokine and immunomodulator; it can stimulate the immune response against the virus and enhance covalently closed circular DNA (cccDNA) degradation. Nucleotide analogues are potent hepatitis B virus replication inhibitors, acting at the reverse transcription step to suppress viral replication, although they do not directly affect cccDNA concentrations. Achievement of complete viral suppression with the nucleotide analogues entecavir and tenofovir has been clearly shown to reduce disease progression[50]; HBsAg loss further reduces the risk of incident hepatocellular carcinoma compared with the achievement of complete viral suppression without HBsAg loss.[50] Use of peginterferon as the primary treatment for hepatitis B virus infection has been limited owing to poor tolerability.

Functional cure

The elimination of both cccDNA and integrated hepatitis B virus DNA (virologic cure) remains unlikely with currently approved antiviral agents and therapies in development for hepatitis B virus infection. The clinically meaningful and more achievable functional cure endpoint, defined as sustained undetectable HBsAg and hepatitis B virus DNA after a finite treatment course, has been widely accepted as the goal for newer treatment regimens. HBsAg loss is increasingly recognised as a major surrogate for outcomes in patients and is associated with a lower risk of liver decompensation, hepatocellular carcinoma, liver transplantation, and death.[52] Male sex, older age, inactive carrier state, and lower pre-treatment concentrations of hepatitis B virus DNA and low levels of quantitative HBsAg are associated with higher rates of spontaneous seroclearance without antiviral treatment.[44]

Current treatments

Selection of antiviral therapy

Currently available therapies for chronic hepatitis B virus infection include pegylated interferon and six nucleotide (or nucleoside) analogues. All major treatment guidelines recommend entecavir, tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide as preferred first line therapies owing to their potent antiviral effect and higher barrier to resistance compared with telbivudine, lamivudine, and adefovir.[11-32] Despite the safety and effectiveness of antiviral therapy, overall use remains low.

Interferon monotherapy

The use of peginterferon monotherapy has been limited by its side effect profile.[51] Side effects include flu-like symptoms, mood disturbances, cytopenias, and

Despite the safety and effectiveness of antiviral therapy, overall use remains low

provocation of autoimmune states such as thyroiditis.[51] Peginterferon is also contraindicated in patients with decompensated cirrhosis, history of suicidal ideation or uncontrolled psychiatric illness, autoimmune disease, and pregnancy.

Nucleotide analogue monotherapy

Globally, nucleotide analogues have been much more widely used than interferons for patients with chronic hepatitis B. Among these, TDF and tenofovir alafenamide are recommended as first line antiviral therapy by the AASLD, European Association for the Study of the Liver (EASL), and Asia Pacific Association for the Study of the Liver (APASL).[11-57] Long term use of nucleotide analogues is safe and has been associated with reduced risk of hepatic decompensation, hepatocellular carcinoma, a reduction in cccDNA, and continued maintenance of virological suppression.[53-58]

Combination therapy

Combining nucleotide analogues with peginterferon has not been shown to significantly increase HBsAg clearance.

Emerging treatments

Current therapies for chronic hepatitis B are effective at suppressing viral replication during treatment but often fail to maintain suppression once treatment ends owing to their limited effect on cccDNA concentrations.[84 121] Strategies for achieving a functional cure are focused on three key areas: inhibiting hepatitis B virus replication, reducing viral antigen production, and enhancing host immune responses. Promising approaches targeting cccDNA include gene editing, epigenetic suppression of cccDNA transcription, and boosting hepatocyte immune responses to induce lethal cccDNA mutations.[122] Other antiviral approaches under study are directed at blocking other steps in the viral life cycle, including viral entry, encapsidation, and replenishment of the nuclear cccDNA pool.[86]

Guidelines

Table 4 (bmj.com) summarises the four major international guidelines for management of chronic hepatitis B.

Competing interests: See bmj.com.
Cite this as: *BMJ* 2025;389:e079579
Find the full version with references at https://doi.org/10.1136/bmj-2024-079579

What support do young carers find helpful?

The study

Young carers' experiences of services and support: What is helpful and how can support be improved?

Stevens M, Brimblecombe N, Gowen S, Skyer R, Moriarty J

PLOS One 2024;19:e0300551

CPD READING

0.5 HOURS

NIHR | National Institute for Health and Care Research

NIHR Alerts are summaries of NIHR-funded research with novel findings and implications for practice. They are intended for health and care professionals, commissioners, researchers and members of the public.

To read the full NIHR Alert, go to: https://tinyurl.com/3xkstdsw

Why was the study needed?

In 2021, the census reported that there are 127 000 young carers (aged 5-18) in England and Wales. These young people often have poorer health, wellbeing, education, and job prospects than their peers who are not carers.

This study investigated what support young carers (aged 9-25) and their families find helpful and how services could better meet their needs.

What did the study do?

Researchers interviewed 133 unpaid young carers and 17 cared-for parents; most took part in focus groups, but 10 were interviewed individually. Participants were from a diverse range of communities, family structures, and cultures.

What did it find?

The researchers identified features of care that young carers valued.

Access—Support could be hard to navigate and understand: "the carers' allowance . . . just isn't really talked about and then it's hard to find [by] yourself." Young carers appreciated referrals to appropriate services, as long as they didn't feel passed around (retelling their story repeatedly, for instance). They appreciated support in trying out a new service, such as a young carers group.

Listening and understanding—Many valued having someone to talk to who would validate their feelings: "I can't talk to my mum about that kind of stuff." Young carers appreciated support that was adapted to their family's needs, including taking place at convenient times and choosing what to talk about.

Trust and confidentiality—It could take time to build trust in support workers; carers wanted to speak with people who had an understanding of the sorts of difficulties faced by young carers. They wanted to be asked for their permission to share sensitive information. Several had experienced broken confidentiality: "You put trust in them and then they tell other teachers and don't help." Some had a deep mistrust of social services, and some parent care recipients feared intervention from child protection services.

Inclusion—Young carers wanted to be involved in decisions, and to be considered in the care plan of the person they cared for: "We're the best judges of our needs, ask us, instead of trying to guess." However, involving young carers sometimes conflicted with their parent's or care recipient's wishes (such as disclosing health information).

Proactivity but not intrusion—Some types of support were thought to add pressure on the family, and young carers sometimes felt pressured by services to accept support: "[It's] good that they help, but it's sometimes too much. You don't need help, but it doesn't stop." Carers wanted to be able to change their mind about the support they received. They wanted some support (such as young carer groups) to be provided more frequently or last longer: "There's not always enough support in young carers [groups] because there are so many young carers." It was distressing when services ended without warning.

Why is this important?

The researchers suggest that young carers would benefit from:

- Improved support for the people they care for (such as more support from a care worker)
- Support from services that takes account of the whole family, and their strengths and needs
- Clear and accessible information about support services, and help in accessing and trying out services.

The researchers held three events in England in 2023, which were planned and delivered by young carers. At each, they shared their findings and discussed how to integrate them into practice with local practitioners and decision makers.

What's next?

The researchers are conducting a further study investigating how the right sort of support for young carers can be made available in a way that meets the needs of the whole family.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. Further details of other interests, disclaimers, and permissions can be found on bmj.com

Cite this as: *BMJ* 2025;390:r896

CASE REVIEW

Febrile thrombocytopenia

A woman in her 30s presented to the emergency department in Trinidad and Tobago during the rainy season, with a two day history of fever, myalgia, arthralgia, retro-orbital pain, headache, and anorexia.

The patient reported a medical history of one functional kidney secondary to previous complicated pyelonephritis, no recent travel history to suggest malaria transmission, and no contact with unwell people or rats.

Vital signs and clinical examination were normal, and a full blood count showed no abnormalities. The patient was assessed as having non-specific viral symptoms and discharged.

Three days later, she returned to the emergency department after an isolated episode of bright red rectal bleeding (less than 100 mL) and associated abdominal pain. On examination, vital signs were within normal limits. Mucous membranes were dry. On abdominal examination, she had left upper quadrant tenderness with no guarding or rebound tenderness. The patient declined a rectal examination. Cardiovascular and respiratory examinations were unremarkable.

Repeat bloods were taken. The table shows the results of key laboratory tests.

1 What are the differential diagnoses?

2 What is the most likely diagnosis?

3 How would you manage this patient?

Laboratory test results at day 2 and day 5 after the onset of symptoms

Blood analyses	Day 2	Day 5
White blood cells ($\times 10^9$/L)	3.59	4.6
Lymphocyte (%)	9.7	46.7
Haemoglobin (g/L)	130	115
Packed cell volume	0.387	0.359
Platelets ($\times 10^9$/L)	194	53
International normalised ratio	Not tested	1.0
Aspartate aminotransferase (U/L)	Not tested	689
Alanine transaminase (U/L)	Not tested	500
Gamma glutamyl transferase (U/L)	Not tested	117
Lactate dehydrogenase (U/L)	Not tested	1101
Albumin (g/L)	Not tested	33

Submitted by Arvind Ramnarine, Joanne Paul, Saleem Varachhia, and Vanessa Ramoutar

Patient consent obtained.

Cite this as: *BMJ* 2025;390:e083769

answers

CASE REVIEW **Febrile thrombocytopenia**

1 What are the differential diagnoses?

Based on local epidemiology, presentation with fever and joint pains, and investigations showing disrupted liver function enzymes in a hepatic picture and thrombocytopenia, the differential diagnoses include viral infections such as yellow fever, dengue fever, chikungunya, and Zika. Non-viral infective causes include leptospirosis, typhoid and typhus, as well as malaria in endemic areas, or in case of a relevant travel history. Non-infectious conditions, including haematological and inflammatory diseases, should also be considered.

2 What is the most likely diagnosis?

Dengue with warning signs. Dengue is one of the most common clinically important arbovirial infections worldwide. Symptomatic dengue initially presents with a 2-7 day febrile phase, which is characterised by high grade, sometimes biphasic fevers, myalgia, arthralgia, anorexia, headaches, retro-orbital pain, and a rash. Leucopenia is the most common blood finding at this stage. A positive tourniquet test makes the diagnosis of dengue more likely.

After resolution of the fever, most patients progress to the recovery phase. However, approximately 5% of patients progress to a critical phase marked by increased capillary leakage, which can be preceded by rapid thrombocytopenia. In less than 1% of cases, patients progress to severe dengue defined by shock, severe bleeding, or organ impairment.

3 How would you manage this patient?

Uncomplicated dengue is usually self-limiting and can be treated with oral fluids, bed rest, and paracetamol for pain and fever. NSAIDs should be stopped irrespective of indication in people with symptomatic dengue until platelet count normalises, due to increased bleeding risk. Patients with warning signs, such as this patient, should be admitted for monitoring and supportive care.

Mortality in people with severe dengue can be up to 5%. Resuscitative fluid management needs to be carefully managed to avoid worsening capillary leakage and is titrated based on the patient's packed cell volume, while addressing any coagulopathy or organ impairment.

PATIENT OUTCOME

See bmj.com.

LEARNING POINTS

- The treatment of symptomatic dengue should focus on supportive care, and the identification and treatment of capillary leakage, haemodynamic instability, coagulopathy, and organ dysfunction.
- During dengue infection, do not initiate drugs with the potential to increase the risk of bleeding, and carefully review existing drugs.
- Resuscitative fluid management in dengue with warning signs and severe dengue needs to be meticulously monitored to prevent worsening the complications of capillary leakage.

CPD READING
0.5 HOURS

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

LEARNING MODULE

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