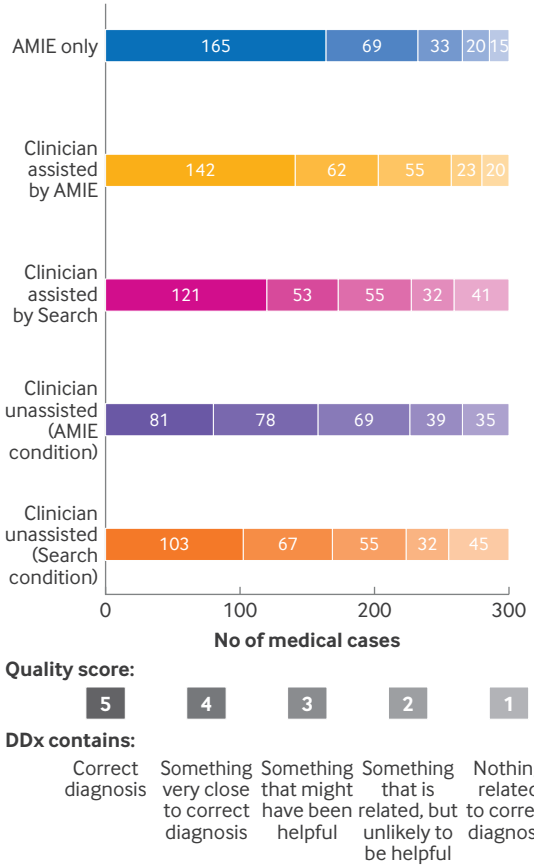
education

RESEARCH REVIEWS Fortnightly round up from the leading medical journals

Differential attainment

During GP training, you soon learn that a differential diagnosis of "nothing serious," "just a virus," and "one of those things" doesn't get you very far with patients. A study in *Nature*, written by employees of Alphabet, suggests that a diagnostic reasoning, large language model chatbot may help clinicians improve their differential diagnoses. The chatbot—called AMIE—may even be better at it. The study involved asking AMIE to come up with a list of 10 differential diagnoses based on a written case history. These were more likely to contain the correct diagnosis than the differentials that clinicians came up with on their own, with the help of AMIE, or with internet searches and standard medical resources (see figure).

Nature doi:10.1038/s41586-025-08869-4



MCDUFF, D., SCHAEKERMANN, M., TU, T. ET AL. TOWARDS ACCURATE DIFFERENTIAL DIAGNOSIS WITH LARGE LANGUAGE MODELS. *Nature* (2025)

Comparing Articulate Medical Intelligence Explorer (AMIE) with clinician performance at developing a differential diagnosis from 302 medical cases. Assessors were asked "How close did the differential diagnoses (DDx) come to including the final diagnosis?"

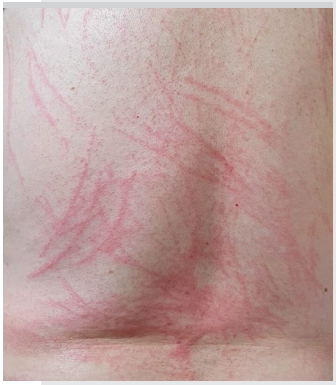
Scancer scare

The scale and impact of modern healthcare can be mind-boggling. "Approximately 93 million computed tomography (CT) examinations are performed on 62 million patients annually in the United States" according to a modelling study in *JAMA Internal Medicine*. The research estimates that the radiation exposure from these scans will result in around 103 000 cancers. That none of these "scancers" (cancer caused by radiation exposure from a scan. Origin: Tom Nolan, *BMJ* 2025) will ever be traced directly back to an individual scan or clinical decision will mean that isn't likely to change any time soon.

JAMA Intern Med doi:10.1001/jamainternmed.2025.0505

In numbers: polygenic risk scores for prostate cancer

Many DNA variants are known to be associated



CLINICAL PICTURE

Flagellate erythema after eating undercooked mushrooms

This man in his late 60s presented with widespread pruritus persisting for two days. Physical examination showed linear erythema in a flagellate pattern on his trunk and extremities. Dermographism or systemic manifestations were absent. The patient reported consuming undercooked shiitake mushrooms two days before the onset of symptoms. On the basis of the history and characteristic examination findings, a diagnosis of shiitake dermatitis was made. He was treated with oral antihistamines and topical steroids, and he was advised to ingest thoroughly cooked mushrooms in the future. The rash resolved within three weeks.

Shiitake dermatitis usually appears between 12 hours and 5 days after the ingestion of raw or undercooked shiitake mushrooms. It is thought to be caused by a toxic reaction to a heat sensitive polysaccharide in the mushrooms. Other conditions presenting with similar flagellate

with an increased risk of prostate cancer. Of 40 292 people aged 55-69 years in the UK who were invited to participate in a study assessing the potential for polygenic risk scores—which detected 130 of the DNA variants from a saliva sample—for prostate cancer screening, 8953 people were interested and 6393 had a risk score calculated. Of the 745 who had a high risk score (defined as the 90th centile of risk or higher), 187 were diagnosed with cancer. Of these, 103 required treatment, and 74 of them would not have been diagnosed through existing UK diagnostic screening pathways (prostate-specific antigen and magnetic resonance imaging).

N Engl J Med doi:10.1056/NEJMoa2407934

Dapagliflozin after TAVI

Trials of sodium-glucose cotransporter 2 inhibitors for heart failure have previously excluded people with valvular heart disease. A new study added dapagliflozin to standard care after transcatheter aortic-valve implantation (TAVI)—commonly offered to people with severe aortic stenosis and high surgical risk—among 1257 patients recruited across 39 sites in Spain. The dapagliflozin group had lower rates of the primary outcome of death from any cause and worsening heart failure after one year (15.0% versus 20.1% in the standard care group; hazard ratio 0.72 (95% CI 0.55 to 0.95)). However, the observed lower 1-year mortality in the dapagliflozin group (7.8% *v* 8.9%) did not reach statistical significance.

N Engl J Med doi:10.1056/NEJMoa2500366

Behavioural activation lifts mood

A randomised clinical trial showed promising results for Moodivate. But what is Moodivate? No, it's not a cow's milk based topical steroid, it's a digital depression treatment. But what is a digital depression treatment? No, it's not using your fingers to cheer yourself up but an online behavioural activation intervention. Participants with at least moderate depression who used the app spent an average of around an hour using the app and showed a modest improvement in depression symptoms after 12 weeks compared with those randomised to usual care.

JAMA Intern Med doi:10.1001/jamainternmed.2025.0494

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Cite this as: *BMJ* 2025;389:r790

linear erythematous eruptions include reactions to bleomycin, peplomycin, and docetaxel therapy, jellyfish stings, dermatomyositis, or adult onset Still's disease. Therefore, asking patients about their food habits is important to differentiate shiitake dermatitis from other conditions.

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Patient consent obtained.

Cite this as: *BMJ* 2025;389:e082709

MINERVA From the wider world of research

Hypertension in older people

The arterial side of the vascular system becomes stiffer with age and intensive treatment of hypertension in older people might do more harm than good if it leads to falls or cerebral hypoperfusion. Observational data from a large US survey suggest that this isn't a practical concern (*J Am Coll Cardiol* doi:10.1016/j.jacc.2025.01.033). Intensive control of systolic blood pressure, to a target of <130 mm Hg, was associated with reduced cardiovascular mortality in patients aged 80 and older.

Laboratory tests in pregnancy

A vast dataset of 40 million laboratory test results, obtained from 300 000 pregnant women during a 140 week period that spanned preconception, gestation, and the postpartum period, tells us what we already knew—although in more detail (*Sci Adv* doi:10.1126/sciadv.adr7922). Profound physiological changes occur during pregnancy to supply energy for fetal growth and to prevent the maternal immune system from rejecting the fetus. Many test results, including liver enzymes, albumin, sodium, and uric acid concentrations don't return to baseline for nearly a year after delivery.

Immunotherapies for Alzheimer's disease

If the amyloid hypothesis of Alzheimer's disease is correct, monoclonal antibodies directed at amyloid beta should slow down the progression of cognitive decline. A meta-analysis combines results from 13 relevant randomised controlled trials, with a total of 19 000 patients with mild cognitive impairment or dementia (*PLoS Med* doi:10.1371/journal.pmed.1004568). On average, people treated with monoclonal antibodies showed a slower decline in cognitive performance than those allocated to placebo, but the size of the benefit was disappointingly small.

Tripe palms

Acquired pachydermatoglyphia is a rare condition characterised by a rugose hypertrophy of the palms and hyper-pigmentation of the palmar creases, which gives the hands a striking tripe-like appearance. In more than 90% of cases, it's a paraneoplastic phenomenon (*JAMA Dermatol* doi:10.1001/jamadermatol.2025.0195). Lung and gastric cancers are the commonest underlying malignancies.

Writing is thinking

An article primarily intended to help graduate students write up the results of their research could well be useful to anyone experiencing writer's block (*Nat Biotechnol* doi:10.1038/s41587-025-02584-1). Apart from down-to-earth, practical advice about ways to tackle tasks that involve writing, it makes the point that writing should be thought of as a central activity for scientists. Without writing, there is no thinking and fewer opportunities for communicating ideas.

Second cancers after a diagnosis of melanoma

Follow-up of 150 000 people diagnosed with a first primary melanoma in Australia finds that nearly a quarter subsequently developed a second primary cancer (*Am J Epidemiol* doi:10.1093/aje/kwaf068). The commonest second cancer was another melanoma. The next most common types were prostate cancer for men and breast cancer for women, with a 5 year risk of around 3%.

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PRACTICE POINTER

Ask the consultant: Stroke

BMJ Learning

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This article was adapted from a BMJ Learning module "Ask the consultant: Stroke": https://new-learning.bmj.com/course/10064619

CPD READING

0.5 HOURS

LEARNING MODULE

See learning.bmj.com for linked learning module

Stroke physician Don Sims provides expert answers to questions from internal medicine trainees on treating patients newly diagnosed with atrial fibrillation, the principles of ischaemic stroke management, anticoagulation and thrombolysis thresholds for stroke and transient ischaemic attack, and how to clinically differentiate an acute stroke from an old stroke with a secondary diagnosis in the context of a patient presenting with confusion and neurological signs.

WHAT YOU NEED TO KNOW

- Long term anticoagulation is indicated for most patients with a new diagnosis of atrial fibrillation
- Offer thrombolysis with alteplase or tenecteplase in patients with acute ischaemic stroke within 4.5 hours of symptom onset, and those with unknown onset of events with confirmatory advanced imaging
- Obtain early intracranial imaging, ideally MRI, for patients who present with an atypical history but features potentially consistent with stroke
- Anticoagulate people with ischaemic stroke and atrial fibrillation or flutter within five days of onset for mild stroke and five to 14 days for moderate to severe stroke

TEST YOURSELF

A 76 year old man is diagnosed with atrial fibrillation and mitral regurgitation after a fall at home. There is no significant traumatic injury. He has hypertension, stage 3 chronic kidney disease, angina, hypertension, and peripheral vascular disease. His CHA_2DS_2-VASc score is 5, HAS-BLED score is 2, and ORBIT score is 2, putting him at a high risk of stroke and low risk of bleeding.

Which one of the following is the most appropriate long term management option for him for stroke risk reduction?

a. Warfarin

b. Direct oral anticoagulant

c. Enoxaparin

d. Aspirin

e. Clopidogrel

(Answer at end of article)

When a patient is newly diagnosed with atrial fibrillation in hospital, what is the best short term and long term stroke prevention strategy?

The risk of ischaemic stroke with atrial fibrillation, depending on presence of other risk factors, ranges from 3% to 15% a year.[1] The National Institute for Health and Care Excellence (NICE) recommends that all patients with new onset atrial fibrillation (AF) who are receiving no or sub-therapeutic anticoagulation should be offered heparin in the absence of contraindications until a full assessment is made and oral anticoagulation established if deemed appropriate.[2] The direct oral anticoagulants (DOACs) allow treatment of patients newly diagnosed with transient ischaemic attack (TIA) in secondary care clinics with AF to be anticoagulated immediately without a long lead-in time via outpatient anticoagulation clinic pathways. However, in people with new onset AF, if there is uncertainty over the precise time since onset, offer oral anticoagulation as for persistent AF.[2]

Strongly consider any patient with a new diagnosis of AF for long term anticoagulation with a DOAC as first-line treatment, such as apixaban, dabigatran etexilate, rivaroxaban, or edoxaban. Alternatively, consider a vitamin K antagonist (such as warfarin) if DOACs are contraindicated or not tolerated.[2] DOACs are considered first-line treatment over warfarin because they are non-inferior in trials assessing stroke prevention and have a lower bleeding risk. See box 1 for practical tips when prescribing either form of anticoagulation.

Assess the risk of stroke and bleeding using the CHA_2DS_2-VASc stroke risk score and a bleeding risk score.[2] Current NICE and European Society of Cardiology guidance recommend that anticoagulation is considered for all men with a CHA_2DS_2-VASc of ≥1 and women with a score of ≥2, balancing the expected stroke reduction, bleeding risk, and patient preference.[2 5 6]

Evidence review from the NICE guidelines has shown that the ORBIT bleeding risk score has a higher accuracy in predicting absolute bleeding risk than other bleeding risk tools such as HAS-BLED and ATRIA.[2 7] Therefore, NICE now recommends using the ORBIT bleeding risk score where possible.

Why don't we anticoagulate all patients following acute ischaemic stroke?

One of the major recent developments in stroke medicine has been the focus on better detection and treatment of AF, and the appreciation of how antiplatelets, such as low dose aspirin, are relatively poor in terms of preventing stroke with a cardioembolic source.[8 9] AF is present and likely causative in 25% of ischaemic strokes,[10]

Box 1 | Practical tips when prescribing anticoagulation

Direct oral anticoagulants (DOACs)

- Calculate creatinine clearance before prescribing a DOAC, as apixaban, rivaroxaban, and edoxaban are not suitable when creatinine clearance is <15 mL/minute
- Dabigatran should be avoided if creatinine clearance is <30 mL/minute

Warfarin

- Use with caution in mild to moderate renal impairment; needs more frequent monitoring in severe renal impairment[3]
- Can interact with multiple medications, leading to an increased risk of bleeding[4]
- All vitamin K antagonists should be used with caution in mild to moderate hepatic impairment and avoided in severe hepatic impairment[3]

and in these patients you should strongly consider anticoagulation.[11 12] However, this does not mean that ischaemic strokes from other causes should necessarily be treated with anticoagulants, and NICE states that anticoagulation should not be used routinely for the treatment of acute stroke.[11]

The use of antiplatelets (aspirin and, in recent years, clopidogrel or ticagrelor) is a proven strategy for preventing strokes not caused by atrial fibrillation.[11 12] About 45% of strokes are caused by atherosclerosis, either in major vessels (such as the aortic arch or carotid arteries) or more distal vessels in the brain.[13] Treat strokes caused by atherosclerosis, plaque rupture, platelet aggregation, and then vessel occlusion by platelet-rich thrombus or embolism of the thrombus with antiplatelets.[11 12]

In practice, most clinicians, when finding or suspecting significant atherosclerosis disease in addition to proven AF and either could be the cause of stroke, would likely consider long term anticoagulation monotherapy after the initial one to two weeks of antiplatelets. The rationale for this is because anticoagulants may protect against platelet-mediated disease. The Intercollegiate Stroke Working Party guidelines (written by representatives from the Scottish Intercollegiate Guidelines Network, the Royal College of Physicians, and the Royal College of Physicians of Ireland) do not currently recommend the use of an antiplatelet and anticoagulant in conjunction.[12]

The Intercollegiate Stroke Working Party guidelines strongly recommend, based on high quality evidence, to treat with 21 days of dual antiplatelet therapy with aspirin plus clopidogrel (or aspirin plus ticagrelor for 30 days) in people with a non-cardioembolic minor ischaemic stroke or high risk TIA in the past 24 hours, and a low risk of bleeding.[12 14] This is followed by monotherapy with clopidogrel or ticagrelor.[12] For patients with TIA or minor ischaemic stroke who are not appropriate for dual antiplatelet therapy, clopidogrel at a loading dose followed by a daily maintenance dose should be given.[12] The guidelines also recommend dual antiplatelet therapy for three months in people with ischaemic stroke or TIA due to severe symptomatic intracranial stenosis.[12]

European Society of Cardiology guidelines state that dual antiplatelet therapy (aspirin plus ticagrelor or clopidogrel) may be a treatment option in patients with symptomatic carotid stenosis in the early phase of minor stroke or TIA. This is often then continued until definitive surgical correction is undertaken.[15] Long term, low dose rivaroxaban plus aspirin may be a treatment option in patients with asymptomatic carotid stenosis or in those with a history of carotid revascularisation, who are considered at very high risk because of associated comorbidities (especially polyvascular patients).[15] However, this strategy is associated with a higher bleeding risk, and a recent meta-analysis found that the benefits and risks were finely balanced.[16]

The important message is to perform a comprehensive assessment for AF, including paroxysmal AF, in patients presenting with ischaemic stroke, as this may determine treatment with anticoagulants. The presence of paroxysmal AF has previously been underestimated, and latest NICE guidance is for patients to undergo longer periods of monitoring and consideration for implantable devices in more patients.[2]

However, if no indication for anticoagulation treatment is identified, then antiplatelet therapy is the evidence-proven treatment for prevention of ischaemic stroke.[11 12] The Intercollegiate Stroke Working Party guideline recommends clopidogrel or ticagrelor as the standard antithrombotic treatment for long term prevention of vascular events in people with ischaemic stroke or TIA without paroxysmal or permanent atrial fibrillation; use aspirin (75 mg daily) for those who are unable to tolerate clopidogrel.[12] The combination of aspirin and clopidogrel is not recommended for long term prevention of vascular events unless there is another indication (such as acute coronary syndrome, or a recent coronary stent).[12] Treat people with ischaemic stroke with acute haemorrhagic transformation with long term antiplatelet or anticoagulant therapy unless the risks outweigh the benefits.[12]

A transient ischaemic attack is often defined as being a transient loss of neurological function that resolves in under 24 hours. However, if a stroke is suspected, should thrombolysis be considered if patients present within the appropriate timeframe?

The cutoff of 24 hours for the duration of a TIA predates brain imaging and can be difficult to apply clinically in the context of modern stroke management. This is for two reasons:

- It suggests most TIAs last several hours, when most last only a matter of minutes or up to an hour or two[17]
- It does not reflect the fact that a patient with neurological symptoms of a TIA lasting 20 hours will likely have significant damage to neuronal tissue, whereas "transient" suggests no damage. These patients are likely to have visible lesions on diffusion-weighted magnetic resonance imaging (MRI) demonstrating this damage, so this presentation is more in keeping with a stroke.

The Intercollegiate Stroke Working Party and NICE guidelines recommend thrombolysis (with alteplase or

Box 2 | Summary of recommendations from NICE on thrombolysis for people with acute ischaemic stroke[11 18]

- Thrombolysis is recommended for treating eligible adults with acute ischaemic stroke if:
  - Treatment is started as soon as possible within 4.5 hours of onset of stroke symptoms, *and*
  - Intracranial haemorrhage has been excluded by appropriate imaging techniques
- Thrombolysis should be administered only within a well organised stroke service with:
  - Staff trained in delivering thrombolysis and monitoring for complications
  - Nursing staff trained in acute stroke and thrombolysis to provide level 1 and level 2 care
  - Immediate access to imaging and re-imaging, and staff trained to interpret the images
- Staff in emergency departments can administer thrombolysis for treating ischaemic stroke if:
  - They are appropriately trained and supported, and
  - Patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support
- Protocols must be in place for delivering and managing intravenous thrombolysis, including post-thrombolysis complications

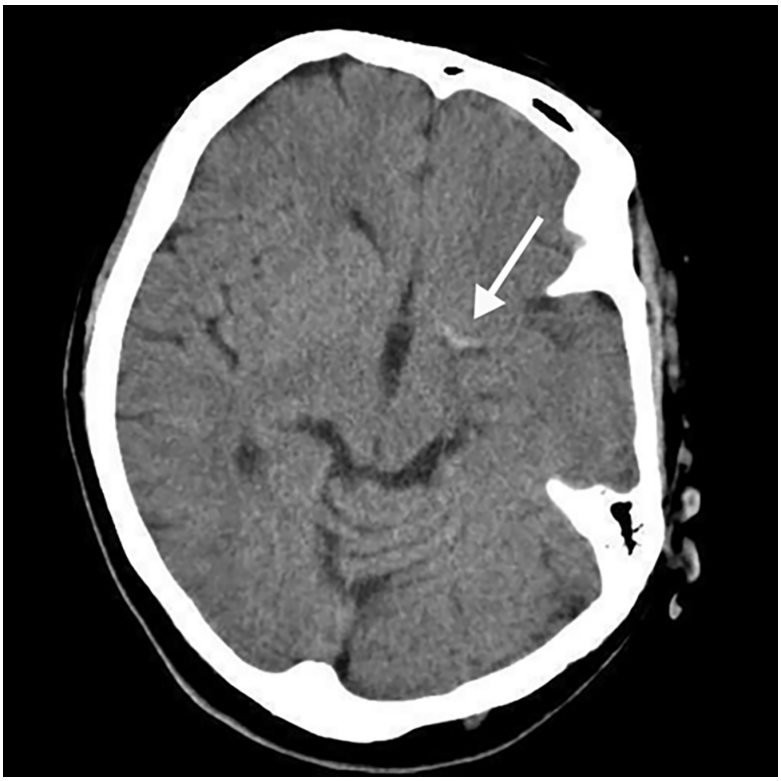

Fig 1 | CT scan showing the hyperdense middle cerebral artery sign in the left hemisphere (arrow)

tenecteplase) in patients with acute ischaemic stroke within 4.5 hours of symptom onset (box 2).[11 12] The Intercollegiate Stroke Working Party guidelines also recommend that patients with acute ischaemic stroke who were last known to be well more than 4.5 hours earlier should be considered for thrombolysis with alteplase if treatment can be started between 4.5 and 9 hours of known onset, or within 9 hours of the midpoint of sleep if a patient has woken with symptoms, and the guidelines report evidence from computed tomography (CT) or magnetic resonance perfusion (core-perfusion mismatch) or MRI (diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) mismatch) of the potential to salvage brain tissue.[12] Consider interventions such as mechanical thrombectomy up to six hours or more following onset of symptoms, although this is not always readily available across some of the UK and other regions.[11 12]

If the patient is rapidly improving, and therefore very likely to have had a TIA, in my clinical experience it may be reasonable to observe. However, you should not delay to assess whether some unseen improvement is coming. The original product licence for alteplase recommended that symptoms should be present for at least 30 minutes before drug delivery on the assumption that this would exclude most genuine TIAs. This length of time has nearly always elapsed by the time of the first assessment in the emergency department, so further delays should be avoided. For patients who have only minor apparent events, treatment with thrombolytics may not be indicated—most trials exclude patients without a disabling stroke. However, what is considered disabling is hard to quantify, and low scores, as measured by the NIH Stroke Scale/Score,[19] involving speech and vision can still be disabling. Use clinical judgment and discuss risks and benefits with patients and their care givers.

Patients who have had a TIA may develop a full stroke within the next 48 hours. Since the use of vascular imaging has become widespread in routine practice, in my experience it has become more common to see patients with what was thought to be a TIA who have significant thrombus occlusion in the cerebral circulation. These patients may be maintaining neurological function only temporarily with collateral vessels, and their condition may worsen.

If a patient is confused and has focal neurology, clinically, how can you determine whether this is due to an acute stroke or to an old stroke with a secondary diagnosis?

Clinically, it can be difficult to differentiate between an acute stroke and an old stroke with a secondary diagnosis. In my experience, patients with an acute stroke as the primary diagnosis are not usually confused, though receptive dysphasia can be mistaken for confusion. However, as with any medical condition, delirium can occur after a stroke. Patients who have delirium following an infection may demonstrate other clues to the cause of their confusion, such as fever and raised inflammatory markers.

Symptoms of delirium include[20]:

- Fluctuations in consciousness level
- Agitation
- Loss of concentration
- Hallucinations (less common).

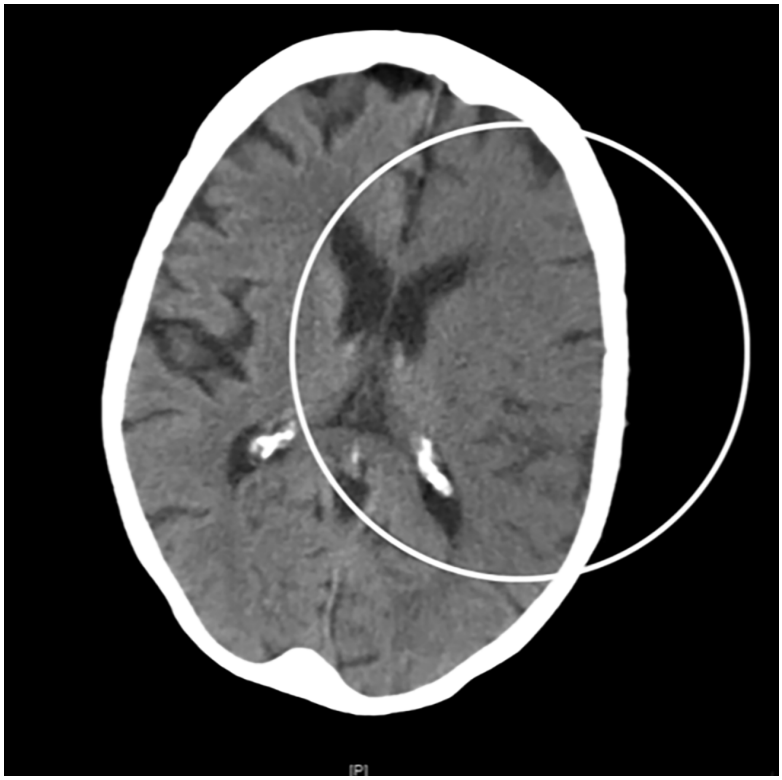

Fig 2 | CT scan showing loss of grey-white differentiation with sulcal effacement in the left hemisphere (circle)

Symptoms of delirium are not usually present in patients with stroke alone, although stroke itself may cause delirium. This highlights the importance of brain imaging to distinguish between the two causes.

Pragmatically, patients should be given thrombolysis only in the event of a clear clinical stroke.[11 12] Confused patients with minor or vague neurology should not be treated with thrombolysis routinely.[11 12] However, clinical assessment has limitations, and in my experience many people are not diagnosed with stroke until confirmatory imaging. This is especially the case in patients with strokes in more unusual areas of the brain, such as away from the middle cerebral artery territory, who present with limited neurology and confusion (for example, infarctions of the thalamus or non-dominant frontal lobe).

It is therefore prudent to consider early CT or preferably MRI, where possible, for this clinical scenario. An old stroke should be readily visible. With modern multi-slice CT scanners, patients with acute stroke often have visible, albeit subtle, signs of ischaemic damage even in the hyper-acute situation (70% sensitivity for detection when using CT angiography source data).[21] Changes such as the hyperdense middle cerebral artery (fig 1), loss of grey-white differentiation and sulcal effacement (fig 2) are visible in many patients.[22]

How long after thrombolysis should you consider anticoagulation for patients with atrial fibrillation?

Anticoagulation was historically started two weeks after an ischaemic stroke irrespective of whether the patient received thrombolysis, balancing the risk of haemorrhagic transformation of the infarction with the risk of leaving patients unprotected from their AF.

The updated Intercollegiate Stroke Working Party guideline suggests a graduated approach to anticoagulation in patients with an ischaemic stroke or TIA and AF.[12] Consider anticoagulation in people with ischaemic stroke and AF or flutter within five days of onset for mild stroke and five to 14 days of onset for moderate to severe stroke.[12] In those with a TIA, start anticoagulation immediately, once brain imaging has excluded haemorrhage, with an agent with a rapid onset.[12]

Whether the patient received thrombolysis on presentation should not necessarily affect when anticoagulation is started. If there has been significant haemorrhagic transformation of the infarction, some clinicians may delay starting anticoagulation beyond two weeks, but there are no clear guidelines covering this area of practice. If there is a full recovery with thrombolysis (or mechanical thrombectomy), consider starting anticoagulation substantially earlier.[12]

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.r436

BMJ Learning

To obtain accredited continuous professional development points, complete the full BMJ Learning module at https://new-learning.bmj.com/course/10064619. The module contains eight additional questions submitted by users of BMJ Learning, including therapeutic cooling, posterior circulation stroke, stroke recovery, and mechanical thrombectomy.

TEST YOURSELF (REVISITED)

B (Direct oral anticoagulant) is the correct answer.

NICE recommends that all patients with new onset AF who are receiving no or sub-therapeutic anticoagulation should be offered heparin in the absence of contraindications until a full assessment is made and oral anticoagulation established if deemed appropriate.[2] However, in people with new onset AF, if there is uncertainty over the precise time since onset (as in this scenario), oral anticoagulation should be offered as for persistent AF.[2] Options include a DOAC such as apixaban, dabigatran etexilate, rivaroxaban, and edoxaban, or a vitamin K antagonist (such as warfarin) if DOACs are contraindicated or not tolerated.[2] DOACs are considered first-line treatment over warfarin because they are non-inferior in trials assessing stroke prevention and have a lower bleeding risk.

Aspirin and other antiplatelet therapies such as clopidogrel are not appropriate treatments for stroke prevention in a patient with atrial fibrillation because they are less efficacious than DOACs or warfarin in reducing stroke risk and carry a similar bleeding risk, especially in older adults.[23 24]

Enoxaparin may be a suitable choice initially, as it provides full anticoagulation, but for long term stroke prevention oral options are preferable.

GUIDELINES

Adrenal insufficiency: identification and management—summary of new NICE guidance

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

CPD READING

0.5 HOURS

Adrenal insufficiency is the inadequate production of the hormone cortisol from the adrenal glands. Global prevalence ranges from 0.4/100 000 (South Korea) to 15-22/100 000 (Nordic countries) for primary adrenal insufficiency, and 14-28/100 000 (Spain and UK) for secondary adrenal insufficiency.[1] It is often unrecognised, which can lead to adrenal crisis and, if not identified and treated, death. From July 2018 to July 2020, NHS England National Reporting and Learning System identified 78 incidents related to adrenal insufficiency, including two deaths and six incidents of severe harm to patients across England.[2]

Care is variable across the UK but there is a lack of understanding on who is at risk of adrenal insufficiency, how to test for it, and how to manage a life threatening adrenal crisis promptly. Here we summarise newly published guidelines from the National Institute for Health and Care Excellence (NICE).

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the guideline committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

WHAT YOU NEED TO KNOW

- Adrenal insufficiency is often unrecognised and can lead to adrenal crisis and death if not identified and treated
- Offer an 8-9am serum cortisol test to people aged one year and older with suspected adrenal insufficiency
- Treat adrenal crises with hydrocortisone and fluid rehydration, and transport the patient to hospital quickly
- Discuss the following with patients who have confirmed adrenal insufficiency: sick day rules, how to administer emergency hydrocortisone, and the need for extra hydrocortisone cover when faced with stressors, including intercurrent illness

Presentation

Adrenal insufficiency can be primary, secondary, or tertiary (box 1). The symptoms and signs of adrenal insufficiency are common to many conditions. They are listed in the order of most to least clinically distinguishing from other conditions and were based on guideline committee opinion and evidence review of six small cross sectional studies. There were concerns around the applicability of the study populations, including people with specific conditions such as human immunodeficiency virus or liver cirrhosis. Therefore, the guideline committee based their recommendations on consensus opinion, drawing on their experience and knowledge of the risk of adrenal insufficiency that is associated with drugs and coexisting conditions and comorbidities (eg, type 1 diabetes or hypothyroidism, hypothalamo-pituitary tumours) and their respective treatments.

The evidence informing the recommendation that people at increased risk includes those who have recently taken glucocorticoids (including duration of treatment thresholds) was based on consensus opinion and informed by clinical guidelines endorsed by the UK Society of Endocrinology and a systematic review and a meta-analysis.[5-7]

Isolated non-specific symptoms, such as lethargy or diarrhoea, are too general as indications for testing, and might lead to overtesting. Symptoms need to be persistent, over the course of weeks or months, and other potential causes ruled out before further investigation. Unexplained hyperpigmentation might be all over the body or in specific areas, such as surgical scars or buccal pigmentation.

Consider adrenal insufficiency in people with unexplained hyperpigmentation, or when there is no other clinical explanation for the presence of one or more of the following persistent symptoms, signs, or features:

- Weight loss
- Salt craving
- Nausea or vomiting
- Lack of appetite or unable to eat a full meal
- Diarrhoea
- Dizziness or lightheadedness on standing
- Hyponatraemia
- Hyperkalaemia
- Lethargy
- Early puberty

Box 1 | Most common causes of adrenal insufficiency[4]

Primary adrenal insufficiency
- Autoimmune disease, Addison's disease
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
- Infections: adrenalitis
  - Tuberculosis, HIV/AIDS, cytomegalovirus, fungal, syphilis
- Bilateral adrenal haemorrhage
  - Adrenal haemorrhage, sepsis, anticoagulants, anti-phospholipid syndrome
- Bilateral adrenal metastases (lung, stomach, breast, colon) or infiltration (primary adrenal lymphoma amyloidosis, haemochromatosis)
- Bilateral adrenalectomy
- Drug induced
  - Anticoagulants, adrenal enzyme inhibitors: mitotane, ketoconazole, itraconazole, voriconazole, metyrapone, etomidate, aminoglutethimide, phenobarbital, phenytoin, rifampicin
- Genetic disorders
  - Congenital adrenal hyperplasia (most common cause in children), adrenoleukodystrophy

Secondary adrenal insufficiency–pituitary disorders
- Pituitary tumours
  - Adenoma, cysts, craniopharyngioma, ependymoma, meningioma, pituitary metastases
- Pituitary surgery
- Pituitary irradiation
- Trauma
- Infections or infiltration
  - Lymphocytic hypophysitis, sarcoidosis, histiocytosis X, haemochromatosis, tuberculosis
- Pituitary apoplexy
- Sheehan's syndrome
- Genetic disorders
  - Transcription factors required in pituitary development

Tertiary adrenal insufficiency
- Hypothalamic tumours (craniopharyngiomas, germinomas, meningiomas)
- Hypothalamic surgery or irradiation (primary brain tumours, nasopharyngeal tumours)
- Infections or infiltration
  - Lymphocytic hypophysitis, sarcoidosis, histiocytosis X, haemochromatosis, TB
- Traumatic brain injury, particularly base of skull fracture
- Cushing's disease or syndrome
- Drug induced
  - Glucocorticoid therapy (any route), mifepristone, chlorpromazine, imipramine

- Feeling of muscle weakness
- Hypoglycaemia (particularly in children)
- Faltering growth (in children)
- Hypotensive crisis (particularly in children)
- Prolonged neonatal jaundice.

When performing an initial assessment in a person who presents with any unexplained symptoms, signs, or features detailed in the list above, be aware that adrenal insufficiency is more common in people who:
- Have recently stopped taking glucocorticoids by any route of administration after taking them for more than four weeks if aged 16 and over, or more than three weeks if under 16
- Are taking glucocorticoids at physiological equivalent doses or above by any route of administration and have had an episode of physiological stress
- Are taking opioids, checkpoint inhibitors, adrenal enzyme inhibitors, or medicines that affect the production, metabolism, or action of cortisol, such as antifungals or antiretrovirals
- Have coexisting conditions such as:
  - Primary hypothyroidism
  - Type 1 diabetes
  - Premature ovarian insufficiency
  - Autoimmune polyendocrinopathy syndrome
  - Hypothalamic or pituitary tumours
  - Hypothalamo-pituitary disease including infections and infiltrative disorders
- Have had cranial, pituitary, hypothalamic, or nasopharyngeal radiotherapy.

Initial investigations

Adrenal insufficiency is diagnosed definitively by a timed short synacthen test or insulin tolerance test. However, there could be delays arranging these tests, they can be practically difficult to perform, and costly.

In current practice, patients may be initially screened by non-specialists by using random cortisol testing. As cortisol secretion is pulsatile and follows a circadian rhythm where secretion is maximal in the early morning, with levels declining during the evening/night, this investigation is rarely helpful and could lead to unnecessary referrals. Therefore, we suggest optimal timing for serum cortisol testing and when to refer a patient (table 1). Management was predicated on value of 8-9 am serum cortisol rather than a synacthen test.

Recommendations were based on findings from eight small cross sectional or diagnostic accuracy studies that examined the sensitivity and specificity of different cut-off points for morning serum cortisol levels compared with a short synacthen test or insulin tolerance test. Owing to variations in the assays and reference standards used, the guideline committee was unable determine a specific cut-off point. Overall, morning serum cortisol testing was adequate for a diagnosis of adrenal insufficiency based on thresholds for clinical decision making, set at 90% sensitivity and 70% specificity. Additionally, serum cortisol tests are already widely used and therefore easier to implement than alternative screening tests (eg, salivary cortisol) that are less readily available and not yet part of routine clinical care.
- Do not test for adrenal insufficiency in people taking oral glucocorticoids at physiological equivalent doses or higher
- Be aware that people taking exogenous glucocorticoids by non-oral routes (eg, inhalation, intramuscular, or topical) at a physiological equivalent dose or higher might have a low 8-9 am cortisol level
- Offer an 8-9 am serum cortisol test to people aged 1 year and over with suspected adrenal insufficiency. Follow table 1 to interpret the results and aid decision making
- For babies under 1 year, measure serum cortisol levels at any time of the day and seek paediatric or paediatric endocrinology advice for interpretation of results
- After an intramuscular or intra-articular glucocorticoid injection, wait four weeks before doing an 8-9 am serum cortisol test.

Table 1 | Interpretation of serum cortisol levels from an 8-9 am test, proposed subsequent management, and referral thresholds to a specialist or the emergency department

Serum cortisol level*	People aged 16 years and over	Children and young people aged between 1 year and over, and under 16 years
<150 nmol/L	The person might have adrenal insufficiency Refer the person to endocrinology Consider starting management for adrenal insufficiency If the person is acutely unwell, commence emergency management of adrenal crisis	The person might have adrenal insufficiency Refer the person urgently to paediatrics or paediatric endocrinology If the person is acutely unwell, commence emergency management of adrenal crisis
150 to 300 nmol/L	Probability of adrenal insufficiency is uncertain Consider repeating the serum cortisol test If it remains at this level seek endocrinology advice or referral	Probability of adrenal insufficiency is uncertain Consider repeating the serum cortisol test If it remains at this level seek paediatric or paediatric endocrinology advice or referral
>300 nmol/L	Adrenal insufficiency is very unlikely	Adrenal insufficiency is very unlikely

*Note that the cut offs are only for use with modern immunoassay assays. Local guidelines might need to be followed if alternative assays are used.

Information and support at diagnosis

After patients are diagnosed with adrenal insufficiency, they require a substantial amount of tailored education to enable them to manage their condition on a daily basis, maintain a good quality of life, and avoid life threatening adrenal crises. This includes taking daily essential glucocorticoid hormone replacement.

Findings from seven qualitative studies, four in children and three in adults, formed the basis of the recommendations, along with the expertise of the guideline committee and experience of lay members. Individual themes from these studies were synthesised into six overarching themes that directly aligned with the guideline committee's experience and knowledge of NHS-based practice. We made recommendations on managing physiological and psychological stress, including when and how to use a hydrocortisone emergency kit and what the kit should contain.

Give information to people with adrenal insufficiency and their families and carers on:

- How to obtain an NHS Steroid Emergency Card for adults,[8] British Society of Paediatric Endocrinology and Diabetes Emergency Steroid Card for children and young people,[9] and medical alert jewellery
- How to set up medical alerts, medical IDs, and apps on mobile phones
- Relevant support groups and charities
- How to access free NHS prescriptions
- How to discuss their diagnosis and treatment with employers, in educational settings, and with friends and family.

Treatment

Glucocorticoid replacement therapy with physiological equivalent doses (ie, doses equivalent to the amount that a healthy adrenal gland would normally produce) is the mainstay of drug management. For people aged 16 years and over, this is a total daily dose of hydrocortisone 15 mg to 25 mg, prednisolone 3 mg to 5 mg, or dexamethasone 0.5 mg. For babies, children, and young people under 16 years this is a total daily dose of hydrocortisone 8 mg/m^2.

- Offer glucocorticoids and mineralocorticoid (if needed) for people with primary adrenal insufficiency or congenital adrenal hyperplasia. Offer glucocorticoids alone for people with secondary and tertiary adrenal insufficiency (table 2 (bmj.com), see the full guideline for babies under 1 year).

Adrenal crisis

Adrenal crisis is a potentially life threatening emergency caused by a lack of cortisol. Patients who have any form of adrenal insufficiency are at risk of adrenal crisis because they are unable to mount the usual response to physiological stress, which is a rise in cortisol. Stressors could include intercurrent illness especially sepsis, surgery, injury, or substantial emotional stress. At these times, there is a need to increase replacement doses by moving to sick day dosing advice (box 2). Patients with, or at risk of, adrenal crisis can present with a range of signs and symptoms that could develop into more severe symptoms indicative of adrenal crisis.

Consider adrenal crisis as a potentially reversible cause in people who are critically unwell with any of the following features:

- Low blood pressure (including postural hypotension)
- Hyperpigmentation (primary adrenal insufficiency only)
- Hyponatraemia
- Hypoglycaemia (particularly in children)
- Circulatory shock or collapse
- Condition failing to respond to initial treatments.

Consider adrenal crisis in people with, or at high risk of, adrenal insufficiency who are unwell with milder symptoms, including:

- Lethargy
- Pallor
- Clamminess
- Feeling cold or feverish
- Confusion or altered mental states
- Weakness.

Emergency management of adrenal crisis

For the emergency management of adrenal crisis in babies, children, and young people under 16 years, follow the British Society of Paediatric Endocrinology and Diabetes consensus guidelines on adrenal insufficiency.[7] In those aged over 16 years, treat adrenal crisis with hydrocortisone and fluid rehydration, and transfer the patient to hospital quickly.

- Give intravenous or intramuscular hydrocortisone for suspected adrenal crisis immediately, being aware that:
  - The intramuscular dose can be given by anyone, including being self-administered by using an emergency management kit

Box 2 | Selected principles of sick day dosing advice for people aged 16 and over

- During periods of substantial physiological stress, offer at least 40 mg oral hydrocortisone daily in 2 to 4 divided doses or at least 10 mg oral prednisolone daily in 1 to 2 divided doses until the acute illness or physical trauma has resolved.
- Advise people taking a daily oral prednisolone dose of 10 mg or more that they do not need additional sick day dosing, but they can split their total daily dose into 2 equal doses.
- Do not increase glucocorticoid dosing for a long duration (ie, no more than a few days if there is no known reason for the increase).
- If the person vomits within 30 minutes of taking an oral dose, advise them to take a further dose once vomiting subsides, at double the original dose. If vomiting recurs within 30 minutes, give intramuscular hydrocortisone, and advise the person to attend the emergency department.
- Admit the person to hospital during periods of physiological stress if they are unable to absorb oral glucocorticoids, for example, during prolonged diarrhoea and vomiting. Give 100 mg intramuscular or intravenous hydrocortisone.

  - In an emergency situation, there is no risk of overdose from hydrocortisone
- Advise people having an adrenal crisis to go immediately to hospital in an ambulance without needing a referral
- In people aged 16 and over, give 1 L of sodium chloride 0.9% w/v intravenous infusion over 30 minutes to the person having an adrenal crisis
- Ensure frequent monitoring of blood pressure, heart rate, electrolyte, and glucose status during an adrenal crisis
- Continue to give hydrocortisone by intravenous infusion over 24 hours (with monitoring to ensure no interruption of the infusion), or intramuscular or intravenous injections (4 times a day) until the person is haemodynamically stable and they are able to take and absorb oral glucocorticoids
- Continue to give sodium chloride 0.9% w/v intravenous infusion, determined by haemodynamic parameters and electrolyte status, until the person is haemodynamically stable
- Offer at least 40 mg oral hydrocortisone daily in 2 to 4 divided doses or at least 10 mg oral prednisolone daily in 1 to 2 divided doses until any underlying cause has resolved and the person is clinically stable.

Implementation

Adrenal insufficiency can present in very non-specific ways, and there is no single symptom or sign to suggest this as a diagnosis, particularly for secondary or tertiary adrenal insufficiency. Access to endocrine specialist nurses across the UK is variable. Patient education, in particular education about sick day rules and how to self-administer emergency intramuscular hydrocortisone, might not be available to all those who need it. All patients diagnosed with adrenal insufficiency should be referred to an endocrinology team, so that they will have access to appropriate education.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Committee members involved in this guideline included lay members who contributed to the formulation of the recommendations summarised here.

GUIDELINES INTO PRACTICE

- Think about the last time you assessed someone with adrenal insufficiency. What principles did you follow in assessing cortisol levels? Did you arrange a serum cortisol test? If so, at what time was the serum cortisol level checked, and did you consider the impact of the glucocorticoid drugs the patient might have been taking?
- How would you recognise and manage an adrenal crisis?

FUTURE RESEARCH

- What is the clinical and cost effectiveness of salivary cortisone or cortisol to identify people with adrenal insufficiency?
- In people at risk of adrenal insufficiency because of prolonged glucocorticoid use, what is the best way to manage glucocorticoid withdrawal when the drugs are no longer needed?
- What increases the risk of adrenal crisis and adverse hospital outcomes in people taking long term glucocorticoids?

Data to inform appropriate prescription of glucocorticoid to cover intercurrent illness remain lacking, and there are few well powered studies addressing this aspect of care.

Patients have highlighted that they have difficulty obtaining hydrocortisone on repeat prescriptions and they are often signposted back to the hospital. This could be overcome if prescribers are aware of a patient's need for a constant supply of glucocorticoid, longer than the standard 28 day prescription for people with adrenal insufficiency, so that they always have supply of medication, including additional supply to cover intercurrent illness.

There remains no agreed tariff for components of an emergency kit, including syringes and needles, so although the guideline provides clarity on the contents of an emergency kit, it remains unclear if primary care, rather than secondary care, will be able to provide the full contents of an emergency kit to patients. In practice, primary care clinicians have raised concerns over who would be responsible for providing the training on how to use the kit, along with the ongoing surveillance and follow-up reviews after prescribing the kit, and consider this a potential barrier to implementation. The initiation of the emergency kits, together with any associated education, training, or monitoring, should be the responsibility of secondary care. Primary care should be informed so that they are aware that patients might need repeat prescriptions for intramuscular hydrocortisone if the drugs go past their expiry date.

Competing interests: See bmj.com

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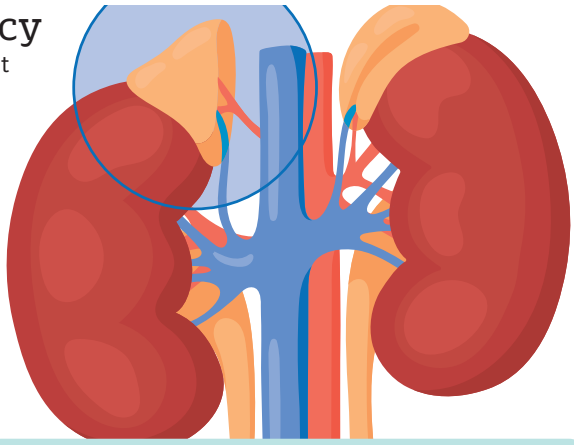
Find the full version with references at http://dx.doi.org/10.1136/bmj.r330

thebmj Visual summary

Adrenal insufficiency

Recognition and initial management



Adrenal insufficiency is the inadequate production of the hormone cortisol from the adrenal glands. It is often unrecognised, which can lead to adrenal crisis and, if not identified and treated, death. This graphic summarises guidelines from the National Institute for Health and Care Excellence (NICE) published in 2024.

Signs and symptoms

Unexplained hyperpigmentation **or** One or more unexplained persistent symptoms

- Weight loss
- Salt craving
- Nausea or vomiting
- Lack of appetite or unable to eat a full meal
- Diarrhoea
- Dizziness or light-headedness on standing
- Hyponatraemia
- Hyperkalaemia
- Lethargy
- Early puberty
- Feeling of muscle weakness

Particularly in children:

- Hypoglycaemia
- Hypotensive crisis
- Faltering growth
- Prolonged neonatal jaundice

Initial investigations

Morning serum cortisol test

Offer an 8 am to 9 am serum cortisol test to people aged 1 year and over.

For children aged <1 year cortisol can be taken at any time because they lack circadian secretion rhythms.

Below 150	150 to 300	Above 300
Person might have adrenal insufficiency	The probability of adrenal insufficiency is uncertain	Adrenal insufficiency is very unlikely

Attend emergency department and commence emergency management

If person is acutely unwell

Adrenal crisis

Adrenal crisis is a potentially life-threatening emergency caused by a lack of cortisol to respond to physiological stress.

Consider adrenal crisis for patients with any of:

- Low blood pressure
- Hyperpigmentation
- Hyponatraemia
- Hypoglycaemia
- Circulatory shock or collapse
- Failing to respond to initial treatments

Initial management

1. Immediate intravenous or patient administered intramuscular hydrocortisone

Dosage by age	
<1 year	25 mg
1-5 years	50 mg
6+ years (includes adults)	100 mg

2. Advise people having an adrenal crisis to immediately go to hospital without needing a referral
3. In people aged 16 and over, give 1 L of 0.9% sodium chloride intravenous infusion over 30 minutes

Referral

Adults
Refer to endocrinology

Children
Urgent referral to paediatrics or paediatric endocrinology

Consider specialist advice

Consider repeating test

Consider starting management

Management

The mainstay of drug treatment is glucocorticoid replacement therapy with physiological equivalent doses (equivalent to the amount that a healthy adrenal gland would normally produce).

* in divided doses

16+ years old	Total daily dose
Hydrocortisone*	15 to 25 mg
Prednisolone	3 to 5 mg

<16 years old

Refer to guidelines or discuss with paediatric endocrinology

Stop smoking intervention in emergency departments helps people quit

The study

Cessation of Smoking Trial in the Emergency Department (COSTED): a multicentre randomised controlled trial

Pope I, Clark LV, Clark A, et al

Emergency Medicine Journal 2024;41:276-282

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/4dm5zcwp

Why was the study needed?

In 2022, around 6.4 million people in the UK smoked. Smoking related illnesses (including respiratory diseases, cancer, and heart disease) caused around 74 600 deaths in 2019 and more than 408 000 hospital admissions in 2022-23 in England.

Encouraging people to stop smoking prevents premature deaths and reduces healthcare use. It also addresses health inequalities: smoking accounts for about half the difference in life expectancy between the poorest and the richest (about 4.5 years of the total 9 year life expectancy difference).

People who attend emergency departments are more likely than others to smoke. Stop smoking interventions in this setting have shown promise. Researchers compared an intervention (vape starter pack, advice, and referral) with written information about stop smoking services.

What did the study do?

Researchers invited 972 adults attending one of six emergency departments in the UK to take part in the trial in 2022. All smoked daily and none used a vape daily.

Half (484 people) received an intervention delivered by a smoking cessation adviser: up to 15 minutes' advice tailored to the patient, a vape starter kit and advice on how to use it, and a referral to stop smoking services. The others (488 people) received written information signposting them to stop smoking services.

At six months, researchers sent participants surveys asking about their smoking status.

What did it find?

The main outcome was abstinence, confirmed by a carbon monoxide reading (but few supplied this). At 6 months:

- In the intervention group, 113 (23%) said they had quit; this was confirmed in 35 people (7% of the original 484)
- In the signposting group, 63 (13%) said they had quit; this was confirmed in 20 people (4% of the original 488).

The researchers assumed that those who did not submit a carbon monoxide reading at six months were still smoking. The intervention therefore led to confirmed quitting in 7% people at six months, compared with 4% of those given signposting only.

No serious adverse events related to the intervention were reported.

Why is this important?

This is the first trial to show that a stop smoking intervention delivered in emergency departments including vapes helps people quit smoking, even among a group not actively looking to give up.

Smoking accounts for more years of life lost than any other modifiable risk factor. Half of those who smoked agreed to take part in the trial, which suggests that emergency departments are an acceptable setting for an opportunistic intervention. People who attend emergency departments are more likely than others to smoke and to come from deprived communities. Stop smoking interventions in emergency departments could therefore reduce health inequalities.

The researchers assumed that people who did not respond were still smoking. This might not be true, and the intervention might have more impact in practice than in the trial. In addition, the signposting-only group discussed smoking with the researchers, which is not typical of care in the emergency department. The signposting-only group might therefore have been more likely to quit than others who received typical care (no discussion about smoking).

What's next?

The researchers held a webinar on this research with Action on Smoking and Health (ASH) and set up a group to help trusts roll out the intervention. As of June 2024, the group had 61 members representing local authorities and NHS trusts from 30 areas across England. The researchers are developing a toolkit to help with implementation.

This intervention required dedicated staff (smoking cessation advisers who were not necessarily clinicians), training, and vape starter kits. The research team is evaluating the cost effectiveness of the intervention.

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

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WHAT YOUR PATIENT IS THINKING

Encourage me to take the rest I need

Ruth Segovia y Mayoral
describes her experience of living with immune thrombocytopenia and why she wishes health professionals were able to prescribe rest

CPD READING
0.5 HOURS

PRIYA SUNDRAM

I have always resisted defining myself by my illness. I am not a "sick person." I am simply a person who happens to have an illness. But living with immune thrombocytopenia has shaped my life in ways I never anticipated. For years I minimised my symptoms, trying to convince myself that if I could push through then everything was fine. But the fatigue that accompanies the condition has been my constant and unpredictable companion. As a result, I have struggled with feelings of inadequacy, stress, and isolation.

In the early stages, the fatigue would come and go, coinciding with flare-ups. As I tapered off medication, I regained some energy, but even this created an unexpected challenge. I felt compelled to make up for lost time, both socially and professionally. I pushed myself to get back to "normal" as soon as I could. The cycle was exhausting. I once requested medical clearance to return to work earlier than I should have, only to find myself overwhelmed by months of crushing exhaustion.

My body's way of demanding care

My condition has evolved unpredictably. At first, my red blood cell levels would drop; later, my platelets became persistently low. I even experienced a decline in white blood cells on one occasion. Stress seemed to amplify everything. Whenever I felt I was reaching my limit, I would experience another drop in platelets, forcing me to rest. At times, I saw this as a strange form of self-protection, as if my body were demanding care when I refused to acknowledge my own needs.

I've learnt that accepting my condition is an essential step in helping me take the rest I now know I need. I have also found that practising meditation helps me listen to my body and allow myself rest without guilt. I wish health professionals would encourage me to take the rest I need. A "prescription" for rest would have helped me to take my condition seriously and really recognise the importance when I was struggling to do so.

I need acknowledgment of the full impact the condition has on my life

Please acknowledge the impact

My experiences within the healthcare system have been mixed. My current team is incredibly supportive. We have made shared decisions at critical moments, helping me to feel empowered and heard. However, I was not as lucky at the beginning of my illness when I encountered professionals who lacked empathy and sensitivity towards what I was going through. This lack of understanding and support made it even more challenging to navigate my condition and accept the accompanying fatigue and need to rest.

What I need from my doctors, more than anything, is acknowledgment. Not just of my lab results, but of the full impact this condition has on my daily life. That kind of understanding would make me feel seen and would make managing the disease less isolating.

Correspondence to: rsegoviaymayoral@gmail.com
Cite this as: *BMJ* 2025;389:r765

WHAT YOU NEED TO KNOW

- Fatigue is a common symptom of immune thrombocytopenia and its unpredictable nature can affect a person's life in many ways
- Understand the value of advising rest in a society that prioritises busyness and productivity
- Acknowledging the impact validates the patient's experience and helps them to feel less isolated in managing the disease

EDUCATION INTO PRACTICE

- How could you ensure that someone experiencing unpredictable fatigue feels able to take the rest they need?
- What could you do to help patients feel you are acknowledging the impact of their condition?

SPOT DIAGNOSIS

A man with indurated plaques and non-pitting oedema on the shins

A man in his 30s presented with an 18 month history of indurated plaques and diffuse non-pitting oedema on the shins. The plaques were not painful or itchy and some were coloured purple-brown. The patient had previously been told that the lesions were possibly lymphoedema but did not receive treatment. He reported a weight loss of 8 kg during this period, an increased appetite, palpitations, tremors, heat intolerance, and excessive sweating. The patient did not report any gritty sensation in the eyes, photophobia, tearing, diplopia, or increased bowel movements. The patient had a history of hypertension and was taking 150 mg irbesartan once daily. There was no relevant family history. On examination, his heart rate was 106/min with a regular rhythm. There was no exophthalmos or lid lag, but fine tremors were noted in the tongue and both hands when held up. Palpation of his neck revealed a grade II diffuse goitre without audible bruit. Indurated waxy plaques, nodules, and diffuse non-pitting oedema were visible on the shins; some were coloured purple-brown (fig 1). There was induration with prominent follicles, leading to a peau d'orange appearance (fig 2).

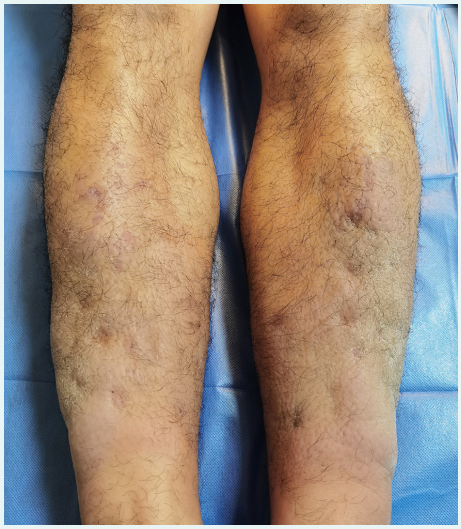

Fig 1 | Indurated plaques, nodules, and diffuse non-pitting oedema on shins, some coloured purple-brown

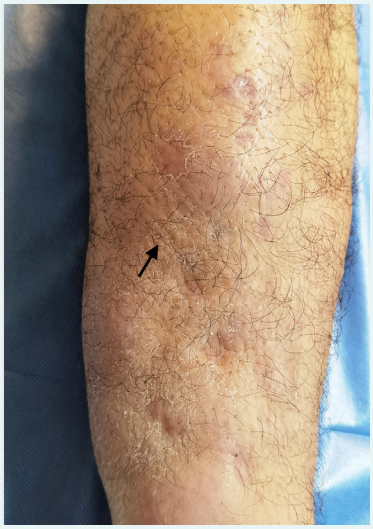

Fig 2 | Presence of peau d'orange (black arrow)

Laboratory investigations showed a lowered level of thyroid stimulating hormone (TSH) (0.01 mIU/L, normal range 0.27-4.2 mIU/L), raised levels of free T4 (35.19 pmol/L, 10-22 pmol/L) and T3 (4 ng/mL, 0.8-1.9 ng/mL), and TSH receptor antibody was positive in high titre (›40 IU/L, 0-1.75 IU/L). Full blood count, biochemistry, and coagulation results were within normal ranges.

What is the most likely diagnosis?

Submitted by Yuan Wang, Fang Wang, Yongzhuo Wu, and Fuqiong Jiang

Patient consent obtained.

Cite this as: *BMJ* 2025;389:e082423

answers

SPOT DIAGNOSIS A man with indurated plaques and non-pitting oedema on the shins

What is the most likely diagnosis?

Pretibial myxoedema secondary to Graves' disease. Graves' disease is an autoimmune disorder caused by autoantibodies to the TSH receptor that stimulate thyroid hormone synthesis and secretion, leading to hyperthyroidism and diffuse goitre. It is the most common cause of hyperthyroidism, with an annual incidence of 20 to 50 cases per 100 000 population.

The typical clinical presentation of Graves' disease includes heat intolerance, tremor, palpitations, insomnia, fatigue, muscle weakness, weight loss, increased stool frequency, menstrual disturbances in women, and eye symptoms (swelling, pain, redness, double vision). Pretibial myxoedema is characterised by non-pitting oedema and induration of the pretibial skin owing to mucin deposition.

Management of Graves' disease includes using antithyroid drugs such as carbimazole and propylthiouracil, which inhibit thyroid hormone synthesis. Ablative treatment (iodine-131 radiotherapy or thyroidectomy) is used to remove or decrease thyroid tissue. Radioiodine therapy is recommended for patients who experience relapses after using antithyroid drugs, are intolerant to antithyroid drugs, or prefer a definitive non-surgical option; however, it is contraindicated for patients who are pregnant or lactating.

Management of pretibial myxoedema includes using topical corticosteroids with or without occlusion, intralesional corticosteroids, teprotumumab (not currently licensed in the UK), and compression therapy.

LEARNING POINTS

- Pretibial myxoedema is characterised by non-pitting oedema and induration of the pretibial skin owing to mucin deposition.
- Pretibial myxoedema might be associated with hyperthyroidism, most commonly due to Graves' disease.
- Patients presenting with pretibial myxoedema should undergo serum thyroid function and thyroid antibody tests, considering the possibility of Graves' disease.

PATIENT OUTCOME

See bmj.com.

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.

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