education

FROM THE JOURNALS Edited highlights of weekly research reviews

Final checkpoint for melanoma trial

Before 2011, when checkpoint inhibitor treatments became available, the median survival for people with advanced melanoma was 11 months. The final results of the Checkmate 067 study, just published in the *New England Journal of Medicine*, confirms the dramatic improvements in survival since then.

The phase 3 study randomised 945 people with stage III or IV melanoma to receive either the checkpoint inhibitors nivolumab plus ipilimumab, nivolumab with placebo, or ipilimumab with placebo. Median survival in those allocated to nivolumab plus ipilimumab was 71.9 months, and 10 year overall survival was 43% with nivolumab plus ipilimumab, 37% with nivolumab, and 19% with ipilimumab.

N Engl J Med doi:10.1056/NEJMoa2407417

Antimicrobial resistance

Since covid-19 happened it feels like we haven't heard so much about antimicrobial resistance (AMR). A global burden of disease study in the *Lancet* shines some light back onto the subject, estimating that in 2021 there were 4.71 million deaths associated with AMR and 1.14 million deaths attributable to AMR. Between 1990 and 2021, deaths from ARM reduced in children under 5 years of age by over 50% but increased in adults over 70 years old by 80%. The study also found a rise in mortality due to carbapenem resistant, Gram negative bacteria: the authors call for the development of new antimicrobials against Gram negative bacteria to be prioritised.

Lancet doi:10.1016/S0140-6736(24)01867-1

Firearm wisdom

"Children who experience an initial firearm injury are at high risk for experiencing a recurrent firearm injury." Do we really need a 10 year retrospective cohort study with 15 authors to tell us that, you might wonder. But when you go back to this conclusion after reading the findings of the study set in St Louis, Missouri, it sounds more like the wisdom of an ancient proverb than stating the obvious. Between 2010 and 2019 a shocking 1340 under 18 year olds were treated for firearm injury across four hospitals—a third were under the age of 15 years, 84% were male, and 87% were Black. The overall risk of another firearm injury was 6% at 1 year and 14% at 5 years: recognising firearm injury as a risk factor for further injury (and death) provides a basis for offering social interventions that may reduce the risk of re-injury.

Ann Intern Med doi:10.7326/M24-0430

Penicillin challenge

Finding alternatives to penicillin can be challenging—and frustrating when you suspect the patient may not have a true allergy. Should we be referring more patients with reported penicillin allergy for direct penicillin challenges? A systematic review and meta-analysis sought to quantify the frequency of reactions to penicillin in direct penicillin challenges in patients reporting penicillin allergy. From 9225 participants across 56 studies only 3.5% had a reaction, and there were only five severe reactions, none of which was fatal.

JAMA Intern Med doi:10.1001/jamainternmed.2024.4606

More GLP-1 agonising

Liraglutide was licensed in the US in 2010, in the same year that Dutch inventor Fred van der Weij created the air fryer. Over a decade later, we seem to be finding more and more uses for both. Fancy an air fried roast chicken, croissant, or pizza? How about a glucagon-like peptide-1 receptor agonist (GLP-1 RA) for chronic kidney disease, substance use disorder, or even to prevent cirrhosis?

A retrospective cohort study compared the rate of progression from metabolic dysfunction-associated steatotic liver disease (MASDL) to cirrhosis in people with diabetes and MASDL who were taking GLP-1 RAs or dipeptidyl peptidase-4 inhibitors (DPP-4is). A small reduction in risk of progression was found in those taking GLP-1 RAs compared with DPP-4is: 9.98 versus 11.10 events per 1000 person-years (hazard ratio 0.86, 95% confidence interval 0.75 to 0.98).

JAMA Intern Med doi:10.1001/jamainternmed.2024.4661

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

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Pelvic organ prolapse: self-management of pessaries can be a good option

The study

Clinical effectiveness of vaginal pessary self-management vs clinic-based care for pelvic organ prolapse (TOPSY): a randomised controlled superiority trial

Hagen S, Kearney R, Goodman K, et al

eClinicalMedicine 2023;66:102326

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: rb.gy/hal6wb

Why was the study needed?

Up to 40% of women in the UK have pelvic organ prolapse, but fewer (up to 10% of all women) report symptoms. Pelvic organ prolapse becomes more likely with pregnancy and childbirth, age, and being overweight, and can cause discomfort, problems emptying the bladder and bowel, and harm women's quality of life.

The condition can be managed with surgery, but most women choose initially to have non-surgical treatment, such as a pessary. Women with a pessary either visit a clinic regularly to have the pessary checked and re-inserted (or replaced) or do this themselves at home (self-management).

Studies suggest that pessary self-management is more convenient, has fewer side effects, and increases the likelihood that women will continue using a pessary. This is the first randomised controlled trial to compare the effectiveness and value for money of self-management with clinic visits.

What did the study do?

The findings were based on data from 340 women from 21 clinics in the UK who had used a pessary for at least two weeks. Half (169 women) were in the self-management group and half (171 women) in the clinic group. Their average age was 64 and most participants (91%) were white.

The self-management group attended a 30 minute in-person session, during which a clinician taught them to remove, clean, and re-insert a pessary. They received an information leaflet, a two week follow-up call, and further telephone support (if needed). The other group visited a clinic roughly every six months to have their pessary cleaned and reinserted.

The main outcomes were quality of life (questionnaire specific to pelvic floor issues) and cost effectiveness (including GP and hospital appointments and prescriptions).

What did it find?

At 18 months, women in the self-management group:

- Had a similar quality of life to women in the clinic group
- Had fewer complications overall (17%) than the clinic group (22%)
- Used fewer healthcare services (£578 per person on average) than the clinic group (£728 per person on average).

No serious adverse events were related to pessary use in either group.

Quality of life was the same regardless of women's age (older compared with younger than 65), whether or not they had a hysterectomy, and/or took hormone therapy.

Why is this important?

Women who self-managed their pessaries had a similar quality of life and fewer complications than those who received clinic based care. Self-management offered better value for money. The findings suggest that self-management could be routinely offered to those women who are physically and mentally able to self-manage.

The researchers suggest that complications in the self-management group may have been less frequent because women had more confidence in their ability to manage the pessary. For example, to take the pessary out, put it back in, or use it for shorter periods of time.

By 18 months, several participants (20%) had crossed over from the self-management to the clinic group, often because they struggled to insert or remove the pessary. This reflects routine practice, and implies that the benefits and savings among women who continued to self-manage may be greater than was shown in the trial. Women could not switch from the clinic group to self-management because they did not receive the teaching and telephone support.

Ethnic diversity in the trial sample was limited. It did not include women who could not speak English, lacked dexterity, or were pregnant. These findings may therefore not apply to these groups of women.

What's next?

The researchers suggest that self-management could be rolled out across the UK. However, they say more research is needed for it to become routine practice. Clinicians may need more training to support women who want to self-manage their pessary.

Women in the study are being followed up after four years to compare long term outcomes for pessary self-management and clinic based care.

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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EASILY MISSED?

Acute aortic syndrome

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. To suggest a topic for this series, please email us at practice@bmj.com.

CPD READING
0.5 HOURS

A healthy woman in her mid 50s experiences sudden, tearing pain, like a lightning bolt from her neck to her chest, radiating to her back, coming in waves, with severity fluctuating over subsequent hours. At times she is able to talk and even walk, but she feels that her consciousness level is mostly reduced, and she has difficulty breathing. She feels dizzy and nauseous. Her mother survived a type A aortic dissection, three years previously, at the age of 77.

An ambulance is called and arrives 90 minutes later. A paramedic makes a tentative diagnosis of aortic dissection based on the presenting features. The woman is given oral morphine and transported to hospital, arriving 45 minutes later. In the emergency department she receives an initial diagnosis of panic attack and is managed conservatively, until reassessment some hours later triggers computed tomography angiography, which shows an aortic dissection.

WHAT YOU NEED TO KNOW

- Acute aortic syndrome is a life threatening condition caused by a tear in the thoracic aorta.
- Consider acute aortic syndrome in all patients presenting with chest pain that is unexplained or associated with a high risk condition, pain feature, or examination finding in the aortic dissection detection risk score.
- Undertake immediate computed tomography angiography if the patient is acutely unwell and has characteristic features of acute aortic syndrome.
- Consider using D-dimer as an alternative to computed tomography angiography for ruling out acute aortic syndrome in patients who have a high risk feature but the diagnosis is considered unlikely.

HOW THIS ARTICLE WAS MADE

This article was made using systematic reviews and meta-analysis undertaken for the Aortic Syndrome Evidence Synthesis study (https://fundingawards.nihr.ac.uk/award/NIHR151853), the clinical and personal experience of the authors, and insights from members of The Aortic Dissection Charitable Trust.

What is acute aortic syndrome?

Acute aortic syndrome (AAS) is a life threatening condition where a tear in the thoracic aorta can lead to rupture of the aorta and death. It encompasses three conditions: acute aortic dissection; intra-mural haematoma; and penetrating ulcer,[1] and is commonly classified into Stanford type A (involving the ascending aorta) and type B (sparing the ascending aorta) or DeBakey classification, with type 1 involving ascending and descending aorta and type 2 involving ascending aorta alone (fig 1). Without treatment, AAS can progress to aortic rupture, with rapid deterioration and death.

How common is it?

AAS is uncommon. Meta-analysis of population based studies from North America, Europe, Asia, and Australasia estimated a pooled incidence of 4.8 per 100 000 individuals per year, with 3.0 per 100 000/year type A and 1.6 per 100 000/year type B aortic dissections.[2] Mean patient age in the studies varied from 58.9 to 77.3 years and the proportion of men varied from 50% to 84%. Hospital episode statistics for England in 2022-23 reported 1542 admissions with dissection of the aorta out of 6 million emergency admissions.[3] Aortic dissection accounts for around three quarters of AAS.[4]

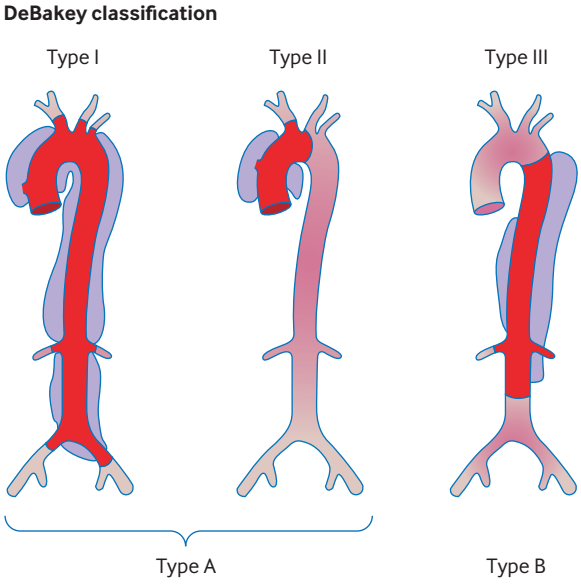

Fig 1 | Classification of aortic dissection

Why is it missed?

AAS is easily missed because similar symptoms are reported by patients with other much more common diagnoses, such as acute coronary syndrome, gastro-oesophageal reflux, and panic attacks. Chest pain is the most common presenting symptom of AAS,[5] but was also the chief presenting reason for 6% of emergency department attendances in England in 2022-23.[6] A US retrospective cohort study of 33 emergency departments estimated that one aortic dissection was diagnosed in every 980 attendances with atraumatic chest pain.[7] Low rates of exposure to a diagnosis of AAS may mean that clinicians fail to consider it as a possible diagnosis alongside other more common causes of chest pain. Our case presentation illustrates the diagnosis of AAS initially being overlooked in the emergency department in favour of a more common diagnosis (panic attack). Clinicians who assess acute chest pain need to be aware of AAS and how it is investigated, to avoid misdiagnosis.

A systematic review of 12 studies (1663 patients) estimated that one in three patients with an eventual diagnosis of aortic dissection was initially misdiagnosed.[8] The most common misdiagnoses were acute coronary syndrome, stroke, and pulmonary embolism. A more recent estimate from a population based retrospective cohort study of 1299 patients diagnosed with AAS in Ontario, Canada, between 2003 and 2018, identified that 13% had attended an emergency department in the previous 14 days with symptoms suggesting AAS.[9]

Why does this matter?

Missed diagnosis can lead to delayed surgery for type A aortic dissection and missed opportunities for medical management (blood pressure control) or emergency intervention for type B aortic dissection. Missed diagnosis of type A dissection is associated with an approximate doubling of mortality (hazard ratio 2.14, 95% confidence interval 0.89 to 5.13)[10] and delayed surgery is associated with increased mortality (67% at 8-12 hours versus 20% at 0-4 hours after diagnosis).[11] Blood pressure control using beta blockers is associated with an approximate halving of mortality in type B dissection.[12]

NHS Resolution, an organisation of the UK Department of Health and Social Care that provides expertise on resolving healthcare based concerns and disputes, identified aortic disease, including dissection, as a common cause of fatality related negligence claims.[13] A study of 135 medical practice litigations across the US involving aortic dissection cited failure to diagnose as the reason for litigation in 64%.[14] A review by the Healthcare Safety Investigation Branch found that half of patients with acute aortic dissection die before reaching any specialist centre in the UK,[15] and a systematic review of 14 studies of out-of-hospital cardiac arrest identified that the 7% caused by aortic dissection had 100% mortality.[16]

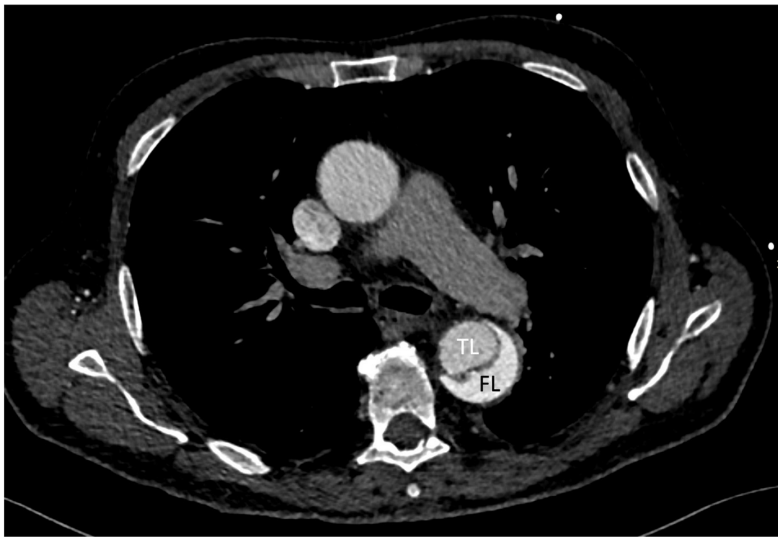

Fig 2| Computed tomographic angiography showing aortic dissection with true lumen (TL) and false lumen (FL)

How is it diagnosed?

AAS is definitively diagnosed by computed tomographic angiography scanning of the aorta (fig 2), or other imaging techniques, such as electrocardiography gated computed tomographic angiography or magnetic resonance angiography. Computed tomographic angiography incurs costs and small risks of radiation induced malignancy and reaction to contrast media. Clinicians therefore use clinical assessment and biomarkers (if appropriate) to assess AAS risk and select patients for imaging. If the patient is unwell with typical features of AAS and AAS is strongly suspected, then arrange a computed tomographic angiography without delay.

The diagnostic challenge of AAS is well recognised[17] but recent research has clarified the role of clinical assessment and biomarkers.[18-20]

Clinical assessment

Consider risk factors, symptoms, and signs to estimate the probability of AAS. Assessment may be structured, using a clinical score or algorithm, or unstructured, using clinical judgment. Several scores or algorithms have been developed for AAS but only the aortic dissection detection risk score (ADD-RS) has been widely studied.[18] ADD-RS gives a score between zero (low risk) and three (high risk) by allocating one point each if the patient has a risk factor for AAS, a symptom suggesting AAS, or a sign of AAS (table 1).

A meta-analysis of 11 cohort studies of ADD-RS[18] reported that a score greater than zero had 94.6% (95% credible interval 90% to 97.5%) sensitivity and 34.7% (95% credible interval 20.7% to 51.2%) specificity for AAS, while a score greater than one had 43.4% (95% credible interval 31.2% to 57.1%) sensitivity and 89.3% (95% credible interval 80.4% to 94.8%) specificity. The included studies were heterogeneous and had variable methodological quality. The low prevalence of AAS in the clinically relevant population means that sensitivity

Table 1 | Aortic dissection detection risk score	
High risk conditions	
• Marfan syndrome • Family history of aortic disease • Known aortic valve disease • Recent aortic manipulation • Known thoracic aortic aneurysm	1 point if any present
High risk pain features	
Chest, back, or abdominal pain described as: • Abrupt in onset • Severe in intensity • Ripping or tearing in quality	1 point if any present
High risk examination features	
• Pulse deficit or systolic blood pressure differential • Focal neurological deficit (with pain) • Murmur of aortic insufficiency (new, with pain) • Hypotension or shock state	1 point if any present

Table 2 | Sensitivity and specificity of ADD-RS and D-dimer, alone and in combination		
Result(s) indicating a positive test	**Sensitivity(95% credible interval)**	**Specificity(95% credible interval)**
ADD-RS>0	95.1%*(88.5% to 98.4%)	38%*(20.1% to 59.1%)
ADD-RS>1	41.6%*(24.8% to 59.1%)	91.7%*(81.7% to 97%)
D-dimer>500 ng/mL	96.7*(92.8 to 98.4)	53.7*(41 to 65.9)
ADD RS>0 or D-dimer>500 ng/mL	99.8%(98.7% to 100%)	21.8%(12.1% to 32.6%)
ADD RS>1 or D-dimer>500 ng/mL	98.3%(94.9% to 99.5%)	51.4%(38.7% to 64.1%)
ADD RS>1 or(ADD RS=1 and D-dimer>500 ng/mL)	93.1%(87.1% to 96.3%)	67.1%(54.4% to 77.7%)

*Estimates are based on data from six studies reporting ADD-RS and D-dimer, and thus differ from those in the previous text that are based on all studies of ADD-RS or D-dimer. ADD-RS=Aortic dissection detection risk score

Clinicians may fail to consider AAS as a diagnosis alongside other causes of chest pain

of 95% could be sufficient to rule out AAS, while specificity of 90% is required to avoid over-investigation. These findings could be interpreted as suggesting that patients with a score of two or three should be selected for imaging while those with a score of zero would not benefit from further testing. How patients with a score of one should be managed is uncertain. The risk of AAS associated with each ADD-RS score depends on the prevalence of AAS in the population being tested. If ADD-RS is used in a very low prevalence population, such as all patients with chest pain, then even scores of two or three will be associated with a low risk of AAS.

The patient in our case presentation had a high risk condition (family history) and high risk pain features, giving a score of two, and suggesting computed tomographic angiography would be of benefit.

Electrocardiography

Electrocardiography can diagnose acute coronary syndrome and other causes of acute chest pain but does not assist with diagnosis of AAS.

Blood tests

Blood tests (biomarkers) can be used to select patients with suspected AAS for imaging. D-dimer is the only biomarker that has been extensively studied for diagnosing AAS. Many other biomarkers have had limited evaluation, but none are ready for clinical use.[19] A meta-analysis of 18 cohort studies of D-dimer using a threshold of 500 ng/mL reported 96.5% (95% credible interval 94.8% to 98%) sensitivity and 56.2% (95% credible interval 48.3% to 63.9%) specificity for AAS, but noted uncertainty around estimates due to risk of bias and heterogeneity.[20] This is similar to the sensitivity and specificity of D-dimer for diagnosing venous thromboembolism[21] and suggests that D-dimer could rule out AAS in patients with a low or intermediate clinical risk (as determined by the ADD-RS or unstructured assessment), but indiscriminate use in patients with a very low clinical risk of AAS could lead to over-use of computed tomographic angiography. D-dimer sensitivity does not appear to be time dependent. A cohort study of 273 patients diagnosed with AAS estimated that D-dimer sensitivity was 97% within one hour of symptom onset and did not vary with time from symptom onset.[22] Age adjusted D-dimer may offer improved specificity compared with a fixed threshold but requires further evaluation.

Transthoracic echocardiography

A systematic review of four studies evaluating emergency physician point-of-care ultrasound for thoracic aortic dissection reported sensitivities ranging from 41% to 91% and specificities of 94% to 100% when an intimal flap was seen.[23] A more recent prospective cohort study (n=1314) of a point-of-care ultrasound protocol combining transthoracic echocardiography with scanning of the abdominal aorta reported 93.2% sensitivity and 90.9% specificity.[24] This suggests a possible role for point-of-care ultrasound in the emergency department diagnosis of AAS, but the role of operator experience needs to be determined. Point-of-care ultrasound is a core skill for emergency physicians, but additional training would be required for diagnosing AAS.

ADD-RS with D-dimer

ADD-RS can be combined with D-dimer in various ways. A recent meta-analysis combined data from six studies of ADD-RS and D-dimer to estimate sensitivities and specificities and provide direct comparisons between alternative strategies.[18] Table 2 outlines the sensitivities and specificities of using ADD-RS with D-dimer to select patients for imaging or using each test alone. These provide a range of trade-offs between sensitivity and specificity. International guidelines vary in their recommendations for using ADD-RS and D-dimer to select patients for computed tomographic angiography (see international guidelines box).

When should AAS be suspected?

AAS should be considered in patients with chest, back, or abdominal pain, syncope, or symptoms related to malperfusion. However, this population has a very low prevalence of AAS.[25] Applying diagnostic strategies for AAS to all such patients would result in low positive predictive value and very high use of computed tomographic angiography. Clinicians therefore need to

GUIDELINES FOR SELECTING PATIENTS WITH SUSPECTED AAS FOR COMPUTED TOMOGRAPHIC ANGIOGRAPHY

- Royal College of Emergency Medicine and Royal College of Radiologists guidelines[31] recommend computed tomographic angiography if no clear alternative diagnosis is apparent (such as myocardial infarction, pulmonary embolism, or pneumothorax) and the patient has a high risk condition, pain feature, or clinical finding for AAS (similar to those in the ADD-RS). https://rcem.ac.uk/wp-content/uploads/2024/01/Diagnosis_of_Thoracic_Aortic_Dissection_RCEM_RCR_v2.pdf
- Canadian clinical practice guidelines[32] recommend clinical probability assessment using risk factors, pain features, examination findings, and alternative diagnosis. Patients at low risk receive no further testing for AAS. Patients at intermediate risk receive D-dimer testing, with computed tomographic angiography if positive and no further testing if negative. Patients at high risk receive computed tomographic angiography. https://www.cmaj.ca/content/192/29/E832
- European Society for Cardiology guidelines[5] recommend stratification to high probably (equivalent to ADD-RS 2-3) and low probability (equivalent ADD-RS 0-1). High probability cases are investigated with computed tomographic angiography, low probability with D-dimer, chest x ray, and transthoracic echocardiography. https://academic.oup.com/eurheartj/article/35/41/2873/407693
- American Heart Association and American College of Cardiology guidelines[27] state that integrating a low aortic dissection risk score and a low D-dimer may be a useful strategy to exclude the diagnosis of AAS but do not recommend a specific structured strategy. https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000001106

RESOURCES FOR CLINICIANS AND PATIENTS

- Royal College of Emergency Medicine learning module on aortic dissection. https://www.rcemlearning.co.uk/reference/aortic-dissection
- Royal College of Emergency Medicine/Royal College of Radiologists best practice guideline. https://rcem.ac.uk/wp-content/uploads/2024/01/Diagnosis_of_Thoracic_Aortic_Dissection_RCEM_RCR_v2.pdf
- NHS acute aortic dissection pathway toolkit. https://aorticdissectioncharitabletrust.org/acute-aortic-dissection-toolkit/
- The Aortic Dissection Charitable Trust patient and professional resources (https://aorticdissectioncharitabletrust.org/resources/) and infographic (https://aorticdissectioncharitabletrust.org/about-aortic-dissection/)

apply diagnostic strategies selectively to those with a non-negligible risk of AAS, such as those with an additional feature suggesting AAS ("chest pain plus one"). A recent cohort study of 5548 patients attending the emergency department with possible symptoms of AAS found that clinicians rated the likelihood of AAS as zero in 2315/4111 (56%).[25] Applying diagnostic strategies only to those with a non-zero likelihood of AAS could result in a more deliverable rate of computed tomographic angiography but it is currently unclear how clinicians determine a zero likelihood of AAS and whether this judgment is accurate.

How is it managed?

In the UK, AAS is managed according to principles set out in the NHS acute aortic dissection toolkit,[26] which NHS England produced to improve outcomes from AAS. Elsewhere, local guidelines are applicable.[5-28] Acute management involves analgesia and reducing systolic blood pressure to 100-120 mmHg. Type A AAS is usually managed operatively in a regional aortic centre. Type B AAS is split into complicated or non-complicated by the presence of haemodynamic instability and/or malperfusion of an organ system or limb. Uncomplicated type B AAS is usually managed medically with blood pressure control. Although patients may not require transfer to a tertiary centre, they should all be discussed with a cardiothoracic or vascular specialist to agree management. Complicated type B AAS may require tertiary transfer for endovascular stent graft placement. In-hospital mortality is 22% for type A and 13% for type B aortic dissection.[29]

Future developments

Research into biomarkers may produce new tests to assist with diagnosis of AAS, while further evaluation of ADD-RS, D-dimer, and point-of-care ultrasound may clarify their role. This could lead to reduced risk of misdiagnosis and reduced reliance on computed tomographic angiography to rule out AAS.

Case revisited

The delay in diagnosis may have been caused by initial misdiagnosis as a panic attack. The patient received appropriate treatment once the correct diagnosis was made and she recovered. However, the diagnostic delay remains a source of anxiety.

Competing interests: SG, GC, and SW have received institutional research funding from the National Institute of Health Research to undertake the ASES study. JZ is supported by a Cancer Research UK Clinical Trials Fellowship Grant and has received institutional research funding from The Aortic Dissection Charitable Trust. VL has no competing interest to declare.

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Find the full version with references at doi: 10.1136/bmj-2024-080870

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Valerie Lechene is a patient with experience of AAS. She described her experience of AAS diagnosis (and misdiagnosis) in the case presentation and contributed to writing all elements of this article. She was also a member of the research team for the ASES study that undertook the systematic reviews for this article. The Aortic Dissection Charitable Trust (https://aorticdissectioncharitabletrust.org/) is a charity uniting patients, families, and the medical community in a shared goal of improving diagnosis, increasing survival, and reducing disability due to aortic dissection. Patients and public representatives from the Trust participated in a public involvement group for the ASES study that informed the study design, helped to interpret the findings, and assisted with dissemination of findings through webinars that informed the development of this article.

EDUCATION INTO PRACTICE

- What would prompt you to consider AAS in your differential diagnoses for a patient and what factors would increase (or decrease) your suspicion for the diagnosis?
- How would you decide whether to request a computed tomographic angiography for a patient with symptoms that could be compatible with AAS?

10-MINUTE CONSULTATION

Optimising inhaled therapy for patients with asthma

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This is part of a series of occasional articles on common problems in primary care. *The BMJ* welcomes contributions from GPs.

CPD READING
0.5 HOURS

A 30 year old woman attends her general practice for her annual asthma review. She says her asthma is well controlled, but she has been issued two inhaled corticosteroid (ICS) preventer inhalers and six short acting beta agonist (SABA) reliever inhalers in the past year. On further questioning, she says that she limits her exercise because this brings on her asthma symptoms, and she experiences occasional night-time waking with cough. She describes irregular use of her ICS preventer inhaler, especially during the summer months, and almost daily use of her SABA reliever inhaler. On demonstrating her inhaler technique, she uses a quick and deep inhalation with her pressurised metered dose inhaler and does not use her spacer device.

Asthma is one of the most common non-communicable diseases and carries a substantial morbidity and mortality burden worldwide.[1] A cross-sectional study from 17 countries carried out by the Global Asthma Network in 2022 found that about 7% of adults were affected by asthma symptoms that were not well controlled, resulting in a high burden of preventable symptoms, restrictions on activity, and an increased risk of asthma attacks.[2] Sub-optimally controlled asthma is also associated with substantially increased medication and healthcare costs.[3]

In this article, we focus on optimising inhaled therapy to support clinicians to empower patients to achieve better control of their asthma.

WHAT YOU NEED TO KNOW

- Sub-optimally controlled asthma is common, in part because of normalisation of symptoms, underuse of preventer therapy, overuse of reliever therapy, and poor inhaler technique. Ensuring patients are using the right inhaled medicine and that this is getting to the right place in the airways is critical to improving asthma control
- Right inhaled medicine: Adherence to inhaled corticosteroid preventer therapy can be encouraged by explaining the role of airway inflammation in causing asthma symptoms and considering the use of inhaled corticosteroid (ICS)-formoterol combination inhaler regimens
- Right place: Ensure patients have the most appropriate inhaler device type, based on their inhaler technique and preferences, which will maximise the likelihood that medication reaches their airways

What you should cover

Every consultation with a patient with asthma is an opportunity to assess their symptom control and risk of future exacerbations. To support an effective, personalised approach to improving asthma control, structure the consultation to include the following questions.

"How is your asthma affecting you?"

- Objective disease control scores, such as the Asthma Control Test,[8] can be used to assess symptom burden and track progress over time. However, patients may normalise symptoms and accept their activity restriction as "living with asthma."[9] We therefore recommend that answers to standardised questionnaires are not taken at face value and an individualised approach is taken to exploring the impact of asthma on a person's life.
- Ask people whether they avoid activities to prevent symptoms and whether asthma is having any impact on their sleep, mental health, work, or school life to identify suboptimal control.
- Ask about the patient's triggers such as pollens, cold air, or viral infections. Patients may not be aware that environmental factors such as air pollution or damp housing conditions can trigger asthma.

"How often are you using your inhalers?"

- When possible, check prescribing records to assess how many inhalers have been issued over the previous 12 months. National guidelines from the British Thoracic Society state that people with well controlled asthma should use their reliever inhaler up to twice a week only.[10] Among patients who are prescribed separate inhaled corticosteroid (ICS) and short acting beta agonist (SABA) inhalers, more than two SABA inhalers a year may indicate SABA overuse, which is associated with poor asthma control.[7]
- Ask if the patient has any concerns about inhaler use. A common reason for patients not to take their preventer medication is because they perceive asthma to be an episodic condition that requires occasional relief rather than a long term condition needing prevention. They may lack understanding of the role of airway inflammation in asthma or how their inhalers work, and may be concerned about potential adverse effects from inhaled corticosteroids.[11]

"What do you do when your asthma gets worse?"

- People with asthma should know what to do when their symptoms get worse or if they have an asthma attack. All patients should have a personal asthma management plan (can be digital, printed, or pictorial), and a routine clinical review is an opportunity to go through this to check the patient's understanding.

Greener Practice have produced a widely endorsed visual aid to support healthcare professionals with asthma reviews (fig 1).

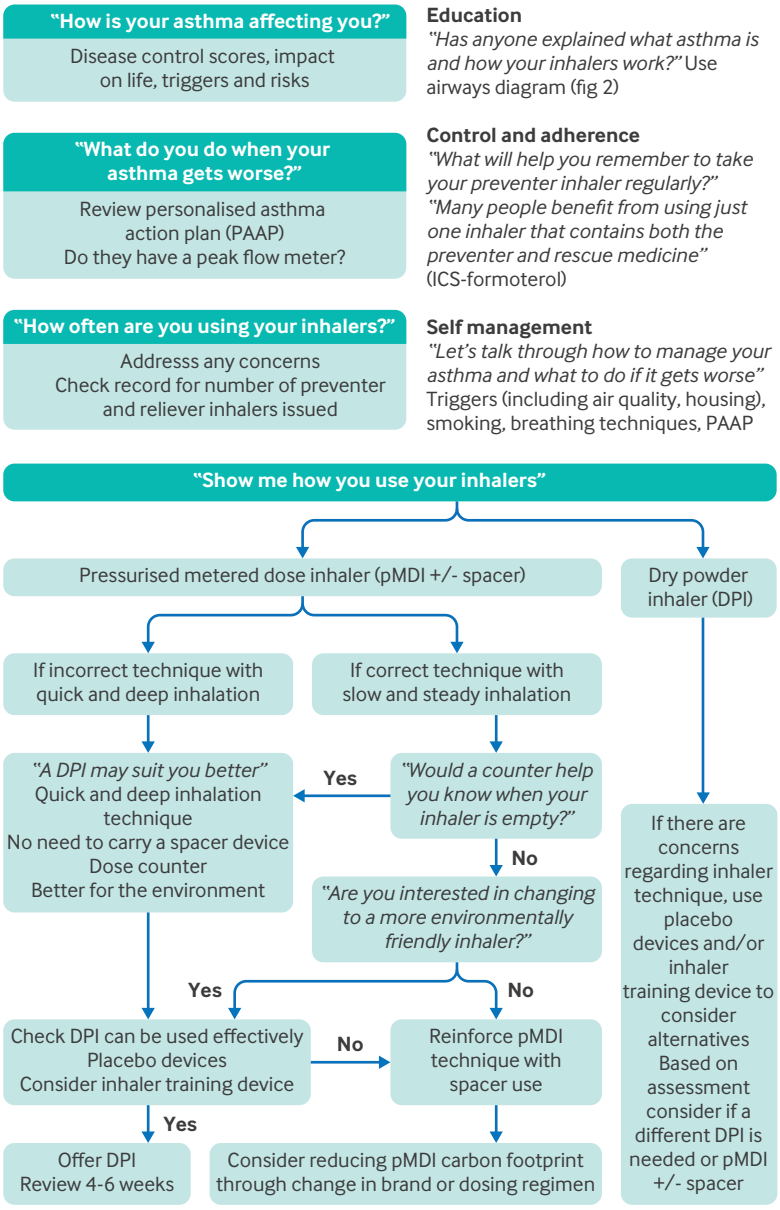

Fig 1 | Guidance for optimising asthma reviews by healthcare professionals in adults and children over 12 years old. Adapted from the Greener Practice High Quality and Low Carbon Asthma Care Quality Improvement Toolkit (https://www.greenerpractice.co.uk/wp-content/uploads/Asthma-Visual-Guide-V1.5.2.pdf)

What you should do

Raise expectations of asthma control

Ensure people with asthma understand what is meant by well controlled asthma—that is, that they should have no or very occasional daytime symptoms, no night time symptoms, and no restriction on their physical activity. You may discuss how stopping smoking, breathing techniques, and choosing a physical activity goal to work towards can improve symptom control.

Explain what asthma is and how the inhaled medications work

Adherence to regular ICS preventer therapy is low (30-70%, varying by country, age, sex, and ethnicity), and poor adherence is associated with increased risk of asthma exacerbations.[12] A study of inhaler prescription data for more than a million people aged ≥12 years with asthma across five European countries found that approximately a third were overusing SABA inhalers (using three or more SABA cannisters a year).[7] Underuse of ICS inhalers is a key driver of this pattern.

Adherence to regular inhaled ICS preventer medication is challenging for multiple reasons, including a lack of understanding of their purpose, concern about side effects, and remembering to take a medication that does not offer immediate symptom relief.

To explain what asthma is and how inhaled medications work, consider using an airways diagram or airways models. These illustrate that asthma is a chronic inflammatory condition of the airways, and treating the inflammation will prevent symptoms and asthma attacks (fig 2). This can help reframe doses of reliever treatment as "rescue" medication that will not be needed if asthma is well controlled, and regular use is a warning sign of poor control. It can also explain why people with asthma should not be taking reliever therapy only, as this does not control the underlying inflammation and leaves people at risk of asthma exacerbations.[5]

Address concerns and habits around using inhaled medicines

Patients and carers may have concerns about systemic side effects from corticosteroid use such as growth retardation, respiratory infections, and bone health. They can be reassured that systemic side effects are linked to oral steroid use and not inhaled steroids at the standard doses needed to control asthma.[13] Furthermore, oral steroids are more likely to be needed if a person's asthma is poorly controlled owing to poor adherence to inhaled steroid medication.[13] Local oral side effects such as oral candidiasis and dysphonia, can be prevented by rinsing the mouth out after using the inhaler and using a spacer device with a pressurised metered dose inhaler.

If a patient finds it challenging to remember to take regular preventer medication, discuss how to incorporate inhaler use into daily activities. People may find it helpful to incorporate taking their inhaler with a daily activity such as toothbrushing, or using reminders on their phone.

If patients raise concerns about side effects of beta agonists, such as palpitations or tremor, this is an opportunity to emphasise that achieving good control with adequate preventer therapy will reduce the need for beta agonists and, thus, these side effects.

Consider inhaled corticosteroid (ICS)-formoterol combination inhaler regimens

The Global Initiative for Asthma now recommends using ICS-formoterol combination inhalers, instead of separate preventer and reliever inhalers, as the preferred asthma treatment in adolescents and adults.[5] Formoterol is a long acting beta agonist (LABA) that works as quickly as salbutamol and can therefore be used as a reliever medication during an acute exacerbation.[14] Patients may also prefer the convenience of having just one inhaler to carry and use.

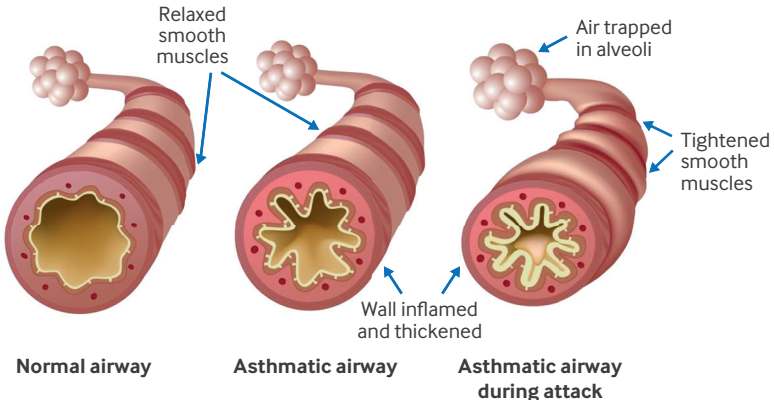

Fig 2 | Changes in airways caused by asthma. Adapted from the Greener Practice High Quality and Low Carbon Asthma Care Quality Improvement Toolkit (https://www.greenerpractice.co.uk/high-quality-and-low-carbon-asthma-care/resources/)

ICS-formoterol inhalers can be used either in an "as-needed" regimen for mild asthma (anti-inflammatory reliever (AIR) therapy) or regularly for moderate and severe asthma (maintenance and reliever therapy (MART)). Anti-inflammatory reliever therapy ensures that patients receive ICS on the days they use their reliever and so are never just receiving SABA monotherapy. In maintenance and reliever therapy regimens, patients take their inhaler regularly, usually twice a day and use the same inhaler as a reliever. As patients take additional puffs to relieve symptoms, they receive the additional steroid they need, preventing worsening of symptoms and exacerbations.

Maintenance and reliever therapy regimens have been shown to reduce severe exacerbations, while achieving similar symptom control and lower overall doses of ICS, compared with either ICS alone or ICS-LABA plus SABA reliever.

Fit the inhaler to the patient

Errors in inhaler use are common, including incorrect preparation of device, incorrect type of inhalation for the inhaler device prescribed, and lack of breath holding after inhalation.[17]

When assessing inhaler technique, first observe the patient using their inhaler. Pressured metered dose inhalers require a slow and steady inhalation, ideally with a spacer device. However, in real world studies spacer device use is low, and it is important to ask whether patients are using them.[17] Dry powder inhalers require a quick and deep inhalation and do not require spacers.

If the patient's inhalation technique is not suitable for their current inhaler but effective for a different inhaler device, consider prescribing the inhaler that best fits the patient's current inhaler technique. For example, if a patient is taking a quick and deep inhalation with a pressurised metered dose inhaler, or if they are not using a spacer, they may be better suited to a dry powder inhaler. Patients who are unable to take a quick and deep breath in may not be suited to dry powder inhalers, which are not licensed for children under 6 years old.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We asked the Patient Reference Group of the Primary Care Respiratory Society to review the article. Suggestions around the language used in relation to activity restriction due to symptoms and the setting of activity goals were incorporated into the final version.

EDUCATION INTO PRACTICE

- Think about the last time you reviewed the number of ICS and SABA inhalers a patient with asthma had been issued in the previous 12 months. Did you consider a ICS-formoterol regimen as a strategy for improving treatment control?
- What tools do you use (such as airways diagrams, models, or placebo/inhaler training devices) to explain the nature of asthma and determine the best inhaler device for each patient?

Ask patients if they would find a dose counter helpful to help keep track of their medication and to know when their inhaler device is empty. Dose counters reduce the risk of patients discarding inhalers with medication remaining or using inhalers that do not contain any medication.[18]

In situations where there is no clear clinical indication for a particular inhaler device, all adolescent and adult patients should be offered the option of lower carbon inhalers and, if they are interested, be assessed to see if they can use them correctly. Dry powder inhalers are the most common low carbon inhaler device in asthma.

Placebo devices and inhaler training devices can be valuable tools to support individualised decisions on device choice. If inhaler devices are changed, ensure that patients have a review within six weeks to check that they are using their device correctly.

Support self management

Ensure patients have an updated written asthma action plan, with guidance on how to use their inhalers and what to do if their asthma worsens. If appropriate, check if the patient has a peak flow meter and if they know how to use it to monitor their asthma. Agree peak flow meter values to include in written asthma management plans, which, alongside symptoms, can help patients know when to step up treatment or call for emergency help.

Link patients to resources that can optimise their control of asthma, such as physical activity, breathing exercises, and avoiding indoor and outdoor air pollution.

Referral to secondary care

For patients who do not demonstrate improved asthma control despite optimisation of inhaled therapy, consider referral to secondary care for clarification of the diagnosis and/or consideration for therapies such as biologics, which can be effective for patients with severe asthma.[23]

Competing interests: AB is a director of Greener Practice, a not-for-profit community interest company which supports primary care to be more environmentally sustainable.

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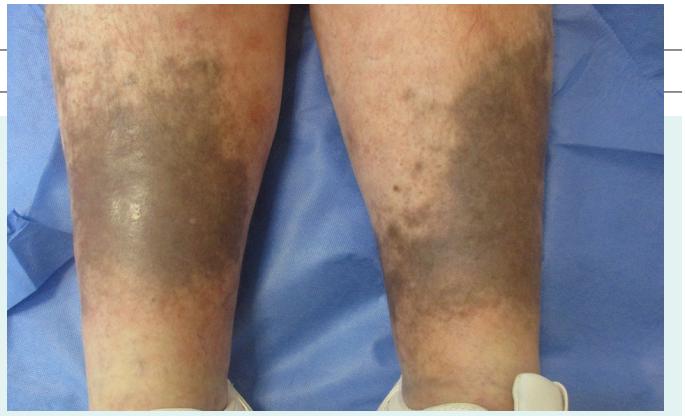
Hyperpigmentation of the legs



This image shows mottled blue-grey hyperpigmentation on the legs of a woman in her late 50s with a history of systemic lupus erythematosus. Her daily drug regimen included hydroxychloroquine, mepacrine, and deltacortril. A skin biopsy sample showed pigment in the dermis. Perls Prussian blue staining was negative, ruling out haemochromatosis, and no melanophages or lymphohistiocytic infiltrate were identified, excluding lichen planus pigmentosa. After a thorough review of the patient's medication timeline and history, drug induced cutaneous dyschromia secondary to hydroxychloroquine was diagnosed. Mepacrine was considered a less likely cause as the patient had started it only recently and, despite stopping the drug, her dyschromia worsened.

Drug induced cutaneous dyschromia can occur owing to changes in melanin synthesis or the accumulation of drugs or drug metabolites in the skin. This type of drug induced hyperpigmentation typically results in an uneven deposition of pigment. Differential diagnoses include post-inflammatory hyperpigmentation, melasma, lichen planus pigmentosa, and haemochromatosis. Hyperpigmentation can improve once the drug is stopped, but complete clearance is rare.

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Patient consent obtained.

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If you would like to write a Minerva picture case, please see our author guidelines at bit.ly/29HCBAL and submit online at bit.ly/29yyGSx

Faecal microbiota transplantation for Parkinson's disease

Gut dysfunction, predominantly constipation, is common in people with Parkinson's disease and it's associated with faster progression of disability. Some evidence supports the use of probiotics, but a small randomised controlled trial of colonic single dose faecal microbiota transplantation finds no worthwhile improvements in either motor or non-motor symptoms, although transient gastrointestinal adverse events were common (*JAMA Neurol* doi:10.1001/jamaneurol.2024.2305).

Melanoma in Sweden

Registry data from Sweden show that, although the incidence of melanoma in people aged 50 to 59 has been rising since 1990, the trend is downward in younger people (*JAMA Dermatol* doi:10.1001/jamadermatol.2024.3514). The incidence in age groups 20 to 49 years showed a peak around 2015 that has since been followed by stable or declining rates. Mortality from melanoma has declined among people younger than 60 but not in older people. The reasons behind these trends aren't clear, but perhaps public health campaigns promoting ultraviolet protection have made a difference.

Skin cancer in US veterans

A large cross sectional investigation reports that the prevalence of skin cancer, including melanoma, is two to three times higher in veterans—that's to say people who served in the active military, naval, or air service of the United States—than in non-veterans (*JAMA Dermatol* doi:10.1001/jamadermatol.2024.3043). A probable explanation is that veterans often incur high levels of sun exposure without proper ultraviolet protection during their active service. The prevalence of psoriasis, however, was also twice as high in veterans as in non-veterans, which is rather harder to explain.

Early glucocorticoids in STEMI

An early dose of glucocorticoids might ameliorate the acute inflammatory response associated with ischaemia and reperfusion after ST segment elevation myocardial infarction (STEMI) and reduce final infarct size. Although reasonable in theory, it doesn't seem to work in practice. In a trial that included 530 patients with STEMI, final infarct size at 3 months was no smaller in those randomised to intravenous injection of 250 mg methylprednisolone given before admission to hospital than in those given placebo. The only ST segment caveat is that, because final infarct sizes were smaller than expected, the trial was probably underpowered statistically (*JAMA Cardiol* doi:10.1001/jamacardio.2024.2298).

Models of obesity

Although weight gain is obviously linked to a chronic positive energy balance, it's not at all obvious which comes first. If endocrine or environmental factors stimulate body fat storage, food intake might increase, or energy expenditure decrease, as a secondary effect. Minerva enjoyed a lucid account of rival theories concerning the pathogenesis of obesity, which focused on the energy balance model and the carbohydrate-insulin model. In the former, it's the easy availability of calorie dense, ultra-processed foods that leads to increased intake and fat deposition. In the latter, a diet rich in carbohydrates and fructose influences how energy content of ingested food is partitioned, directing it away from oxidation pathways towards storage in adipose tissue (*Nature Metabolism*https://doi.org/10.1038/s42255-024-01106-8).

Health of only children

Data from the 1946, 1958, and 1970 British birth cohort studies refute the notion that only children are disadvantaged in comparison to people who have siblings—at least as far as health in middle age is concerned. No differences in risk of heart problems, hypertension, high triglycerides, high glycated haemoglobin, or high C reactive protein were found between individuals who were only children and those with siblings, at any age, in any of the cohorts. Compared with only children, however, the likelihood of cancer and poor general health was higher among those with three or more siblings (https://doi.org/10.1093/ije/dyae119).

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