

# education

**RESEARCH REVIEWS** Fortnightly round up from the leading medical journals

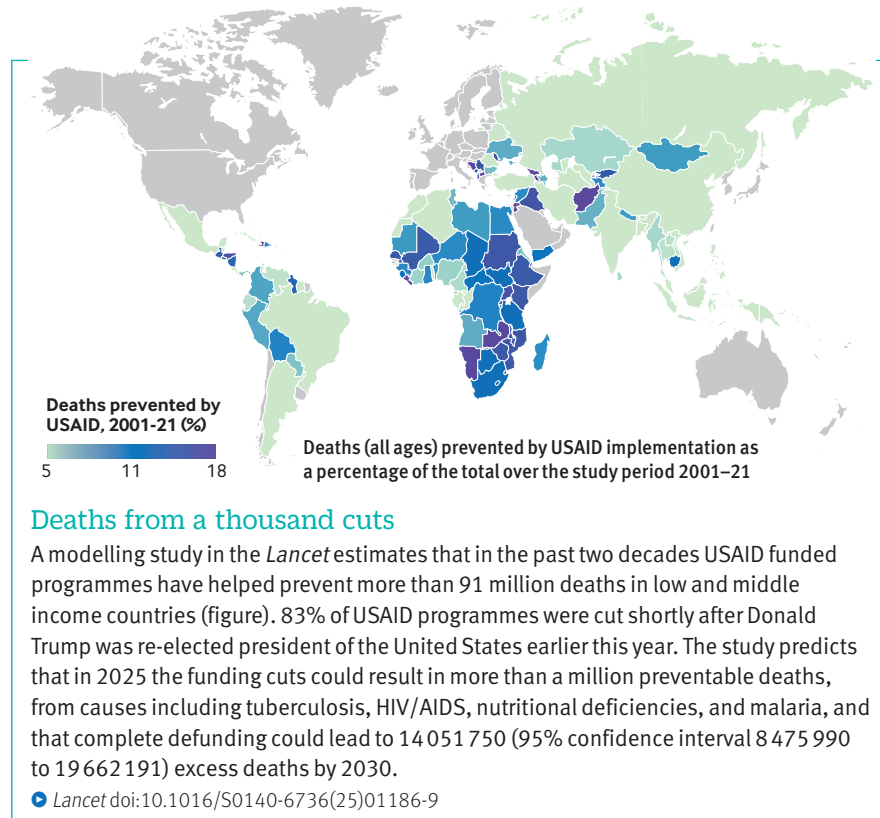
## Abnormal liver enzymes and CBD

Cannabinol—aka CBD—is a modern day tonic for almost any ailment, available in all good vape shops and petrol stations. In 2023, the Food Standards Agency cut the recommended safe dose of CBD from 70 mg per day to 10 mg per day. However, as these are only recommendations for what's classed as a "novel"

food, people will often take much higher doses.

A randomised control trial assessed the frequency of abnormal liver enzymes with a higher dose of 5 mg/kg/day. Eight out of 151 participants allocated to take CBD had liver enzyme level elevations greater than three times the upper limit of normal by the end of the 28 day study, compared with none of the 50 people in the placebo group.

• *JAMA Intern Med* doi:10.1001/jamainternmed.2025.2366



## Deaths from a thousand cuts

A modelling study in the *Lancet* estimates that in the past two decades USAID funded programmes have helped prevent more than 91 million deaths in low and middle income countries (figure). 83% of USAID programmes were cut shortly after Donald Trump was re-elected president of the United States earlier this year. The study predicts that in 2025 the funding cuts could result in more than a million preventable deaths, from causes including tuberculosis, HIV/AIDS, nutritional deficiencies, and malaria, and that complete defunding could lead to 14 051 750 (95% confidence interval 8 475 990 to 19 662 191) excess deaths by 2030.

## Benefits of exercise after colorectal cancer treatment

A new trial shows the benefits of exercise in people with colon cancer. Participants—most of whom had stage III colon cancer and had completed

adjuvant chemotherapy—were randomised to receive an exercise programme or health education. The exercise programme was intensive, featuring 74 sessions over a three year period delivered by a certified physical

activity consultant. It focused on increasing aerobic exercise of at least moderate intensity (such as brisk walking). After a median follow-up of 7.9 years, disease free survival was significantly longer in the exercise group



## CLINICAL PICTURE

### Hypertrophic plaques on the legs

This man in his 70s presented with a four year history of progressive non-pitting, hypertrophic plaques on both legs (figure). He did not report any fatigue, palpitations, changes to his weight, or intolerance to heat or cold. Blood test results indicated primary hypothyroidism, with positive thyroid peroxidase antibodies, and positive thyroid stimulating hormone (TSH) receptor antibodies. Ultrasonography detected a multinodular goitre. A skin biopsy showed abundant dermal mucin,

compatible with pretibial myxoedema (PTM).

Pretibial myxoedema is thought to occur when serum TSH receptor antibodies interact with TSH receptors on skin fibroblasts and stimulate the synthesis of glycosaminoglycans, which accumulate within the skin. Most commonly, TSH receptor antibodies are functionally stimulatory, so PTM is most often seen as a manifestation of Graves' disease. More rarely, TSH receptor antibodies can be functionally neutral or inhibit the

CAVALCANTI, DM, DE OLIVEIRA FERREIRA, DE SALES, L, FERREIRA DA SILVA, A, ET AL. LANCET 2025; DOI:10.1016/S0140-6736(25)01186-9



GENT SHKULAKUZUMA/JALAMY

than in the control group (hazard ratio for disease recurrence, new primary cancer, or death=0.72, 95% confidence interval 0.55 to 0.94).

• *N Engl J Med* doi:10.1056/NEJMoa2502760

### Battle of the weight loss giants

Novo Nordisk and Eli Lilly have had differing experiences over the past couple of years with their respective weight loss blockbuster semaglutide and tirzepatide. Eli Lilly funded a head-to-head open label trial of tirzepatide versus semaglutide for weight reduction in people with obesity. They recruited 751 people with obesity, but without diabetes and allocated them to be titrated up to a maximum tolerated dose of semaglutide or tirzepatide. Average weight loss with semaglutide after 72 weeks was 13.7% (95% confidence interval -14.9 to -2.6) versus 20.2% (-21.4 to -19.1) with tirzepatide.

• *N Engl J Med* doi:10.1056/NEJMoa2416394



### Inhaler churn

In this world nothing can be certain, except death and taxes... and that your local medicines optimisation team is considering another change to their recommended inhalers for asthma and chronic obstructive pulmonary disease (COPD). In July 2021 the Veterans Health Administration in the United States replaced metered dose budesonide-formoterol with dry powder fluticasone-salmeterol as the preferred inhaled corticosteroid plus long acting beta-2 agonist combination for patients with COPD and asthma. This created a natural experiment to monitor the real world effects of this switch in more than 260 000 patients. Increased rates of hospital admissions, respiratory hospital admissions, and pneumonia hospital admissions were found after patients switched and compared with those who didn't switch inhalers.

• *JAMA Intern Med* doi:10.1001/jamainternmed.2025.2299

## MINERVA From the wider world of research

### Fetal risk from maternal seizures

Among 900 women with epilepsy studied throughout their pregnancy in China, around half remained free of seizures, whereas a quarter experienced deterioration of seizure control (*J Neurol Neurosurg Psychiatr* doi:10.1136/jnnp-2024-335751). Seizures during gestation, particularly status epilepticus, doubled the risk of neurodevelopmental delay, low birth weight, and fetal death in the offspring, but there was no increase in the incidence of major congenital malformations.

### Cash transfers

Mothers and children in low income households have poorer health than those from high income households. A trial in four cities in the United States explored whether monthly unconditional cash transfers would make a difference (*JAMA Pediatr* doi:10.1001/jamapediatrics.2025.1612). A total of 1000 mothers were randomly assigned to receive either \$333 per month or \$20 per month until their child was 6 years old. Evaluated four years into the trial, no differences between groups in maternal mental health, maternal or child BMI, or maternal report of children's health had emerged.



### Alzheimer's disease in breast cancer survivors

A retrospective analysis of 70 000 Korean women who underwent breast cancer surgery finds that they are no more likely to develop Alzheimer's disease than a cancer free control group (*JAMA Open Netw* doi:10.1001/jamanetworkopen.2025.16468). Indeed, over seven years of follow-up breast cancer survivors showed a slightly reduced risk, especially if they had also had radiation therapy.

### Brain amyloid in centenarians

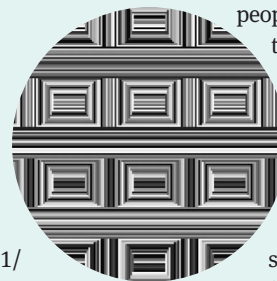
More than 20 years ago, an autopsy study of older people whose cognitive function had been measured during life failed to identify thresholds of Alzheimer-type and vascular pathology that predicted cognitive status (*Lancet* 2001 doi:10.1016/S0140-6736(00)03589-3). An investigation of the brains of centenarians finds something similar (*JAMA Neurol* doi:10.1001/jamaneurol.2025.1734). Although low loads of amyloid  $\beta$  at post mortem were generally associated with better cognitive performance during the final months of life, several centenarians with heavy amyloid loads had been functioning at a high cognitive level.

### Physical activity and cognitive function

Many studies have linked physical activity with better cognitive performance, but the direction of cause and effect is far from obvious. Data from a UK birth cohort, in which participants underwent cognitive testing throughout midlife in addition to reporting their exercise habits, suggest the relation works both ways (*Am J Epidemiol* doi.org/10.1093/aje/kwaf144). Better cognitive test results meant an increased likelihood of being active. Conversely, becoming more active led to improved cognitive performance.

### Optical illusions

The Coffer illusion is an ambiguous image that appears either as a pattern of rectangles or of circles, but not both simultaneously. When presented to people living in the UK and the US, the vast majority reported seeing rectangles on first inspection. By contrast, around half the people living in rural villages in northern Namibia, where rectilinear structures are rare, saw circles first. One interpretation is that people's vision is permanently influenced by the environment in which they grew up (*PsyArXiv* https://osf.io/preprints/psyarxiv/gxzcp\_v3). [Cite this as: \*BMJ\* 2025;390:r1469](https://doi.org/10.1093/aje/kwaf144)



action of TSH, so PTM can sometimes be seen in euthyroidism or hypothyroidism.

This patient was treated with levothyroxine and intralesional triamcinolone injections every three weeks for three months, resulting in flattening of the skin lesions.

Yi-Jun Chen; Ming-Hsiu Lin (living-white@yahoo.com.tw), Taipei Medical University Hospital, Taipei, Taiwan

Patient consent obtained.

Cite this as: *BMJ* 2025;390:e082716

# Asthma: diagnosis, monitoring, and chronic asthma management: guidance from BTS/NICE/SIGN

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**Asthma is one of the commonest long term diseases, affecting around 8% of the population in the UK, Europe, and North America.<sup>1,2</sup> However, about one third of people categorised as having the disease are misdiagnosed,<sup>3</sup> largely because objective testing is poorly utilised, and diagnostic tests may not be available in primary care where asthma is most commonly diagnosed.**

**As a result, diagnosis is often made clinically on the basis of history and examination alone. This approach is not standardised and the accuracy of clinical diagnosis remains unknown.**

**This article summarises updated recommendations from the joint British Thoracic Society (BTS)/National Institute for Health and Care Excellence (NICE)/Scottish Intercollegiate Guidelines Network (SIGN) guideline for asthma diagnosis, monitoring, and chronic management published in 2024.<sup>4</sup>**

## WHAT YOU NEED TO KNOW

- Before initiating treatment, perform objective testing that may help support a diagnosis of asthma
- Do not perform peak expiratory flow recording to monitor asthma in adults, and instead measure fractional exhaled nitric oxide
- In patients newly diagnosed with asthma, do not prescribe salbutamol monotherapy, and instead prescribe anti-inflammatory reliever therapy
- If the patient's asthma is still uncontrolled despite following the recommended treatment algorithms, or if symptoms are still exacerbating, refer to a specialist in asthma care

## 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 development group'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](https://www.bmj.com).

### Initial clinical assessment and diagnosis

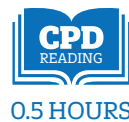
Typical symptoms of asthma include cough, chest tightness, wheeze or noisy breathing, and breathlessness. The key feature in determining whether these symptoms may be caused by asthma or an alternative (eg, obesity) is their variability. Symptoms consistent with asthma can be diurnal (typically worse in the early hours) or in response to triggers, such as viral infections, exercise, or occupational and environmental exposures. The main diagnostic sign on examination is expiratory polyphonic wheeze, but this is variable, and may not be present when the patient is asymptomatic. "Highly symptomatic" refers to people who experience symptoms daily or who wake in the night frequently because of symptoms. In people with a clinical history that may be consistent with asthma, undertake objective testing before starting treatment (table 1, [bmj.com](https://www.bmj.com) figure).

Treat people immediately if they are acutely unwell or highly symptomatic at presentation, and perform objective tests that may help support a diagnosis of asthma (for example, blood eosinophil count, fractional exhaled nitric oxide, spirometry or peak expiratory flow (PEF) before and after bronchodilator) if the equipment is available.

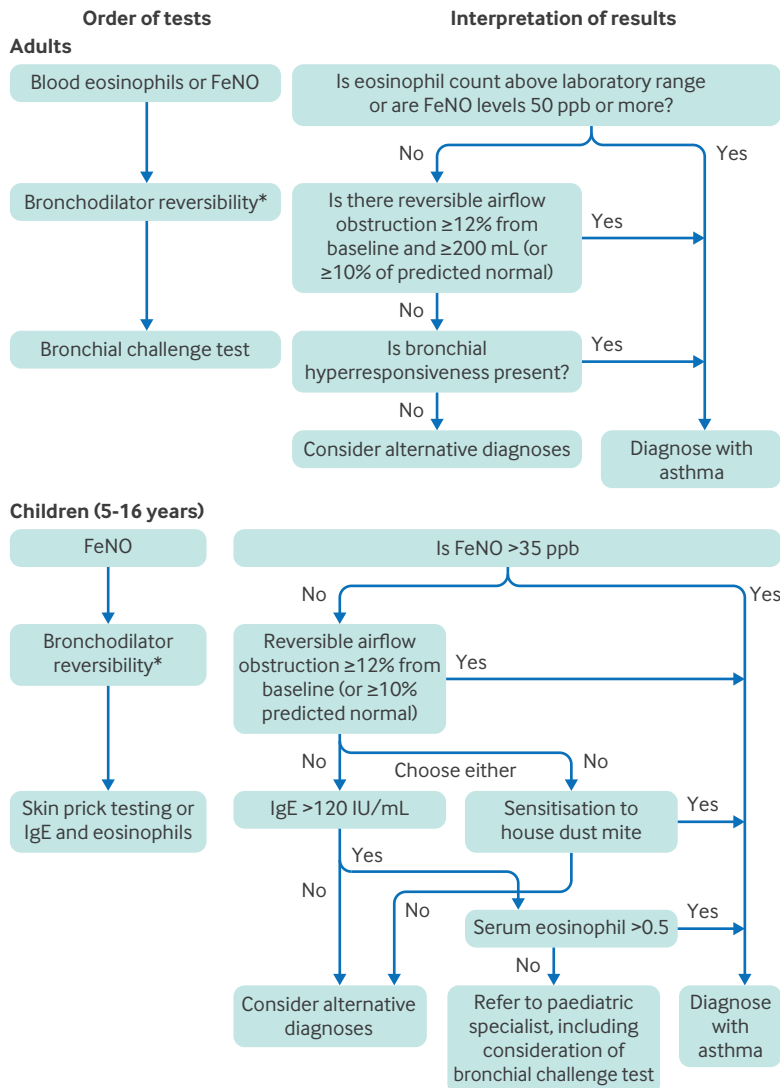
If the clinician decides that long term treatment should be started because there might be a significant delay in obtaining second and third line tests, then patients should commence anti-inflammatory reliever therapy as required. To inform this new recommendation, a cost utility analysis was developed using diagnostic accuracy data from an observational study of symptomatic adults and children, and healthy controls, with clinician suspected asthma.<sup>5,6</sup>

The economic model tested several diagnostic strategies, and estimated the impact on exacerbations, healthcare costs, life expectancy, and quality of life. The substantial initial costs of diagnostic tests were offset by a reduction in wasted NHS resources owing to overdiagnosis. The model found two optimal strategies:

- A gradual rule-in strategy in adults, where adults receive highly specific tests first—for example, blood eosinophils or fractional exhaled nitric oxide. If negative, people undergo bronchodilator reversibility to rule in asthma, and where diagnostic uncertainty remains, a bronchial challenge test
- A rule-in rule-out strategy in children, where children first undergo highly specific tests, such as fractional exhaled nitric oxide. If negative, people undergo a highly sensitive test, such as skin prick test or total immunoglobulin E (IgE) measurement, and finally a specialist referral for consideration of bronchial challenge test if there is still uncertainty.



0.5 HOURS



\*If delayed and treatment needs to be started then can do 2 weeks PEF variability testing

**Proposed algorithms to diagnose asthma. FeNO=fractional exhaled nitric oxide**

Although the cost effective pathways minimise the need for bronchial challenge testing, which is not widely available, all pathways with acceptable performance still required access to challenge testing, particularly for adults.

**Adults**

- Measure the blood eosinophil count or fractional exhaled nitric oxide level in adults with a history suggestive of asthma. Diagnose asthma if the eosinophil count is above the laboratory reference range or the fractional exhaled nitric oxide level is 50 ppb or more.
- If asthma is not confirmed by eosinophil count or fractional exhaled nitric oxide level, measure spirometry with bronchodilator reversibility. Diagnose asthma if the forced expiratory volume in 1 second (FEV<sub>1</sub>) increase is 12% or more and 200 mL or more from the pre-bronchodilator measurement (or if the FEV<sub>1</sub> increase is 10% or more of the predicted normal FEV<sub>1</sub>).
- If spirometry is not available or it is delayed, measure PEF twice daily for two weeks. Diagnose asthma if PEF variability (expressed as amplitude percentage mean) is 20% or more.

- If asthma is not confirmed by eosinophil count, fractional exhaled nitric oxide level, bronchodilator reversibility, or PEF variability but still suspected on clinical grounds, refer for consideration of a bronchial challenge test. Diagnose asthma if bronchial hyper-responsiveness is present.

**Children aged 5 to 16**

- Measure the fractional exhaled nitric oxide level in children with a history suggestive of asthma. Diagnose asthma if the fractional exhaled nitric oxide level is 35 ppb or more.
- If the fractional exhaled nitric oxide level is not raised, or if fractional exhaled nitric oxide testing is not available, measure spirometry with bronchodilator reversibility. Diagnose asthma if the FEV<sub>1</sub> increase is 12% or more from baseline (or if the FEV<sub>1</sub> increase is 10% or more of the predicted normal FEV<sub>1</sub>).
- If spirometry is not available or it is delayed, measure PEF twice daily for two weeks. Diagnose asthma if PEF variability (expressed as amplitude percentage mean) is 20% or more.
- If asthma is not confirmed by fractional exhaled nitric oxide, bronchodilator reversibility, or PEF variability but still suspected on clinical grounds, either perform skin prick testing to house dust mite or measure total IgE level and blood eosinophil count.
  - Exclude asthma if there is no evidence of sensitisation to house dust mite on skin prick testing or if the total serum IgE is not raised
  - Diagnose asthma if there is evidence of sensitisation or a raised total IgE level and the eosinophil count is more than 500 cells  $\times 10^9/L$ .
- If there is still doubt about the diagnosis, refer to a paediatric specialist for a second opinion, including consideration of a bronchial challenge test.

**Children under 5**

Diagnosis is difficult in this age group because of limitations in objective testing, transient and unstable symptoms of asthma, common frequencies at which people experience cough, wheeze, and shortness of breath, particularly with viral infections, and limited reference standards.

- For children under 5 with suspected asthma, treat with inhaled corticosteroids in line with the recommendations on medicines for initial management in children under 5, and review the child on a regular basis. If they still have symptoms when they reach 5 years, attempt objective tests.
- If a child is unable to perform objective tests when they are aged 5:
  - Try doing the tests again every six to 12 months until satisfactory results are obtained
  - Refer for specialist assessment if the child's asthma is not responding to treatment.
- Refer to a specialist respiratory paediatrician any preschool child with an admission to hospital, or two or more admissions to an emergency department, with wheeze in a 12-month period.

## Monitoring

At every asthma review, whether routine, during an exacerbation, or after a treatment change, assess patient's asthma and the impact of the condition (box 1, [bmj.com](#)). PEF monitoring is no longer recommended as it is not reliably performed and difficult to interpret. Instead, measure fractional exhaled nitric oxide, which can help guide the inhaled corticosteroid dosage. In adults, a high fractional exhaled nitric oxide (50 ppb or higher) suggests persistent inhaled corticosteroid sensitive inflammation is present. A low fractional exhaled nitric oxide (under 25 ppb), especially when symptomatic, suggests there is no need for higher dose inhaled corticosteroid. In children, however, current evidence does not support making routine treatment decisions based on fractional exhaled nitric oxide.<sup>8</sup>

- Do not use regular PEF monitoring to assess asthma control unless there are person specific reasons for doing so (for example, when PEF measurement is part of the personalised asthma action plan).
- Consider fractional exhaled nitric oxide monitoring for adults with asthma:
  - At their regular review, and
  - Before and after changing their asthma therapy.

## Treatment

### *Principles of treatment*

Overuse of salbutamol, along with underuse of inhaled corticosteroid, has been consistently associated with adverse outcomes, including death.<sup>9</sup> This, along with the strong evidence for the benefits of alternatives, such as anti-inflammatory reliever therapy,<sup>10 11</sup> convinced the guideline committee to recommend against salbutamol monotherapy in asthma.

- Do not prescribe short-acting beta-2 agonists for people of any age with asthma without a concomitant prescription of an inhaled corticosteroid.

### *Treatment of asthma in people aged 12 and over*

Recommended first line therapy in this patient group has changed, with the withdrawal of short acting beta agonists, typically salbutamol, and introduction of first line anti-inflammatory reliever therapy. This employs a single inhaler containing both inhaled corticosteroid and the rapid and long acting bronchodilator formoterol (eg, budesonide/formoterol 200/6 and, currently unlicensed in the UK, extra-fine beclomethasone/formoterol 100/6). This has been shown to reduce exacerbation rates and is cost effective compared with inhaled corticosteroid with as-required short acting beta agonist.<sup>10 11</sup> Further, it offers the advantage of facilitating straightforward treatment escalation.

Recommendations on when to review and consider therapy escalation are listed in box 2 ([bmj.com](#)). If anti-inflammatory reliever therapy is unsuccessful as initial therapy, then escalate to one puff twice daily plus as required (low dose maintenance and reliever therapy (MART)), and if further treatment escalation is required, to two puffs twice daily plus as required (medium dose MART). As part of the guideline development, a bespoke cost utility analysis showed that this

straightforward escalation strategy is cost effective. The benefits of further add-on options, such as oral leucotriene receptor antagonist (eg, montelukast) and inhaled long acting anti-muscarinic (eg, ipratropium), were equivalent. Therefore, discuss this choice with the patient. For example, a patient with other atopic disease (eg, hay fever), or one favouring a tablet medication, may favour a leucotriene receptor antagonist. Conversely, a patient with persistent airflow obstruction may favour the addition of a long acting anti-muscarinic.

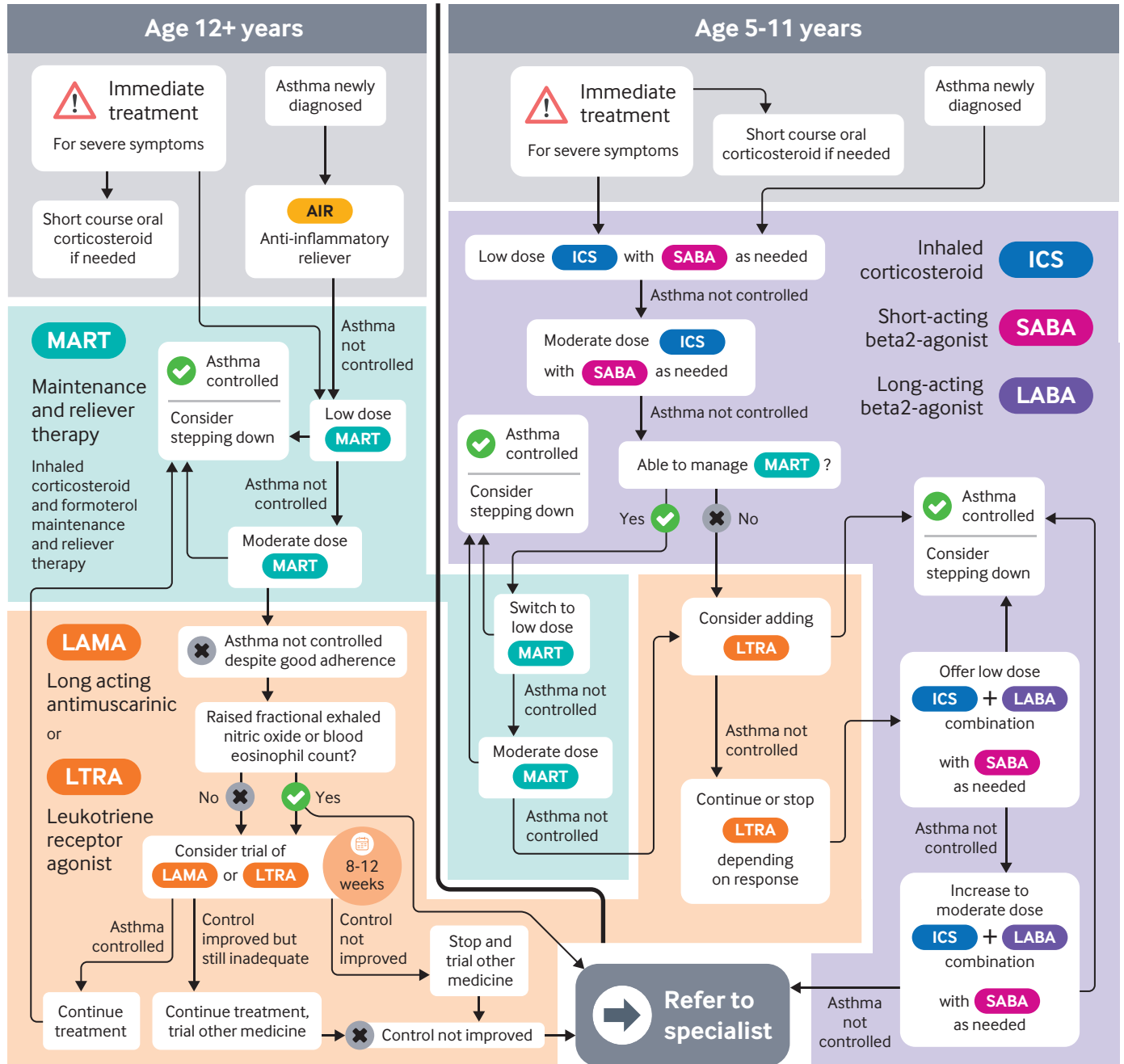
If the patient's asthma is still uncontrolled, or if they are still experiencing exacerbations, refer to a specialist in asthma care. Non-asthma specialists should not prescribe other treatment options, such as oral theophylline or high dose inhaled corticosteroid therapy (eg, adult: >800 µg or paediatric >400 µg budesonide or equivalent), in view of poor evidence for benefit and their narrow therapeutic indices.

- Offer a low dose inhaled corticosteroid/formoterol combination inhaler to be taken as needed for symptom relief (as-needed anti-inflammatory reliever therapy) to people aged 12 and over with newly diagnosed asthma.
- If the person needing asthma treatment presents highly symptomatic (for example, regular nocturnal waking) or with a severe exacerbation, start treatment with low dose MART in addition to treating the acute symptoms as indicated (that is, a course of oral corticosteroids may be needed). Consider stepping down to as-needed anti-inflammatory reliever therapy using a low dose inhaled corticosteroid/formoterol inhaler at a later date if their asthma is controlled.
- Offer low dose MART to people aged 12 and over with asthma that is not controlled on a low dose inhaled corticosteroid /formoterol combination inhaler used only as needed.
- Offer moderate dose MART to people aged 12 and over with asthma that is not controlled on low dose MART.
- For people aged 12 and over with asthma that is not controlled on moderate dose MART despite good adherence:
  - Check the fractional exhaled nitric oxide level if available, and/or the blood eosinophil count. If either of these is raised, refer to a specialist in asthma care.
  - If neither fractional exhaled nitric oxide level or eosinophil count is raised, consider a trial of either a leucotriene receptor antagonist or a long acting muscarinic receptor antagonist used in addition to moderate dose MART. Give the medicine for a trial period of 8 to 12 weeks unless there are side effects. At the end of the trial:
    - If asthma is controlled, continue the treatment
    - If control has improved but is still inadequate, continue the treatment and start a trial of the other medicine (leucotriene receptor antagonist or long acting anti-muscarinic)
    - If control has not improved, stop the leucotriene receptor antagonist or long acting anti-muscarinic and start a trial of the alternative medicine (leucotriene receptor antagonist or long acting anti-muscarinic).

About one third of people categorised as having asthma are misdiagnosed



There have been major changes in the 2024 update to NICE guidelines on asthma, particularly for patients aged 12 years or older. Short-acting beta2-agonist monotherapy is no longer recommended, and anti-inflammatory reliever therapy has been introduced. The flow diagram below summarises the new management pathways from the guideline for people aged 5 years and older. For information on testing required before treatment, and on management of people aged under 5 years, please see the full article in *The BMJ*



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- Refer people to a specialist in asthma care when asthma is not controlled despite treatment with moderate dose MART, and trials of a leucotriene receptor antagonist, and a long acting anti-muscarinic.

### Treatment of asthma in patients aged 5 to 11

#### Initial treatment:

- Offer a twice daily paediatric low dose inhaled corticosteroid, with a short acting beta-2 agonist as needed, as initial treatment for children aged 5 to 11 with newly diagnosed asthma.

#### Follow on treatment 1: MART pathway

- Consider paediatric low dose MART for children with asthma that is not controlled on paediatric low dose inhaled corticosteroid plus short acting beta-2 agonist as needed, as long as they are assessed to have the ability to manage a MART regimen.
- Consider increasing to paediatric moderate dose MART if asthma is not controlled on paediatric low dose MART.

#### Follow on treatment 2: Conventional pathway

- Consider adding a leucotriene receptor antagonist to twice daily paediatric low dose inhaled corticosteroid plus short acting beta-2 agonist as needed when a child has uncontrolled asthma and is assessed as unable to manage the MART regimen. Give the leucotriene receptor antagonist for a trial period of eight to 12 weeks (unless there are side effects), then stop it if it is ineffective.
- November 2024: Follow the MHRA safety advice on the risk of neuropsychiatric reactions in people taking montelukast.<sup>12</sup>
- Offer a twice daily paediatric low dose inhaled corticosteroid/long acting beta-2 agonist combination inhaler plus short acting beta-2 agonist as needed to children assessed as unable to manage the MART regimen if their asthma is not controlled on paediatric low dose inhaled corticosteroid plus short acting beta-2 agonist as needed (with or without a leucotriene receptor antagonist depending on previous response).
- Offer a twice daily paediatric moderate dose inhaled corticosteroid/long acting beta-2 agonist inhaler plus short acting beta-2 agonist as needed to children with asthma that is not controlled on paediatric low dose inhaled corticosteroid/long acting beta-2 agonist plus short acting beta-2 agonist as needed (with or without a leucotriene receptor antagonist depending on previous response).

#### All children aged 5 to 11

- Refer children to a specialist in asthma care if their asthma is not controlled on paediatric moderate dose MART or paediatric moderate dose inhaled corticosteroid/long acting beta-2 agonist maintenance treatment (with or without a leucotriene receptor antagonist, depending on previous response).

### Treatment of asthma in children under 5

- Consider an 8-12 week trial of twice daily paediatric low dose inhaled corticosteroid as maintenance

**Diagnosis is often made on the basis of history and examination alone**

therapy (with a short acting beta-2 agonist for reliever therapy) in children under 5 with suspected asthma and:

- Symptoms at presentation that indicate the need for maintenance therapy (eg, interval symptoms in children with another atopic disorder), or
- Severe acute episodes of difficulty breathing and wheeze (eg, requiring hospital admission, or needing two or more courses of oral corticosteroids).
- If symptoms do not resolve during the trial period, take the following sequential steps:
  - Check inhaler technique and adherence
  - Check whether there is an environmental source of their symptoms (eg, mould in the home, cold housing, smokers, or indoor air pollution)
  - Review whether an alternative diagnosis is likely.
- If none of these explain the failure to respond to treatment, refer the child to a specialist in asthma care.
- Consider stopping inhaled corticosteroid and short acting beta-2 agonist treatment after eight to 12 weeks if symptoms are resolved. Review the symptoms after a further three months.
- If symptoms resolve during the trial period, but then:
  - Symptoms recur by the 3 month review, or
  - the child has an acute episode requiring systemic corticosteroids or admission to hospital
  - restart regular inhaled corticosteroid (begin at a paediatric low dose and titrate up to a paediatric moderate dose if needed) with short acting beta-2 agonist as needed and consider a further trial without treatment after reviewing the child within 12 months.
- If suspected asthma is uncontrolled in children under 5 on a paediatric moderate dose of inhaled corticosteroid as maintenance therapy (with short acting beta-2 agonist as needed), consider a leucotriene receptor antagonist in addition to the inhaled corticosteroid. Give the leucotriene receptor antagonist for a trial period of eight to 12 weeks (unless there are side effects), then stop it if it is ineffective.
- Follow the MHRA safety advice on the risk of neuropsychiatric reactions in people taking montelukast<sup>13</sup>
- If suspected asthma is uncontrolled in children under 5 on a paediatric moderate dose of inhaled corticosteroid as maintenance therapy and a trial of a leucotriene receptor antagonist has been unsuccessful or not tolerated, stop the leucotriene receptor antagonist and refer the child to a specialist in asthma care for further investigation and management.

Competing interests: See bmj.com.

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Find the full version with references at <http://dx.doi.org/10.1136/bmj.r1162>

#### HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

SJ, coauthor, is a patient and committee member. Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

# New UK asthma guideline: challenges to change

Effective implementation will require greater provision of tests, services, and support

**A**sthma is a common inflammatory airway condition that affects around six million people in the UK.<sup>1</sup> Inaccurate diagnosis and delayed access to appropriate treatment are longstanding problems that still disadvantage patients.<sup>4-6</sup> Joint guidelines from the British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN)<sup>7</sup> and the National Institute for Health and Care Excellence (NICE)<sup>8</sup> offer a “focused reset” of approaches to diagnosing and treating asthma and are welcome and long overdue.<sup>10</sup>

On diagnosis, the new guideline emphasises upfront confirmation of inflammatory traits characteristic of asthma—that is, raised levels of blood eosinophils and fractional exhaled nitric oxide (FeNO). Measures of variable airflow limitation (bronchodilator reversibility or peak flow variability) or airway hyper-responsiveness follow later in the diagnostic pathway for adults, as does skin prick testing for allergies in children.

The guideline moves away from starting treatment with inhaled short acting  $\beta_2$  agonists, instead recommending early initiation of anti-inflammatory treatment based on inhaled corticosteroids. This includes inhalers containing both low dose corticosteroid and the rapid onset long acting  $\beta_2$  agonist formoterol. The inhaler can be used solely for symptom relief (anti-inflammatory reliever therapy, AIR) or for regular maintenance in addition to symptom relief (maintenance and reliever therapy, MART).

Other notable features of the new guideline include use of asthma action plans and annual asthma reviews, and increased awareness of how air quality affects patients and the environmental consequences of asthma treatments.



**Only 53% of primary care networks have access to FeNO testing**

## How feasible is implementation?

The new diagnostic pathway will be difficult in areas without access to FeNO testing. After NHS England’s national FeNO programme finished in March 2023, around 53% of primary care networks had access.<sup>13</sup> This coverage will decline without investment.<sup>14</sup> Incorporation of testing for house dust mite allergy in the diagnostic pathway for children also appears aspirational given skin prick testing is not available in primary care and provision is scarce in secondary care.<sup>15</sup>

Baseline investigations should inform personalised treatment approaches as well as diagnosis. Where testing is available, identifying patients in whom both eosinophil and FeNO levels are raised is helpful as these individuals are at greatest risk of exacerbations<sup>16</sup> and may benefit more from MART. If FeNO and bronchodilator reversibility testing are available together, conducting both tests can facilitate early detection of people with partly reversible or fixed airway obstruction.<sup>17</sup> These patients may require additional bronchodilator therapy or referral for specialist opinion if they do not respond adequately to medium dose MART.

Although the guideline advises clinicians to consider monitoring FeNO at asthma reviews, the evidence in this area is still evolving. Results of a recent meta-analysis suggest that FeNO guided strategies are more effective than symptom

guided strategies at reducing risk and incidence of exacerbations.<sup>18</sup> However, the meta-analysis included data from trials conducted in pregnant women<sup>19</sup> and respiratory outpatient clinics<sup>20,21</sup> rather than primary care, and the FeNO guided interventions and outcome definitions used varied considerably between studies.<sup>22</sup> Although FeNO testing in primary care may lead to cost savings from deprescribing of unnecessary medications,<sup>13</sup> evidence on its cost effectiveness for diagnosis or management is limited.<sup>23</sup>

The shift towards the use of corticosteroid-formoterol inhalers allows patients more flexibility to adjust their dose to their needs, but monitoring to ensure appropriate usage will be challenging because of variations in optimal dose requirements between individuals and within the same person over time. Overuse may occur in people with a history of high use of short acting  $\beta_2$  agonists driven by anxiety and habitual behaviours.<sup>24</sup> If not promptly recognised and addressed, inhaled corticosteroid-formoterol overuse may result in corticosteroid overexposure and adverse effects.

Additionally, patients who have used short acting  $\beta_2$  agonists for a long time may be apprehensive about changing to a new inhaler and unsure about how to adjust their dose. Provision of safe, effective monitoring and support to help patients adopt new inhalers and regimens will require accessible, comprehensive training.

Translating the recommendations into better clinical outcomes requires sufficient investment to ensure prompt access to the right tests and services, and appropriate training and resources for clinicians, patients, and healthcare services to meet the challenge to change.

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# Cancer related lymphoedema

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This is a summary of Clinical Review Cancer related lymphoedema. The full version can be read here: <https://www.bmj.com/content/390/bmj-2024-081351>



**Cancer related lymphoedema (CRL) is a prevalent consequence of injury to lymph vessels and nodes that could be caused by cancer treatment or cancerous infiltration of lymphatic structures. CRL is chronic, progressive swelling with potential for metaplasia involving one or more body parts owing to impaired lymph removal and transport. CRL adversely impacts patients' healthcare utilisation, clinical outcomes, and quality of life, particularly their functional, financial, and psychological wellbeing.<sup>1</sup> Once established, lymphoedema is incurable, though it can be mitigated by continuous use of maintenance activities. These might be burdensome and also lessen quality of life.<sup>2</sup> Unfortunately, patients with CRL often report diagnostic delays, inappropriate management, and clinician disinterest in their CRL.<sup>3</sup> CRL's negative impact, chronicity, and requirement for indefinite temporisation have spurred clinical efforts to protect and repair the lymphatic system during and after cancer treatment.**

Surgical lymph sparing procedures are now extensively integrated into standard cancer care. Sentinel lymph node biopsy, for example, reduces CRL in patients with melanoma, breast, gynaecological, and urological cancers by minimising lymph node removal.<sup>4-6</sup> Procedures to restore lymphatic function also show promise. Technologies that detect incipient CRL have become clinically available, which enable earlier detection and proactive mitigation. Improved cancer care has also impacted CRL by permitting less anatomically disruptive treatments and increasing survival in the advanced stages of cancer. Together, these advances have altered the prognosis, epidemiology, and management of CRL over the past decade.

## WHAT YOU NEED TO KNOW

- Cancer related lymphoedema is a chronic condition that can reduce quality of life for people living with cancer, and after treatment for cancer
- Early detection and evidence-based treatments, including resistive exercise, can help to prevent and slow progression of cancer-related lymphoedema
- Manual and behavioural therapies, delivered by a multidisciplinary team, remain the cornerstone of reductive cancer-related lymphoedema treatment

## Epidemiology

The incidence of CRL has been most extensively characterised in association with breast cancer treatment, affecting between 2% and 74% of survivors.<sup>16</sup> Patients also develop CRL from treatment for other solid tumours such as melanoma, prostate, head and neck, gynaecological, and urological cancers. The mean CRL incidence rate is 15.5% across all cancers, however, rates vary markedly by cancer type and location.<sup>17</sup> For example, up to 40% of gynaecological cancer survivors report lymphoedema.<sup>18</sup> Among melanoma survivors, lymphoedema incidence varies by location of melanoma and nodal basin involved and is markedly higher in the lower extremity (28%) relative to the upper extremity (5%).<sup>17</sup>

## Lymphatic system

The lymphatic system is a unidirectional network that returns filtered interstitial fluid and tissue metabolites to the blood circulation and fulfils important roles in immune cell trafficking and lipid absorption.<sup>7-8</sup> Virtually all interstitial fluid requires lymphatic transport.<sup>9</sup> Lymph capillaries are blind, finger-like projections of loosely adherent endothelial cells that create subpapillary and deep dermal networks. Lymph capillaries are larger than blood capillaries and lack basement membrane permitting ingress of interstitial fluid and solid debris into the lymphatic circulation. At this point, the fluid and solids become lymph and flow from the capillaries to collector vessels that converge to form larger vessels which drain into lymph nodes. Lymph vessels rely on the intrinsic contractility of smooth muscle in the collecting vessel walls, as well as contraction of adjacent, extrinsic muscles; arterial pulsations; and diaphragmatic excursion for lymph propulsion.<sup>10-11</sup> Unidirectional valves in lymph collecting vessels prevent backflow and stasis.

Lymph nodes regulate lymph viscosity, filter recyclable debris, and support the system's immunoregulatory functions. Lymph nodes play a vital role in triggering and modulating immune responses.<sup>12</sup> Lymph typically flows through chains of superficial and deep nodes before re-entering the venous circulation. The lymphatic system plays a vital role in maintenance of tissue fluid homeostasis, particularly the regulation of interstitial fluid volume and composition.<sup>13-15</sup>

## Pathophysiology

Initially, impaired lymphatic return and hypertension cause mismatch between lymph production and removal. Increasing mismatch exhausts the system's

Clinical presentation and evaluation of the stages of lymphoedema from the International Society of Lymphology				
Stage	Clinical presentation		Evaluation	
	History	Physical exam	Diagnostic	Monitoring
0	Local heaviness, aching after vigorous or sustained activity*	No change on inspection or palpation		Symptom diary, patient reported outcome measure
I	Fluctuating swelling; near resolution with sustained elevation; worsening with activity, prolonged dependency, and hot, humid weather; moderate local heaviness and aching in swollen areas	Focal or regional oedema, normal to mildly increased tissue turgor, focal or generalised pitting	Lymphoscintigraphy	Patient reported outcome measure
			Volumetry, bioimpedance spectroscopy	
II	Chronic, variable swelling with fluctuation in affected body parts; improvement with elevation but not to baseline; situational worsening as in stage I, but exacerbations are more pronounced and sustained	Stemmer sign, increased tissue turgor, tense pitting with sustained pressure, loss of normal anatomic architecture and contour	Lymphoscintigraphy, palpation	Patient reported outcome measure
			Volumetry, bioimpedance spectroscopy	
III	Chronic enlargement of the affected body part with limited fluctuation; changes in skin colour, texture, and appearance; seepage of lymph through intact skin (lymphorrhoea) might occur	Rigid tissue turgor; pitting possible with sustained pressure; dysmorphism might be pronounced; dermal metaplasia (keratinisation, papillomas, verrucous hyperplasia)	Lymphoscintigraphy, palpation, magnetic resonance imaging, biopsy of unhealing wounds	Patient reported outcome measure
			Volumetry, bioimpedance spectroscopy	

\*Provocative situations increase net ultrafiltrate in the interstitium and increase lymph transport requirements.

reserve leading to tissue oedema. Venous obstruction related to cancer and treatment effects might further increase lymphatic load and oedema.<sup>22</sup> Tumour-specific biological features are also thought to be involved.<sup>23</sup> Once lymphatic vascular dysfunction is established, a self-perpetuating cycle of local stasis, inflammation, fibrosis, adipose deposition, and metaplasia advances CRL pathophysiology.<sup>21 24</sup>

Tissue inflammation plays a causal role in CRL progression, and is attributed to chronic interstitial fluid accumulation, and impaired transit of inflammatory cells and mediators in the interstitium (fig 1, see bmj.com).<sup>13 25</sup> Complement activity, stress response, remodelling of the extracellular matrix, and immunological responses are believed to mediate inflammation.<sup>26</sup> Research has clarified the pleiotropic roles played by T cell and macrophage subtypes in the inflammation, fibrosis, and lymphangiogenesis that cause and exacerbate lymphoedema.<sup>27 28</sup>

Late stage CRL is characterised by elaborate deposition of extracellular matrix components and fibrotic remodelling in the interstitial space which further impedes lymph sequestration and transport. Fibrosis contributes to stagnant interstitial fluid, and impaired nutrient and oxygen diffusion. A further pathological hallmark of late stage lymphoedema is progressive expansion of the subcutaneous adipose layer which is related to lymph vessel impairment and, potentially, T<sub>H</sub>2 cell activity.<sup>13</sup>

The endothelial glycocalyx, a gel-like layer that covers the luminal surface of lymph collectors and assists with endothelial function, has been implicated in CRL pathogenesis.<sup>33</sup> Inflammation causes the lymphatic glycocalyx to remodel, leading to increased permeability, impaired regulation of fluid balance, and profibrotic conditions.<sup>34 35</sup>

## Natural history

### Onset and progression

Often oedema initially follows a stuttering pattern with episodes of transient swelling alternating with periods of resolution. Over time, swelling becomes chronic,

and improvement with overnight elevation diminishes and eventually ceases. In the absence of treatment, CRL progresses through a series of stages marked by increasing tissue metaplasia of the interstitium and dermis (table). Progression might be more rapid in lower extremity CRL and could be accelerated in the upper and lower extremities by cellulitis.<sup>40</sup>

## Risk factors for the onset and progression of lymphoedema

### Cancer and cancer treatment

The risk of CRL is associated with the extent of lymph node resection, radiation, and receipt of systemic therapies, though many other risk factors have been identified.<sup>41</sup>

#### Extent of nodal surgery

Extent of nodal surgery has long been considered the primary risk factor for CRL and removing more nodes results in higher lymphoedema rates. In breast cancer, CRL rates after axillary lymph node dissection can range from 10% to 60%, whereas rates after sentinel lymph node surgery are only 0% to 7%.

#### Radiation

Regional nodal irradiation increases the risk of CRL when performed in addition to nodal surgery.<sup>43 44</sup> Rates in cancer survivors can be as high as 17% to 41% for breast cancer and 6% to 49% for gynaecological cancers.<sup>45</sup>

#### Systemic therapies

Chemotherapy is associated with CRL. Anthracycline drugs (particularly doxorubicin) have been associated with CRL.<sup>43</sup>

## Diagnosis, differential, and clinical evaluation

### Diagnosis

Lymphoedema could be distinguished from other causes of swelling by its discrete involvement of one or more body parts, asymmetry, insidious onset and progression, and characteristic tissue texture and skin changes.

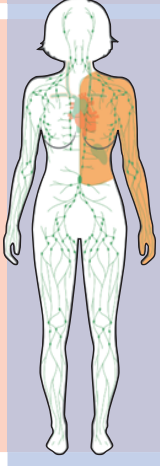
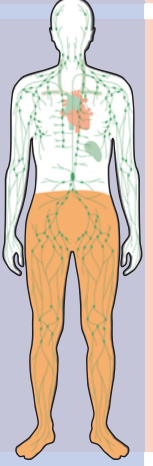

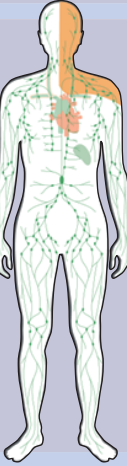
<b>Surgery</b>	Axillary lymph node dissection	Pelvic and periaortic lymph node dissection	Inguinal lymph node dissection	Cervical lymph node dissection
<b>Cancers</b>	Breast Melanoma Merkel cell Squamous cell	Ovarian Cervical Endometrial Vulvar Prostate	Penile Vulvar Melanoma Anal	Head and neck Thyroid Melanoma
<b>Risk of progression</b>	SLN - very low CLND - moderate	CLND - moderate	SLN - very low CLND - moderate	Low <sup>39</sup>
<b>Lymph drainage territory at risk</b>				
<b>Areas that might be initially affected</b>	Peri-cubital area Medial upper arm Dorsal hand Breast	Lower pelvis Thighs Ankles Dorsal feet	Distal leg Ankle Dorsal feet	Jowls Submental

Fig 2 | Characteristics of cancer-related lymphoedema associated with surgical dissection of specific lymph node beds. SLN=sentinel lymph node; CLND=completion lymph node dissection

Lymphoedema secondary to cancer treatments could also be identified by its confinement to the drainage territories of resected lymph nodes (fig 2). Diagnosis is often suggested by history and clinical exam findings with confirmation provided by clinical evaluations and imaging.

#### Differential

The differential diagnosis varies with the pattern of onset, distribution, and the presence of systemic and/or local symptoms. Venous conditions lead the differential because thrombosis of upper and lower extremity veins is common in patients with cancer.<sup>73</sup> Most diagnoses in the differential exacerbate rather than cause the asymmetrical and unilateral swelling that characterises CRL. These include myxoedema, organ failure (kidney, heart, or liver), obstructive sleep apnoea, obesity, inactivity, malabsorption, polycystic ovarian syndrome, and hypercortisolism.<sup>74</sup> Medication effects also feature prominently in the differential because many common drugs (NSAIDs, steroids, gabapentinoids, and calcium channel blockers) might cause or worsen oedema.

#### Clinical evaluations

Clinical evaluations are used to identify non-lymphatic causes of oedema, confirm lymphoedema diagnoses, prognosticate, individualise treatment, and monitor

patients with and at risk of developing CRL.<sup>75</sup> Limb volumes are a common and pragmatic means of monitoring CRL. Bioimpedance spectroscopy offers high sensitivity and specificity for early detection of extracellular fluid in subclinical stage 0 CRL.<sup>76,77</sup> Lymphoscintigraphy, by contrast, offers clinically useful insight about residual lymphatic function in the later stages of lymphoedema.

#### Circumferential measurements

Circumferential measurement uses a standard tape measure to obtain the girth of a limb at specific intervals, which is then used to calculate volume. Circumferential measurements of the upper extremity demonstrate excellent inter-rater and intrarater reliability.<sup>69</sup>

#### Optoelectronic volumetry

Optoelectronic volumetry (perometry) uses infrared light and sensors to indirectly measure extremity volume and has been validated for use in lymphoedema.<sup>81</sup> A perometer obtains multiple measurements at extremely small intervals and then the computer calculates the volume. It uses the same principles as sum of tape circumferences but is more accurate. Perometry has been validated and shows high intrarater and inter-rater reliability.<sup>82</sup>

#### Water displacement

Water displacement is accurate but is less commonly used clinically owing to infection control concerns. Water displacement measures the amount of water displaced when the extremity is immersed in a tank. It can measure the entire limb including the hand and foot.

## Anatomical studies

#### Lymphoscintigraphy

Lymphoscintigraphy involves the injection of radiolabeled tracer, followed by monitoring tracer ascent by using gamma camera images (fig 3, see bmj.com). Lymphoscintigraphy has a moderate sensitivity (0.62) and high specificity (1.0) for diagnosing lymphoedema when compared with the unaffected limb.<sup>69</sup>

#### Ultrasonography

Ultrasound scanning has been used to identify the CRL stage and to map different stages and severity in an affected body part.<sup>100</sup> Skin thickness, subcutaneous tissue thickness, and subcutaneous echogenicity all correlate with the International Society of Lymphology stages.<sup>101</sup>

#### Computed tomography lymphangiography

Computed tomography (CT) and computed tomography lymphangiography have a supportive role in lymphoedema diagnostics. CT provides high resolution imaging of the lymphatic system and identifies obstructions, leaks, or tumours. CT can assess the degree of tissue oedema, but it cannot differentiate between lymphoedema and oedema.<sup>104</sup>

### Magnetic resonance lymphography

Magnetic resonance lymphography is a non-invasive imaging technique used to visualise the lymphatic system, including its anatomy and function.<sup>105</sup> The technique could detect abnormalities at earlier stages than lymphoscintigraphy. There are two primary types of magnetic resonance lymphography: dynamic contrast enhanced magnetic resonance lymphography and non-contrast magnetic lymphography. Both types of magnetic resonance lymphography provide detailed anatomical information that is unavailable with other imaging approaches. However, access and cost constrain the use of magnetic resonance lymphography in many clinical settings.

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## Complications of lymphoedema

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### Cellulitis

Cellulitis occurs when common skin bacteria, typically *Staphylococcus epidermidis*, enter the interstitial environment. Methicillin resistant *Staphylococcus aureus* accounts for fewer than 5% of cellulitis related to lymphoedema.<sup>106</sup> A recent study reported cellulitis prevalence and recurrence rates of 12.6% and 56.6%, respectively, in extremity lymphoedema.<sup>106</sup> Although cellulitis might require hospitalisation, most episodes are effectively managed as outpatients with oral antibiotics. Rapid initiation of antibiotic therapy is critical because a single episode of cellulitis could cause permanent damage to an already impaired lymphatic system.<sup>40</sup>

### Wounds

Stage III CRL of the legs could be complicated by non-healing wounds due to impaired interstitial homeostasis with diminished oxygen and nutrient transport. Additionally, the fibrosis characteristic of stages II and III CRL might undermine the skin's elasticity and ability to withstand sustained pressure and traction.

### Pain

Pain, characterised as persistent heaviness or aching, could affect patients with lymphoedema. Sensations might be provoked or intensified by activity; maintaining the limb in a dependent position; and hot, humid weather.

### Malignant transformation

The occurrence of angiosarcomas, known as Stewart-Treves syndrome, is a very rare complication of lymphoedema.<sup>108</sup> The syndrome initially manifests as violaceous skin nodules, subdermal masses, and eschar productive of serosanguinous ooze; all of which warrant scrutiny and biopsy.

### Lymphorrhoea

Lymphorrhoea is the leakage of lymph through intact skin or a skin defect due to increased interstitial pressure. Often, lymphorrhoea presents as yellowish, clear fluid (lymph) that beads up and trickles along the skin overlying affected body parts.

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## Treatment of lymphoedema

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### Manual and behavioural therapies

Manual treatments remain the mainstay of lymphoedema management.<sup>98</sup> Multicomponent manual programmes that strategically combine and deliver treatments daily for a minimum period of two weeks reduce long established lymphoedema. Referred to as complex or complete decongestive therapy (CDT), the programme's unprecedented effectiveness (limb volume reductions up to 70%) led to its adoption as the international standard of care.<sup>128-130</sup> In addition to acute volume reduction, CDT can improve patients' quality of life, function, and symptoms.<sup>131 132</sup> The distinct but overlapping treatments used to reduce (phase 1) and maintain (phase 2) CRL volume and tissue quality are depicted in figure 4.

### Compression garments

Compression garments worn during waking hours are the mainstay of maintenance CDT (phase 2). Garments vary with respect to compression class, extent of coverage, fabric, and cost, with higher compression and made-to-measure flat knit garments being the more difficult to access and fit properly.

### Exercise

Resistive exercise has been shown to reduce the risk of CRL onset and progression among breast cancer survivors.<sup>164 165</sup> Resistance exercise is empirically safe and should be considered integral to preventive and maintenance CRL treatment when it is monitored, performed with compression garments, and initiated and advanced gradually.

### Compression pumps

Systematic reviews and meta-analyses do not consistently suggest that compression pumps offer benefit during phases 1 and 2 CDT. Nonetheless, most current guidelines mention intermittent pneumatic compression pumps as an adjunctive treatment option while acknowledging the low to very low quality of evidence.

### Weight management and dietary approaches

Weight management is an integral component of CRL treatment. However, a previous assumption that weight loss would reduce CRL volume has been effectively challenged. A trial of 351 overweight breast cancer survivors with CRL randomised participants to one of four cohorts: control, exercise, weight loss, or exercise and weight loss. Exercise included a 52 week home based strength and resistance training twice weekly and 180 minutes of walking weekly. The weight loss component included meal replacement therapy for 20 weeks and 52 weeks of lifestyle modifications and counselling. The trial found no evidence of arm volume reduction in any cohort (all  $P > 0.40$ ) at 12 months follow-up.<sup>173</sup> These results should not be generalised to lower extremity CRL given its greater tendency to rapidly progress.

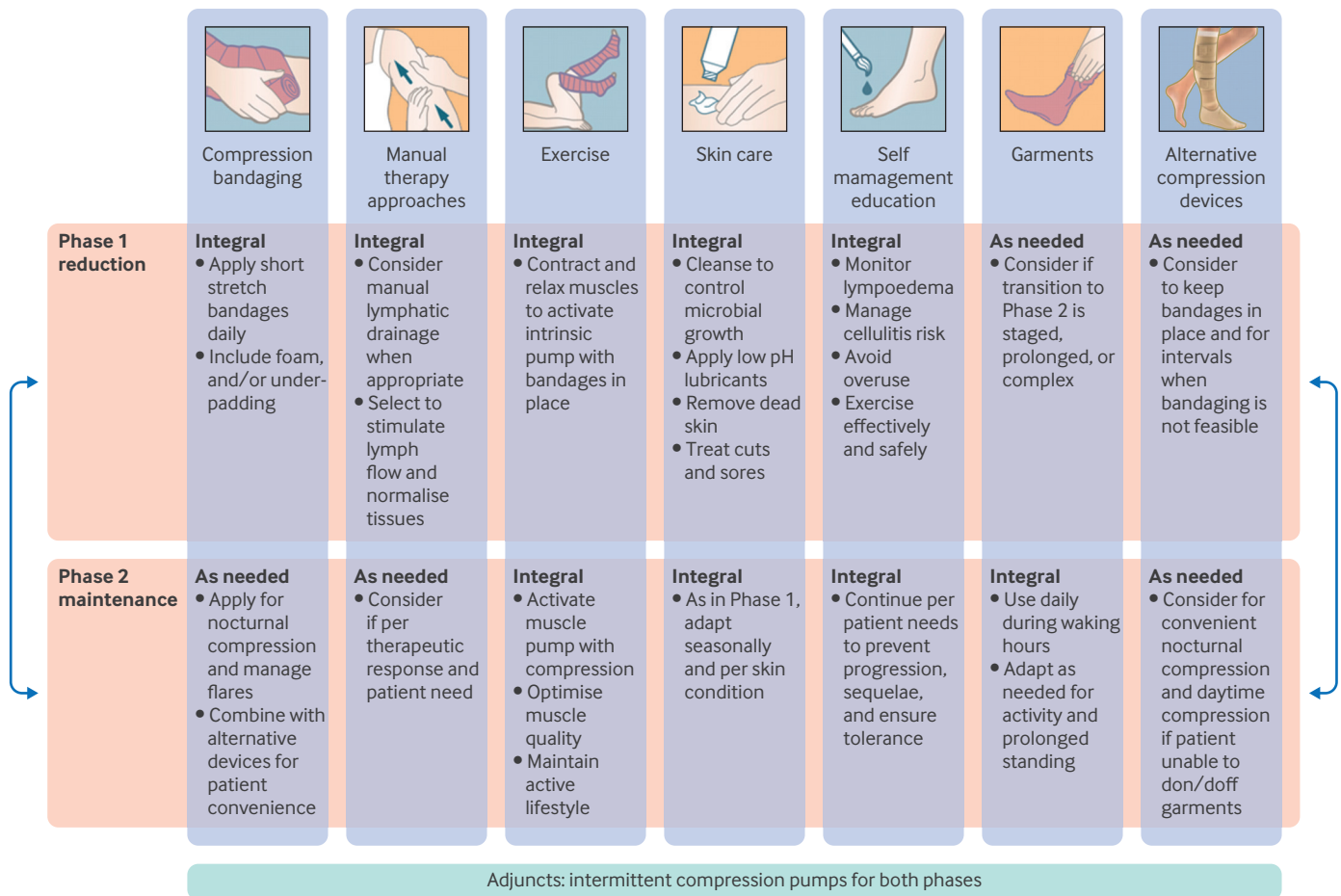


Fig 4 | Components of phases 1 and 2 complete decongestive therapy for cancer related lymphoedema

### Drugs

Recently there has been growing interest in ketoprofen, a unique non-steroidal anti-inflammatory drug, for the management of lymphoedema. Two small exploratory studies have been performed that show reduced skin thickness and improvements in histopathology with use of ketoprofen.<sup>51</sup>

Oral and topical retinoids can help normalise keratinisation and decrease inflammatory and fibrotic changes.<sup>177 178</sup> Topical emollients and keratolytics (eg, ammonium lactate, urea, and salicylic acid) can be used to help with secondary epidermal changes.

### Surgery

Surgical approaches are broadly categorised as those resecting lymphoedematous tissue and those reconstructing or improving lymphatic function. Contemporary resection techniques tend to favour large bore cannula suction assisted protein liposuction for tissue resection.

Suction assisted protein liposuction is effective in removing most of the excess extremity volume,<sup>179</sup> and can improve mobility. However, post suction assisted protein liposuction treatment mandates strict lifelong compression therapy to maintain volume reductions because tissue resection does not restore lymphatic function.

### Guidelines

In 2020, the Oncology Nursing Society and the American Physical Therapy Association issued guidelines for managing lymphoedema related to cancer treatment and breast cancer, respectively.<sup>135 185</sup> The guidelines are consistent about key treatment recommendations. Both endorse monitoring and educating patients who undergo surgery for cancer and initiating tailored exercise programmes that include resistance training. Neither guideline endorses the use of prophylactic compression sleeves in the absence of symptoms or swelling. Both guidelines endorse integration of compression pumps, and other adjunctive approaches, but differ between the guidelines.

National Institute for Health and Care Excellence (NICE) offers guidance only with regard to interventional procedures for lymphoedema. Specifically, NICE endorses liposuction for chronic lymphoedema irrespective of aetiology.<sup>187</sup>

Most lymphoedema treatment guidelines are over five years old and vulnerable to disciplinary bias, with varying degrees of explicit supporting evidence. Guidelines consistently emphasise the importance of interdisciplinary lymphoedema management, yet virtually all guidelines reflect the perspectives of individual disciplines.

Competing interests: None declared.

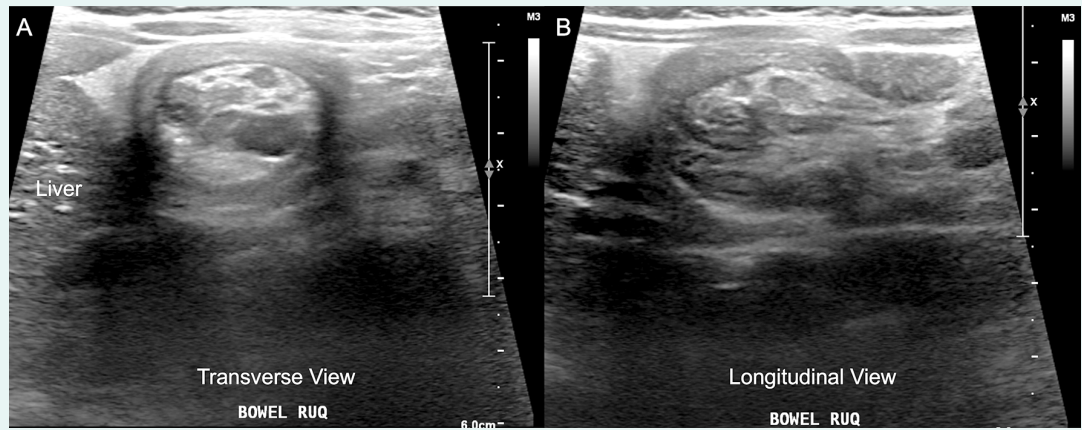
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Find the full version with references at <https://doi.org/10.1136/bmj-2024-081351>

CASE REVIEW

Waxing and waning distress in an infant

A 9 month old girl presented to the emergency department with a two day history of a few episodes of non-bilious non-bloody vomiting, diarrhoea, and intermittent distress with curling up of the legs. She had recovered from a viral upper respiratory tract infection one week earlier. The patient, who was breastfed and eating solid foods, also had reduced oral feeds for the past two days. There were no similar previous episodes. Micturition was normal and urine was not malodorous. Physical examination



Greyscale transverse (A) and longitudinal (B) imaging of the right upper abdominal quadrant

revealed tenderness in the right upper abdomen with hyperactive bowel sounds and no palpable mass. No skin rashes were seen. In view of her

persistent symptoms, an urgent ultrasound of the abdomen was performed, which showed a mass in the right upper abdominal quadrant (figure).

- 1 What are the differential diagnoses?
- 2 What is the most likely diagnosis?
- 3 How would you manage this patient?

Submitted by Ca Yi Yoon and Timothy Shao Ern Tan  
Parental consent obtained.  
Cite this as: *BMJ* 2025;390:e083510

answers

LEARNING POINTS

- Intussusception is a common abdominal emergency in children under 3 years of age, with most cases being idiopathic.
- Ultrasound is the imaging method of choice to evaluate for intussusception and its associated complications as well as excluding other important causes of abdominal pain.
- Management of intussusception typically involves hydrostatic or pneumatic enema reduction.

PATIENT OUTCOME

See [bmj.com](http://bmj.com).

CASE REVIEW Waxing and waning distress in an infant

1. What are the differential diagnoses?

at age 5-9 months. Most cases are idiopathic, but about 5% of cases involve a pathological lead point such as Meckel's diverticulum, duplication cyst, intestinal polyps, or enlarged mesenteric lymph nodes. Most childhood intussusceptions are ileocolic, but small bowel and colonic intussusceptions can also occur.

Differential diagnoses include gastro-intestinal causes such as acute gastroenteritis, gastric reflux, colic, food allergies, intussusception, and (less likely) malrotation with or without midgut volvulus, as well as non-gastrointestinal causes such as incarcerated hernia and urinary tract infection.

2. What is the most likely diagnosis?

Ileocolic intussusception is the most likely diagnosis. It is the most common abdominal emergency in children under 3 years of age. Ileocolic intussusception has a yearly incidence of 3-40 cases per 10 000 live births, is more common in males, and peaks

3. How would you manage this patient?

Ileocolic intussusception should be promptly treated to reduce the risks of bowel ischaemia and perforation. All patients should be referred to the surgical team. Typical management is with fluoroscopically guided pneumatic reduction or hydrostatic enema reduction.

which are both diagnostic and therapeutic. In cases of initial incomplete reduction or recurrent intussusception, a delayed repeat enema is considered safe and effective if the child remains clinically stable. Recurrent intussusception can occur in as many as 10% of cases after initial enema reduction, with 2.5% of cases within the first 48 hours, and in 1% of cases after surgical reduction.

Surgical management of intussusception is indicated when these radiological reduction methods are unsuccessful, if the patient develops peritonitis, bowel perforation, shock, or persistent small bowel obstruction.

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0.5 HOURS



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