education

RESEARCH REVIEWS Fortnightly round up from the leading medical journals

High flow nasal oxygen's non-inferiority complex

The RENOVATE study has found high flow nasal oxygen to be non-inferior to non-invasive ventilation (NIV) in patients with acute respiratory failure.

However, the clinical implications are more complicated. For instance, there may be broader clinical considerations than the primary outcome of endotracheal intubation or death at seven days, and the relatively low numbers recruited to the study with COPD exacerbations (79) and acute cardiogenic pulmonary oedema (274) leaves greater uncertainty in these presentations. The study also stopped recruiting people with immunocompromise and hypoxia early due to worse outcomes in those assigned to high flow nasal oxygen.

> Clinical implications of high flow nasal oxygen are complicated

The main clinical take home message, according to one of the two editorials accompanying the paper, is that "the results are best interpreted as indicating that initiating treatment with high-flow oxygen is generally not harmful."

JAMA doi:10.1001/jama.2024.26244

How to help people with chronic pain reduce opioid use

People stuck on long term opioid therapy for chronic pain can reduce the dose of opioid they take with support, according to a new study set in the US. It recruited 820 people taking regular opioids for moderate to severe chronic pain and allocated them to a 12 month intervention delivered through an integrated pain team or pharmacist-led collaborative management. Neither strategy had much effect on pain (around 15% of participants had a reduction in pain score of ›30% in both groups), but a quarter of people in each group managed to reduce their opioid dose by half.

JAMA Intern Med doi:10.1001/jamainternmed.2024.6683

The cost of being NICE

Between 2000 and 2022 NICE appraised 332 pharmaceuticals (with 83% getting positive recommendations).

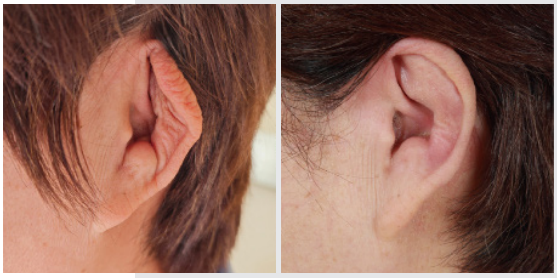
Had they rejected all of the drugs, England would have been £75.1 bn better off, and if that money had instead been spent on existing NHS services, England would have a healthier population: 1.25 million quality adjusted life years (QALYs) healthier. This is all according to a retrospective analysis published in the *Lancet* by a team of prominent health economists and policy experts.

It estimated that new drugs generated 3.75 million QALYs across nearly 20 million patients, but 5 million additional QALYs would have been gained

CLINICAL PICTURE

Auricular atrophy

This woman in her 50s presented with a three month history of swelling and pain in both ears and multiple joints, recurrent fever, and cough that was unresponsive to antibiotics. Physical examination showed bilateral auricle atrophy (figure, left), saddle nose deformity, and joint tenderness. Laboratory test results included raised C reactive protein levels and erythrocyte sedimentation rate, 1+ proteinuria, no UBA1 mutations, and antinuclear antibodies at 1:160 titre with negative extractable nuclear antigen, rheumatoid factor, anti-cyclic citrullinated peptide antibody, and anti-neutrophil cytoplasmic antibody. Cartilaginous inflammation without evidence of vascular involvement or malignancy was identified on positron emission tomography-computed tomography.



Differential diagnoses for auricular chondritis include relapsing polychondritis, granulomatosis with polyangiitis, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammation, somatic) syndrome (an x-linked autoinflammatory disorder caused by somatic mutations in UBA1), infectious chondritis, and traumatic otohaematoma.[1]

Based on McAdam's criteria, relapsing polychondritis was diagnosed in this patient. Relapsing polychondritis is a rare immune mediated systemic disease affecting cartilage and connective

by spending the money on existing services. The authors call for NICE technology appraisal recommendations to be presented relative to the health opportunity costs to show the trade-offs in funding decisions.

Lancet doi:10.1016/S0140-6736(24)02352-3

Rethinking sentinel nodes biopsy

Sentinel node biopsy has been an integral part of breast cancer treatment for the past two decades, but its value is less clear these days with advances in tumour biology and systemic therapy. A randomised trial compared omission of axillary surgery with sentinel lymph node biopsy in people with clinically node-negative stage T1 or T2 invasive breast cancer who were scheduled to undergo breast conserving surgery. The estimated five year invasive disease-free survival rate was similar in each group (91.7% in those who had a sentinel node biopsy and 91.9% in those who didn't), but those who didn't undergo axillary surgery had lower rates of lymphoedema and arm or shoulder pain.

N Engl J Med doi:10.1056/NEJMoa2412063

Comparing types of medical assisted dying

Now that MPs have voted through proposals to legalise assisted dying in England and Wales, the details will be thrashed out in parliament.

One of the many unknowns is how many people are going to seek medical assistance in dying. A study of data from eight countries where medically assisted dying is legal offers some clues. Overall, it found that, between 1985 and 2023, medical assistance in dying occurred in 1.4% of all deaths. The highest rates were in the Netherlands at 3.2% of all deaths and 5.1% in the most recently reported year; the lowest rates (just 0.1% of all deaths) were in the US state of New Jersey and Washington, DC.

JAMA InternMed doi:10.1001/jamainternmed.2024.6643

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

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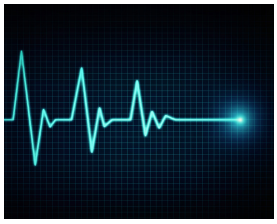

tissue, particularly in the ears, nose, larynx, trachea, and bronchial cartilage.[1] To prevent severe complications, including tracheal collapse and acute renal failure, the patient was treated with methylprednisolone and cyclophosphamide and showed clinical improvement (figure, right). At eight month follow-up she remained stable on a tapering dose of prednisolone.

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Patient consent obtained.

Provenance and peer review: Not commissioned; externally peer reviewed.

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MINERVA From the wider world of research

Nuts

The ASPREE study, which started as a trial of low dose aspirin in healthy older adults, morphed into a longitudinal study of ageing (*Age Ageing* doi:10.1093/ageing/afae239). It recently reported that people who eat nuts every day tend to have a longer disability-free survival. The explanation may be nutritional, because nuts are rich in vitamins, minerals, polyphenols, phytosterols, and unsaturated fats. Another possibility is that the sort of people who choose to eat nuts are the sort of people who have a generally healthy way of life.

Antiseizure medication in fathers

Although valproate is a highly effective treatment for idiopathic generalised epilepsy, guidelines recommend restricting its use to people older than 55 because of the drug's teratogenicity (NICE bnf.nice.org.uk/drugs/sodium-valproate). Where men are concerned, this may be an over-reaction. A systematic review of 10 studies of the offspring of fathers taking antiseizure medication at the time of conception found no consistent evidence of an increased risk of neurodevelopmental disorders, major congenital malformations, small for gestational age, or low birth weight (*J Neurol Neurosurg Psych* doi:10.1136/jnnp-2024-334077).

Age at onset of type 2 diabetes

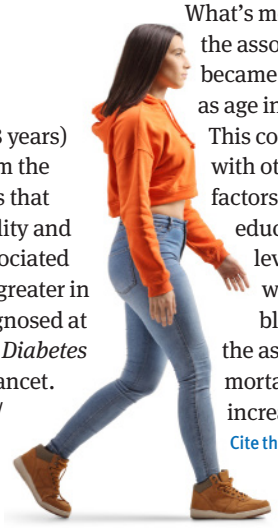
A long running study (median follow-up 18 years) of type 2 diabetes from the United Kingdom finds that the increase in mortality and vascular diseases associated with the condition is greater in people who were diagnosed at younger ages (*Lancet Diabetes Endocrinol* www.thelancet.com/journals/landia/article/PIIS2213-8587(24)00242-0/fulltext). Standardised mortality ratios were roughly 50% higher in people diagnosed under 40 years than in people with later onset diabetes. At any given age, the incidence of diabetes related complications was higher in people with younger onset disease.

Driving after cardioverter-defibrillator implantation

People fitted with an implantable cardioverter-defibrillator are usually advised not to drive for several months. A study from Canada reckons this might be unnecessary. Vehicle crashes serious enough to be attended by police or to result in an insurance claim occurred about 30% less often in the first six months after the device was implanted than in a similar period in age and sex matched controls (*Heart* doi:10.1136/heartjnl-2024-324541).

Physical activity and mortality by age

If any doubt remains that being physically active contributes to longevity, it's laid to rest by an analysis of four large studies from the US, UK, China, and Taiwan with data on more than two million people (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2024.46802). At all ages, increased activity was associated with lower mortality. What's more, the strength of the association became greater as age increased. This contrasted with other risk factors, such as educational level, body weight, and blood pressure, where the associations with mortality diminished with increasing age.



At all ages, increased activity was associated with lower mortality

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CLINICAL UPDATE

Fever of unknown origin

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0.5 HOURS

See learning.bmj.com for linked learning module

Fever of unknown origin (also known as fever of undetermined origin or pyrexia of unknown origin) is often a debilitating clinical syndrome. Patients with this syndrome present to medical practitioners across all levels of healthcare, including general practice, emergency department, and secondary care services, across all geographic areas.[1-5] There are limited epidemiological data on this syndrome, and no data related to primary care presentations.

This article outlines the current diagnostic defining criteria, causes, and evaluation strategies, including newer diagnostic methods that have emerged over the past 20 years. We also outline management recommendations.[6-9]

What is fever of unknown origin?

Fever of unknown origin is a diagnosis based on a set of clinical, laboratory, and radiographic criteria.[6 7 10-12] It is a syndrome characterised by a prolonged febrile illness with a set of medical signs and symptoms that lacks an obvious cause despite initial assessment and diagnostic tests.[6 7 10-12]

The original 1961 definition of fever of unknown origin, herein referred to as the "classic" criteria, has evolved over time (see full article on bmj.com for details). While the three week duration, essential to exclude acute self limiting infections (such as viral infections), has remained unchanged, changes over time have included the temperature threshold, exclusion of immunocompromised patients, replacement of time-based investigations to a standard minimal set of investigations, and increased number of outpatient evaluations.[6 7 10-12] With these modern revisions and the removal of immunocompromised patients from the criteria, the three additional groups of patients proposed by Durack and Street in 1991[11] (nosocomial (healthcare associated), neutropenic (immune deficient), and human immunodeficiency virus (HIV) related) are now considered largely irrelevant for current medical practice and will not be discussed in this update.

Historic and current proposed definitions of fever of unknown origin, largely based on expert consensus only, lack a single agreed uniform criteria that all patients with this condition must meet.[6 7 10-12] However, the 2024 Delphi-generated consensus-based recommendation on behalf of the International Fever and Inflammation of Unknown Origin Research Working Group[7] defines fever of unknown origin using the following criteria: three weeks or more of fever (≥38.3°C on three or more occasions) without explanation, despite completing a minimum set of standard diagnostic tests in an immunocompetent patient.

What are the causes?

Studies typically use five diagnostic categories to classify causes associated with fever of unknown origin: infections, non-infection inflammatory disorders, neoplasms, miscellaneous conditions, and undiagnosed illnesses (that is, idiopathic fever of unknown origin).[2 13-18] Recent meta-analyses have indicated causes differ according to geographic location, country income classification, duration of symptoms, and which definition is used.[2 13-18] For example, a 2019 systematic review reported higher proportions of infections among studies (using the classic criteria established in 1961) of lower or upper middle income countries in Southern Asia and Far East Asia compared with high income countries in Europe, where non-infectious inflammatory disorders were more prevalent.[2]

A recent retrospective study involving 21 countries of differing economic status in Europe, Eastern Mediterranean, and South East Asia with 788 participants with fever of unknown origin reported infection to be the most common associated disease category (52%), followed by undiagnosed illnesses (20%), neoplasm (11%), non-infectious inflammatory disorders (9%), and miscellaneous conditions (8%).[1] Additionally, a recent, hospital based, prospective observational study involving 51 consecutive patients aged 60 years and above reported that infections and neoplasms contributed to 72.6% of cases, suggesting that aetiologies also differ by age groups.[19]

WHAT YOU NEED TO KNOW

- Fever of unknown origin is a clinical syndrome, and updated criteria (based on international consensus) are a raised temperature on several occasions with a prolonged illness (>3 weeks) in an immunocompetent patient and uncertain diagnosis on completion of a recommended set of minimal laboratory and imaging studies
- Causes can be classified as infections, non-infection inflammatory disorders, neoplasms, miscellaneous conditions, and undiagnosed illnesses, and they vary with geographic region and patient's age
- It is more often explained by a common disease with an atypical presentation rather than by a rare disease
- Consider early referral to a specialist for patients with confirmed fever, with or without elevated inflammatory markers, who remain undiagnosed in a generalist setting

thebmj Visual summary

Fever of unknown origin: evaluation

Proposed systematic approach for patient assessment

History & physical examination

Patient history should include:

Account for local and regional prevalence of diseases when considering diagnostic testing

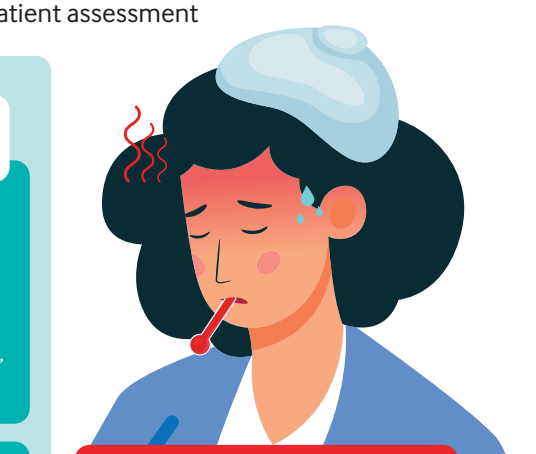
Medical
Current and prior comorbid conditions (such as endocarditis, lymphoma, rheumatic fever), surgeries and postoperative complications, indwelling foreign devices

Women: Take a comprehensive obstetric and gynaecological history

Social
Geographical residence, recent travel, tuberculosis risk factors, exposure to pets or other animals, consumption of foods (such as unpasteurised dairy products or undercooked meats), work environment, use of illicit drugs, sexual practices

Medication
Current and recent medications, including over the counter, and duration of use, to consider drug induced fever

Family
Ethnic background for possible hereditary causes (such as Familial Mediterranean Fever)



If patient is/has:
Haemodynamically unstable, clinically deteriorating, suspected giant cell arteritis, high suspicion of *Mycobacterium tuberculosis* infection, immunocompromised, or neutropenic with fevers

Immediately refer for hospital evaluation

Minimal standard investigations

Blood tests
Full blood count with differential, comprehensive metabolic panel with calcium and liver function tests, erythrocyte sedimentation rate, C reactive protein, ferritin, thyroid stimulating hormone, rheumatoid factor, antineutrophil cytoplasmic antibodies, and antinuclear antibodies

Microbiological investigations
Human immunodeficiency (HIV) 1/2 serology, urine analysis (with addition of culture if there is significant pyuria), Mycobacterium tuberculosis skin test or whole blood interferon-γ release assay, and blood cultures (3 sets)

Imaging
Both abdominal ultrasonography and posteroanterior lateral view chest plain radiography or chest/abdominal/pelvic computed tomography

Potential diagnostic clues?

No

Yes

Objectively verify fevers
in patients without symptoms or signs of an underlying chronic illness, such as anaemia or elevated inflammatory markers

Order appropriate investigative studies for the suspected differential diagnoses of diseases

New potential diagnostic clues?

Yes

No

Criteria for fever of unknown origin met?

FUO — Fever for >3 weeks + Fevers >38.3˚C (100.9˚F) on at least 3 occasions + No cause identified from set of minimal standard investigations in an immunocompetent patient

Yes

No

Refer patient to specialist

Consider early use of FDG-PET/CT

Positive

Negative

Repeat history and physical examination periodically

New potential diagnostic clues?

Yes

No

Consider diagnostic testing
Repeat laboratory testing, imaging (such as venous duplex), histopathologic examination of tissues obtained by excisional or needle biopsy

If infection(s) suspected
Consider early use of molecular assays

Patient remains ill without a diagnosis other than fever of unknown origin

Discuss empirical treatments
Non-steroidal anti-inflammatory drugs, immunosuppressive medications such as corticosteroids and anti-infectives

Box 1 | Examples of physical findings* associated with specific conditions in patients with fever of unknown origin[24 25 27]

- Camel-back fevers (two fever peaks per week)—Rat bite fever
- Conjunctival suffusion—Relapsing fever
- Double quotidian fevers (twice daily fever spikes)—Malaria, miliary tuberculosis
- Epididymitis, orchitis, or epididymal nodule—Behcet's disease, Epstein-Barr virus, renal tuberculosis
- Generalised lymphadenopathy—Epstein-Barr virus (primary infection), HIV, or hyper-IgD syndrome
- Hepatomegaly (without splenomegaly)—Hepatoma, metastatic liver disease, granulomatous hepatitis, rat bite fever, relapsing fever, or renal cell carcinoma
- Lacrimal gland enlargement—Rheumatoid arthritis and/or Sjögren's disease
- Localised lymphadenopathy—Cat scratch disease, hyper-IgD syndrome, lymphoma, Kikuchi's disease, or toxoplasmosis
- Morning temperature spikes—Miliary tuberculosis
- Oral ulcers—Behcet's disease or Crohn's disease.
- Perirectal pain or fluctuance—Perianal or prostatic abscess
- Relative bradycardia—Drug fever, factitious fever, or lymphoma
- Renal angle tenderness—Perinephric abscess, pyelonephritis (chronic), or renal cell carcinoma
- Roth spots—Atrial myxoma, endocarditis
- Spinal tenderness—Myeloproliferative disorder, preleukaemia, tuberculosis, or vertebral bacterial osteomyelitis
- Splenomegaly—Cat scratch disease, cirrhosis, cytomegalovirus, Epstein-Barr virus, hyper-IgD syndrome, malaria, psittacosis, rat bite fever, rheumatoid arthritis, or subacute bacterial endocarditis

*When these signs are present they might help with ruling in a disease (that is, high specificity), but their absence does not rule out disease (low sensitivity).

This syndrome has a wide differential diagnosis (table 2 lists on bmj.com the common and uncommon underlying causes stratified by World Health Organization geographic region).

How should I assess someone?

The most important lesson learnt from data is that most patients do not have an unusual or rare condition; instead, they exhibit atypical manifestations of common illnesses.[10-23] The practical implication is that physicians should consider more common conditions initially, based on geographic disease prevalence, when evaluating patients and use potential diagnostic clues gleaned from the patient's history (including risk factors and travel history), physical examination, laboratory studies, and imaging tests when searching for an underlying cause.[7 22] We refer to any localising signs, symptoms, and abnormalities that can suggest a potential diagnosis as potential diagnostic clues.[22 23]

In the infographic, we outline a proposed systematic approach for evaluating patients with suspected fever of unknown origin, in line with recent publications and the 2024 Delphi-generated recommendations.[6 7 22 24-26]

Initial evaluation

History and physical examination

A comprehensive history and physical examination are the foundation for evaluating patients with fever of unknown origin.[22 24-26] Potential diagnostic clues found from the history and examination can then be used to create a list of likely diagnoses to guide further testing (see table 3 on bmj.com for examples).[24 25]

Among several recent meta-analyses, fever of unknown origin affects males slightly more than females (49-79% *v* 43-55% respectively).[2 13 20 21] Based primarily on observational data, patients with fever of unknown origin also present more often with a continuous prolonged fever pattern, rather than a recurrent fever pattern, for three weeks or more.[13 20 21] Continuous fever patterns are defined as daily or near daily fevers, whereas recurrent fevers are defined as at least two episodes of fever with fever-free intervals of at least two weeks not related to empirical treatments.[13]

Patients can also present with or without additional symptoms or signs (such as anaemia of chronic illness or elevated inflammatory markers).[7] In box 1 we list examples of physical findings associated with specific conditions in patients with fever of unknown origin.[24 25 27]

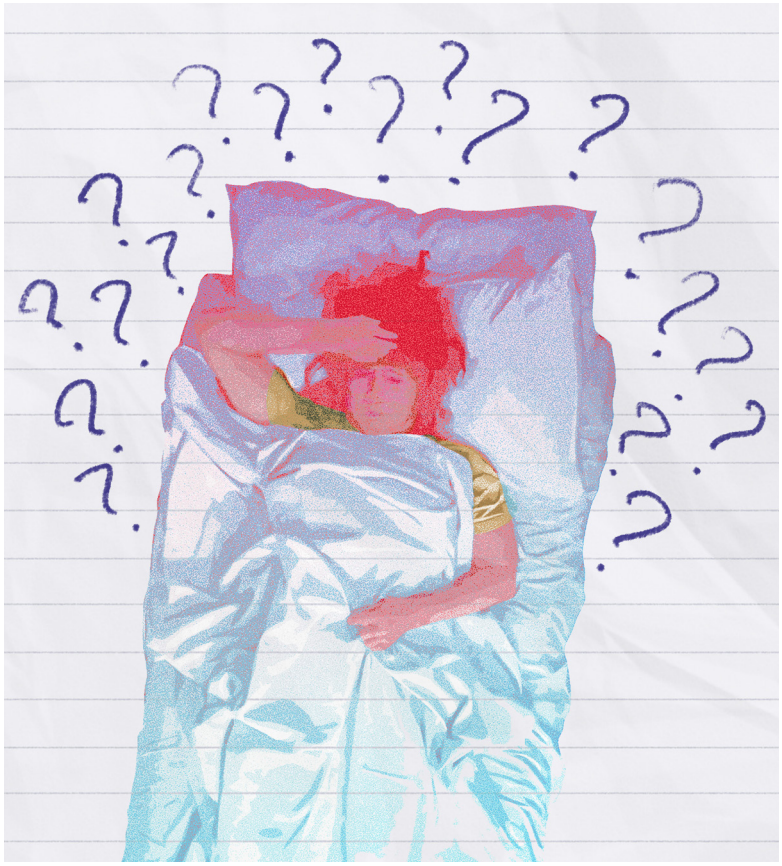
Minimal standard investigations

Despite the use of routine laboratory tests, including cultures and serological examination, these methods in several studies have yielded the diagnosis in approximately a quarter of cases only.[13 16 23 29] A recent meta-analysis of 19 prospective studies published between 1997 and 2021, with 2667 total cases, reported serological tests for microbial pathogens and autoimmune disorders have been the most useful in establishing an underlying diagnosis.[16] Examination of blood smears are occasionally diagnostic, especially in patients with malaria or relapsing fevers.[15]

Of the commonly used diagnostic imaging methods, a 2007 multicentre prospective study involving 73 patients reported sensitivities for diagnosis of underlying causes of 60% for plain-film chest radiography, 82% for chest computed tomography, 86% for abdominal ultrasound, and 92% for abdominal computed tomography.[23] In two prior prospective studies involving 457 patients,[13 23] transthoracic echocardiography was useful in only 13 of 258 (5%) tests, but it should be pursued if potential diagnostic clues suggest cardiac disease (such as pericarditis or known heart valve abnormality).

According to the recent Delphi-generated consensus-based recommendations,[7] the components of minimal standard investigations include:

- *Bloods*—Full blood count with differential, comprehensive metabolic panel including calcium and liver function tests, erythrocyte sedimentation rate, C reactive protein, ferritin, thyroid-stimulating hormone, rheumatoid factor, antineutrophil cytoplasmic antibodies, and antinuclear antibodies.
- *Microbiological investigations*—Blood cultures (minimal 3-sets with spacing, incubation 5 days), urine analysis (with addition of culture if there is significant pyuria) (minimal 1-set), HIV 1/2 serology, and tuberculin skin test or interferon-gamma release assay.
- *Imaging*—Must include both abdomen ultrasonography and posteroanterior-lateral view chest plain-film or chest/abdominal/pelvic computed tomography.



MALCOLM WILLETT

Verification of fever

In patients with normal inflammatory markers (such as erythrocyte sedimentation rate and C reactive protein) and absence of anaemia of chronic illness, the recent Delphi consensus panel guidelines recommend to verify fevers objectively during your intial evaluation before completing further investigations, and also exclude factitious fevers.[7 26]

Taking into consideration the diurnal nature of the normal temperature cycle, morning nadir (6-8 am) and late afternoon apex (4-6 pm) temperature measurements should be documented for patients admitted to hospital.[22] Patients managed in the outpatient setting should be instructed to keep a fever log of both morning and late afternoon temperatures, the site of measurement, and instrument used.[22 26 35] Delphi panel guidelines also recommend that researchers and clinicians indicate the fever threshold used, the anatomical site at which temperatures are taken, and the specific instrument used to measure temperatures so as to improve scientific and clinical communication when fever is reported in clinical investigations.[7 26 35] Contact thermometers that are placed on the forehead or in the mouth, ear, axilla, or rectum are preferred over non-contact infrared devices for monitoring patients' temperatures.[35] From a practical perspective, it is important to document the site at which measurement is taken when verifying fever given the variation in temperature at different sites of the body.[35]

Patients managed in the outpatient setting should be instructed to keep a fever log of both morning and late afternoon temperatures

Characteristics more likely to be associated with factitious fever include markedly elevated temperatures (>41.1°C), discrepancy between simultaneous oral and rectal temperatures, lack of diurnal temperature variation, rapid defervescence, absence of fever related tachycardia, disparity between the physical examination and temperature recording, and a history of other factitious illnesses (such as factitious disorder imposed on self).[22]

Referral to establish diagnosis

After completion of initial evaluation, refer patients to a specialist in fever of unknown origin, who may vary according to area of practice, such as internal medicine, infectious diseases, or rheumatology. After referral, further potential diagnostic clues may be assessed in the patient's history and physical examination, and additional laboratory or specialised imaging studies undertaken (such as fluoro-deoxy-glucose positron emission tomography/computed tomography (^{18}FDG-PET/CT)).[5 7 26]

Nuclear medicine

The preferred imaging technique is ^{18}FDG-PET/CT for adults, which allows detection and localisation of foci of hypermetabolic lesions with high sensitivity because of the ^{18}FDG uptake in glycolytically active cells that may represent inflammation, infection, or neoplasia.[29 36]

- Pooled data from a consensus guideline for use of nuclear medicine[29] and several other meta-analyses[36] demonstrate diagnostic yields for underlying causes of 84-98% for ^{18}FDG-PET/CT.
- Patients with infection or malignancy benefited more from ^{18}FDG-PET/CT than those with non-infectious inflammatory disorders.[36]
- ^{18}FDG-PET/CT is useful for detection of mural inflammation or luminal changes of extracranial arteries in patients with suspected giant cell arteritis, a large vessel vasculitis commonly associated with polymyalgia rheumatica and fever of unknown origin.[15 37]

A limitation of ^{18}FDG-PET/CT is differentiating pathology from the normal physiological uptake of ^{18}FDG in the brain, bowel, urinary tract, liver, spleen, and, to varying degrees, bone marrow.[29 36] Barriers to use include limited access in some geographical locations and the costs of performing scans.[29 36]

Venous duplex imaging

Few reports have listed venous thrombosis as a cause of fever of unknown origin, with the prevalence ranging from 2.0% to 6.0%.[39-41] In a two year retrospective study of 44 patients meeting the 1961 classic criteria for fever of unknown origin, three (6.0%) were diagnosed with lower extremity venous thrombosis as the cause.[39] Symptoms and signs of venous thrombosis (such as leg swelling) were lacking among these patients. For cost-effective use, venous duplex imaging is best reserved for when all other initial diagnostic testing methods have not elicited an explanation.[41]

Box 2 | Situations in which empirical therapy should not be withheld[6 7 22 24-26 49]

- High risk of serious bacterial infection among discovered immuncompromised or neutropenic patients
  - Start empirical broad-spectrum antipseudomonal antimicrobial therapy after obtaining appropriate cultures
- Patients with suspected giant cell arteritis and visual complaints
  - Start corticosteroid treatment due to the high risk of permanant visual loss, and undergo urgent confirmation or exclusion of the diagnosis using biopsy or imaging. Be aware that corticosteroid can reduce the sensitivity of diagnostic tests
- High risk of sepsis in patients who are not immunocompromised or neutropenic but are haemodynamically unstable
  - Consider appropriate spectrum antibiotic treatment for the particular infection under consideration[49]
- If high clinical suspicion for tuberculosis (for example, patients presenting from or within a highly prevalent area)
  - Consider anti-tuberculosis therapy before appropriate diagnostic tests return

Invasive and molecular diagnostic investigations

Bone marrow aspirate and biopsy are usually only worth undertaking if there are abnormal full blood cell counts present in the initial work-up. In three observational studies of 168 adults with fever of unknown origin, bone marrow aspirate and biopsies contributed to the diagnosis in about a quarter of cases.[42-44] Histopathological examination of tissues obtained by excisional biopsy, needle biopsy, or laparotomy in most published series resulted in an appropriate diagnosis in fewer than half of the cases but should be considered when the cause of fever remains unidentified in the presence of a potential diagnostic clue (such as lymph node or pleural biopsy in a suspected case of tuberculosis with pleural effusion).[45]

Molecular diagnostic assays, such as broad-based molecular methods (for example, next-generation sequencing, multiplex and universal 16S ribosomal RNA (rRNA) gene polymerase chain reaction followed by Sanger sequencing, and broad fungal sequencing using the D1/D2 region of the large subunit of the 28S rRNA gene and the internal transcribed spacer region) and pathogen-specific imaging, have received widespread attention.[25 46 47] With our current knowledge base and limited access, molecular methods should be reserved for patients referred to a fever of unknown origin specialist for unexplained fevers due to suspected infections.[7 26]

How is it managed?

Withhold therapy whenever possible until the underlying cause of the fever has been determined so that treatment can be tailored to a specific diagnosis.[6 7 22 24-26] This approach is based on the observation that non-specific treatment rarely cures fevers and has the potential to delay reaching a final underlying diagnosis. Some clinicians may favour a practical approach for managing febrile illnesses and employ empirical antimicrobial therapy or corticosteroids before undertaking expensive diagnostic exercises. However, this approach is less likely to succeed in patients with fever of unknown origin and may obfuscate diagnoses needing specific treatment as an underlying cause. Box 2 lists exceptions to withholding therapy.[6 7 22 24-26 49]

When should I refer?

Immediately refer any outpatient with confirmed or suspected fever of unknown origin for inpatient hospital evaluation and treatment if the patient is haemodynamically unstable, is clinically deteriorating fast, has suspected giant cell arteritis, there is a high suspicion of *Mycobacterium tuberculosis* infection, or in the initial course of evaluation is found to be immunocompromised or neutropenic with fevers.[6 7 24-26]

For patients without these immediate concerns, refer to a specialist (such as internal medicine, infectious diseases, or rheumatology) in fever of unknown origin when the cause remains uncertain after completing initial evaluation, or seek further management advice regarding potentially underlying diseases. In a 2017 retrospective study from The Netherlands involving 236 hospitalised patients who remained undiagnosed despite extensive evaluations and referred to a fever of unknown origin specialist for a second opinion reported a final diagnosis or resolution of fever in 68.2% of cases evaluated using a standardised diagnostic protocol with early access to specialised diagnostic methods.[5] The benefit of referral to a fever of unknown origin specialist should therefore be considered in patients with confirmed fever with or without elevated inflammatory markers that remains undiagnosed after completing initial evaluation in a generalist setting.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Colleen Forry, a patient author who had fever of unknown origin, reviewed the article and contributed with her experiences of this syndrome. We specifically developed the assessment and management sections in response to her feedback on incorporating travel history, occupational history, earlier use of nuclear medicine imaging testing, and empirical therapies. Her experiences of the diagnostic dilemma of this syndrome helped shape the approach to investigating fever of unknown origin in primary care.

EDUCATION INTO PRACTICE

- In a patient who is suspected to have fever of unknown origin, what do you ask about and what physical examination findings would you assess for, specifically?
- How would you discuss the possible causes and investigation plan of fever of unknown origin with patients, including risk-benefit ratio?

Competing interests: None declared.

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STATE OF THE ART REVIEW

Management of alcohol withdrawal syndromes in general hospital settings

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This is a summary of Clinical Review *Management of alcohol withdrawal syndromes in general hospital settings*. The full version can be read here: https://www.bmj.com/content/388/bmj-2024-080461.

State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

CPD READING

0.5 HOURS

The covid-19 pandemic was associated with an increase in alcohol consumption and associated morbidity, including hospitalisations for alcohol withdrawal.[1 2] Clinicians based in hospitals must be ready to identify, assess, risk-stratify, and treat alcohol withdrawal with evidence based interventions.

Epidemiology

From 2021 to 2023, the prevalence of alcohol use in the previous month in the US remained consistent at 47.5% in the general population, with 5.8% reporting heavy alcohol use, 21.7% reporting binge alcohol use, and 10.2% to 10.6% meeting the criteria for alcohol use disorder.[8 9] Hospital admission typically interrupts alcohol intake for an average of 5.9 days, creating an opportunity for emergent alcohol withdrawal.[10] Among individuals with heavy alcohol use or alcohol use disorder, 15% to 50% will experience some symptoms of alcohol withdrawal during early abstinence.[11 12] Studies suggest 4% to 16% of all admissions to hospital involve, or are complicated by, alcohol withdrawal syndromes.[13-15] Of all individuals experiencing untreated alcohol withdrawal syndromes, 2% to 9% might experience severe symptoms, including alcohol related seizures, hallucinosis, or alcohol withdrawal delirium.[16-19] Severe alcohol withdrawal syndrome is more prevalent in intensive care unit (ICU) settings, affecting up to 21% of patients.[13 20 21] Severe presentations are associated with increased morbidity, and a 1% to 8% mortality rate for alcohol withdrawal delirium.[19 22-24]

WHAT YOU NEED TO KNOW

- Alcohol withdrawal symptoms typically emerge within 6-24 hours of abstinence. Seizure risk is greatest within 8-24 hours and the risk of delirium is highest 48-96 hours after the last drink
- Symptom triggered management with benzodiazepine drugs is common, although this treatment approach might be inadequate for those at risk of severe alcohol withdrawal syndromes
- It is important to assess for and treat thiamine deficiency in patients with alcohol withdrawal syndromes to prevent progression to encephalopathy or neurocognitive disorder. In the UK, National Institute for Health and Care Excellence (NICE) recommends parenteral thiamine administration for any hospitalised patient with heavy alcohol use
- After treatment of alcohol withdrawal, the underlying alcohol use disorder should be dealt with

Clinical manifestations

Alcohol withdrawal symptoms emerge within 6-24 hours of abstinence or marked reduction in alcohol intake.[14 19] Seizure risk is greatest within 8-24 hours, with most alcohol related seizures being single or a burst of self-limited, generalised motor seizures.[48 49] Transition to status epilepticus is rare and could signal additional pathology. The risk of delirium is highest 48-96 hours after the last alcoholic drink.[14 19] Recognising the risk for severe alcohol withdrawal syndromes in a patient in hospital and administering appropriate drugs with the onset of symptoms is recommended to reduce the incidence of seizures, delirium, and associated morbidity and mortality.

Signs of withdrawal include tachycardia, hypertension, tremor, hyperreflexia, diaphoresis, and hyperthermia. Tremor is typically 8-12 Hz, an exaggerated normal physiologic tremor that is best elicited on extension of hands or tongue.[50 51] In non-severe cases, patients might experience headache, anxiety, nausea/emesis, tremor, disrupted sleep with rapid eye movement (REM) rebound, and photophobia or phonophobia. These are usually self-limiting and might respond to supportive measures.[14 52 53] Across general population surveys, 5% to 15% of individuals experience at least mild alcohol withdrawal during early abstinence, with the most common symptoms being insomnia, nausea/emesis, anxiety, and mood reactivity.[11 12]

Alcohol induced psychotic disorder (often termed alcoholic hallucinosis) should be distinguished from alcohol withdrawal delirium, as their prognoses and treatments are different. Psychotic symptoms induced by alcohol use often present early, before the expected onset of alcohol withdrawal delirium, and symptoms could persist beyond the acute withdrawal period.[54] Psychotic symptoms that occur without associated encephalopathy and autonomic dysregulation distinguish psychotic disorder that is induced by alcohol use from alcohol withdrawal delirium.[54] The perceptual disturbances in alcohol withdrawal syndromes vary in severity. In less severe cases, paraesthesia and photophobia or phonophobia occur in patients without psychosis. In

more severe cases, illusions or frank hallucinatory experiences with or without associated paranoia or delusions define alcohol induced psychotic disorder. These symptoms respond to supportive measures and benzodiazepines, in addition to dopamine antagonist drugs when clinically indicated.[54] Psychotic disorder induced by alcohol use does not necessarily correlate with increased mortality or risk for alcohol withdrawal delirium.[54] Outpatient follow-up and prospective monitoring of psychotic symptoms by mental health clinicians is warranted to assess for progression to schizophrenia or bipolar spectrum disorder, which could occur in up to 10% of cases.[55]

Alcohol withdrawal delirium typically presents later in the withdrawal course with an escalating progression of dysautonomia, diaphoresis, tremulousness, confusion, impaired attention, hyperarousal, and perceptual disturbances, usually arising 48 hours after the last alcohol intake.[19 23] When diagnosing alcohol withdrawal delirium, other aetiologies must be considered, including thiamine deficiency (Wernicke-Korsakoff syndrome), benzodiazepine toxicity, intoxication from other substances including stimulants, withdrawal from other central nervous system depressants, or other active medical illness.

Clinical assessment in the general hospital

Screening tools for at-risk alcohol use

Despite the prevalence of heavy alcohol use and alcohol use disorder, these patients often go unrecognised in clinical settings. Detection of at-risk alcohol use is a critical first step in intervening to treat alcohol withdrawal syndromes.

Multiple validated screening instruments can detect at-risk alcohol use. A single-item instrument, Single Alcohol Screening Question (SASQ), is helpful for rapid screening in the general hospital.[57] A positive SASQ screen occurs with four or more drinks in women or five or more drinks in men on one occasion in the past year. Another rapid screening tool is the Alcohol Use Disorders Identification Test - Consumption (AUDIT-C), a modified three-item version of the longer AUDIT.[58] The AUDIT-C has good sensitivity and specificity for detecting unhealthy alcohol use and assesses drinking frequency, amount consumed, and occasions of heavy use.[58]

Biomarker testing

Given the prevalence of at-risk use in the general hospital, alcohol biomarker testing is generally recommended to inform diagnosis and treatment recommendations. Although biomarker tests have limitations, when used appropriately they provide valuable information.[64 65] Importantly, biomarker testing alone is insufficient to diagnose an alcohol use disorder, and results should always be interpreted in the patient's broader clinical context.

There are two broad categories of alcohol biomarkers used in the general hospital. The first includes direct measures of ethanol and its metabolites. The second includes indirect measures of organ damage or alcohol related toxicity.

Among the indirect markers, hepatic enzymes might be elevated by alcohol use, reflecting toxic effects on hepatocyte cell membrane integrity. Classically, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in a 2:1 ratio with alcohol associated hepatic inflammation.[74] Gammaglutamyltransferase (GGT) is another hepatic enzyme that is more specifically elevated by alcohol use. Mean corpuscular volume might be elevated by chronic alcohol consumption, although sensitivity and specificity are both low for detecting at-risk use.

Risk stratification for severe alcohol withdrawal

A previous history of alcohol related seizures or alcohol withdrawal delirium is a consistent risk factor predicting future severe alcohol withdrawal syndromes.[23 76 77] Smaller studies identify family history of alcohol withdrawal delirium as a potential risk factor, suggesting genetic susceptibility.[31 79 80] Interestingly, previous inpatient alcohol detoxifications and quantity of alcohol use have been inconsistent risk factors across studies.[16 23 76 77 81] This could be owing to the quality of the alcohol history gathered, with low accuracy of self-report potentially adversely affecting the performance of these variables.[76 82]

Physiological and laboratory predictors for severe alcohol withdrawal syndromes have also been studied. Hepatic cirrhosis is negatively associated with severe alcohol withdrawal syndromes,[76] suggesting that advanced fibrosis could lead to lower alcohol intake by reduced capacity for ethanol metabolism. By contrast, there is a positive association between AST and ALT elevations and severe withdrawal, marking acute hepatocellular injury because of heavy alcohol use. Further, elevated GGT might predict incident seizures, although it has not been associated with alcohol withdrawal delirium.[7 77 83] An association between low initial platelet count and severe alcohol withdrawal syndromes, including alcohol related seizures, has been found in some studies.[7 77 84] Several studies also show an association between initial potassium and severe alcohol withdrawal syndromes, with lower potassium in patients who developed alcohol withdrawal delirium and alcohol related seizures.[7 23 77]

In patients who develop any alcohol withdrawal syndromes, hypertension and tachycardia are present in those who progress to more severe symptoms. However, this dysautonomia occurs across severe and non-severe alcohol withdrawal syndromes cases, not necessarily distinguishing those truly at higher risk for severe alcohol withdrawal syndromes.[7 76]

Alcohol withdrawal severity scales

Several alcohol withdrawal severity scales exist for the purpose of alcohol withdrawal risk assessment, as well as monitoring symptom course and response to treatment.

The most studied and utilised scale is the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar).[90] CIWA-Ar was designed to measure

the severity of alcohol withdrawal for research studies using a 10-item standardised scale with demonstrated validity and inter-rater reliability.[91]

Despite its common and widespread use, the CIWA-Ar has several limitations. As with any symptom triggered scale, its use requires clinician training for reliable administration and could take significant time to administer and score.[90 94] It also requires patients to be able to accurately self-report subjective symptoms, including nausea, anxiety, tactile and auditory disturbances, and headache.

Alternative scales have been created to address these limitations, although their reliability and validity remain under study.

Drugs for alcohol withdrawal management

Benzodiazepine drugs

Benzodiazepine drugs are positive allosteric modulators of γ-aminobutyric acid (GABA) A anion channels, binding at the interface of specific α and γ subunits, leading to GABA-dependent increased channel opening and resulting inhibitory membrane hyperpolarisation.[101] By 1999, 11 randomised controlled trials including 1286 patients demonstrated clear benefit from benzodiazepine therapy, with benzodiazepine drugs preventing 7.7 seizures and 4.9 cases of alcohol withdrawal delirium per 100 patients treated.[18] These data form the basis of the current preferred treatment recommendations for alcohol withdrawal management.[103]

Longer half-life benzodiazepine drugs—diazepam or chlordiazepoxide—are recommended over shorter half-life drugs because their pharmacokinetics allow for a more consistent wean of GABAergic tone over a longer period, mitigating breakthrough withdrawal symptoms. This might also lead to greater efficacy in preventing seizures, which can occur with shorter half-life benzodiazepine drugs.[103] However, longer half-life drugs risk oversedation and respiratory depression in individuals with impaired hepatic metabolism (eg, older age, hepatic synthetic dysfunction), concurrent central nervous system depressant medication, or pulmonary disease. Lorazepam or oxazepam are often chosen in individuals with impaired hepatic synthetic function because they do not require cytochrome P450 activity for clearance, instead relying on glucuronidation which is relatively preserved.[103 104] When using short-acting benzodiazepine drugs, a scheduled taper should be considered to prevent late onset or delayed seizures from rapid loss of GABAergic effect when short half-life drugs are discontinued abruptly or dosed at intervals longer than the expected duration of effect.

Loading doses of long-acting benzodiazepine drugs have been studied for individuals with severe alcohol withdrawal syndromes, with some evidence for more rapid alcohol withdrawal symptom improvement, lower incidence of seizures, shorter duration of delirium, and an association with shorter stays in hospital.[110 111] However, studies in non-severe alcohol withdrawal syndromes have found no difference in outcome or a reduced total benzodiazepine dose requirement and shorter stays in hospital with a symptom triggered approach.[112-114]

Some patients with severe alcohol withdrawal syndromes demonstrate relative benzodiazepine resistance despite appropriate benzodiazepine therapy, suggesting poor cross-tolerance between ethanol and the chosen benzodiazepine drug. A consensus definition of alcohol withdrawal that is resistant to treatment with benzodiazepine drugs has not yet been established, although a high total dose of benzodiazepine drugs and requiring over 40 mg diazepam equivalents per hour have been suggested as possible thresholds.[119]

Phenobarbital

Phenobarbital is a positive allosteric modulator of the GABA-A receptor with a different binding site to benzodiazepine drugs. It has effects on glutamate activity through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainite receptors. This effect on both GABA and glutamate receptor pathways is unique to phenobarbital and could partly explain its efficacy in individuals with benzodiazepine resistant severe alcohol withdrawal syndromes.[124]

In emergency department settings, phenobarbital monotherapy improved and helped stabilise withdrawal symptoms and resulted in an equal or reduced need for inpatient and/or ICU admission compared with the use of benzodiazepine drugs.[112 125] In a study of trauma patients, there was a significant decrease in the rates of progression to severe alcohol withdrawal syndromes and medication adverse effects with phenobarbital compared with a fixed dose benzodiazepine drug protocol.[126] A retrospective study of general medical patients treated with phenobarbital showed equivalent outcomes to a fixed dose benzodiazepine drug protocol, despite a more prevalent history of complicated alcohol withdrawal in the phenobarbital group.[117]

Despite concerns that combining phenobarbital with benzodiazepine drugs could increase adverse events, studies using phenobarbital with benzodiazepine front-loading strategies in ICU settings suggest that adjunctive phenobarbital results in lower rates of mechanical ventilation, fewer ventilator days, decreased length of stay in ICU and hospital, and a variable impact on benzodiazepine drug requirements.[129 130]

Alpha-2 adrenergic agonists

Increased noradrenergic tone leads to many symptoms observed in alcohol withdrawal syndromes, including tachycardia, hypertension, and coarse tremor. In severe cases where benzodiazepines have limited effect on the management of these symptoms, α-2 agonists have been used adjunctively.

Clonidine

Clonidine has been studied as adjunctive treatment in alcohol withdrawal syndromes, showing efficacy in reducing excessive adrenergic tone.[131-136] Clonidine has no direct effect on the GABA or glutamatergic system, therefore, it is not recommended as monotherapy.[136]

Dexmedetomidine

Dexmedetomidine is used adjunctively with benzodiazepines or phenobarbital, typically in ICU settings. Dexmedetomidine is a highly selective α-2 agonist, with high receptor affinity. Studies have shown benefit for hypertension, tachycardia, and a reduction in total benzodiazepine drug requirement in severe alcohol withdrawal syndromes.[137-143] Emerging evidence suggests dexmedetomidine has additional physiological mechanisms that could benefit individuals with alcohol withdrawal syndromes. The role of dexmedetomidine is currently limited by the need for administration in the ICU or emergency department setting.

Antiseizure medications

Meta-analyses examining the effects of antiseizure medications when combined as a single group have reported no differences in clinical alcohol withdrawal syndromes outcomes compared with placebo.[147 148] However, aggregate meta-analysis could potentially bias the findings against individual antiseizure medications with some efficacy, because the mechanisms of action differ across these drugs.

Carbamazepine

Carbamazepine is a voltage gated sodium channel blocker, with approval as a treatment for alcohol withdrawal syndromes in Germany.[149] The efficacy of carbamazepine in mitigating the risk of alcohol related seizures and alcohol withdrawal delirium remains uncertain with some studies showing delirium and seizures occurring in individuals treated with carbamazepine, limiting its use as monotherapy in at-risk general hospital inpatients.[155 156] Drug-drug interactions are common, rare but severe adverse effects are possible, and the hepatic metabolism is complex with carbamazepine, further limiting its use.[149]

Valproic acid

Valproic acid has both antiseizure and anti-kindling properties through multiple described mechanisms of action, including voltage-gated sodium channel blockade and generalised GABAergic potentiation and glutamate/N-methyl-D-aspartate (NMDA) inhibition.[157] Two double blind comparative studies suggest that valproate reduces total benzodiazepine drug requirements and lessens the severity of withdrawal symptoms.[156 158] Whether valproate is effective in preventing seizures or alcohol withdrawal delirium in patients with more severe alcohol use disorder requires further study, although older evidence suggests no protective effect against alcohol withdrawal delirium.[156] Similar to carbamazepine, valproate is hepatically metabolised and highly protein bound which could affect safety and tolerability in hospitalised patients with liver dysfunction.[157]

Gabapentin

Studies evaluating gabapentin, a voltage dependent calcium channel modulator, as monotherapy or adjunctive therapy to benzodiazepine drugs have shown inconsistent benefits for alcohol withdrawal.[160-162]

Benzodiazepine-sparing protocols

Antiseizure medications, including gabapentin and valproate, have been suggested in novel benzodiazepine-sparing protocols for inpatient alcohol withdrawal syndromes prophylaxis and management.[165] The goal of these protocols is to reduce the risks and harms associated with benzodiazepine drugs.[165] Notably, these protocols lead to increased use of drug combinations (eg, gabapentin, clonidine, valproate, etc) that could reduce exposure to benzodiazepines while increasing exposure to complex polypharmacy with associated risks.

Antiseizure medication class overall

Overall, current evidence does not support antiseizure medications use as the preferred treatment for alcohol withdrawal in the general hospital, although there could be a role for specific drugs in mild withdrawal management, particularly in ambulatory care settings or in lower risk populations requiring preventive treatment. Further study is needed to better characterise the risks and benefits of antiseizure medications in benzodiazepine-sparing protocols, with particular attention to risks of polypharmacy.

Nutritional repletion

Nutritional deficiencies are common in individuals with alcohol withdrawal syndromes, including deficiencies in thiamine, folate, vitamin B_6, vitamin B_{12}, vitamin C, magnesium, and zinc. Malnutrition in this population is often multifactorial, including decreased dietary intake and reduced nutrient absorption. Risk of developing nutritional deficiencies increases significantly as the amount of alcohol consumed reaches 30% of the total intake of calories.[170]

For patients with alcohol withdrawal syndromes who are in hospital, it is important to assess for and aggressively treat thiamine deficiency, which can lead to Wernicke encephalopathy and progress to Korsakoff syndrome. Wernicke encephalopathy is characterised by the acute onset of three symptoms: encephalopathy, oculomotor dysfunction, and gait ataxia. Korsakoff syndrome is a late manifestation of thiamine deficiency characterised by marked deficits in anterograde and retrograde memory which might not improve with thiamine supplementation, often leading to persistent major neurocognitive disorder with significant disability.[171] Atypical presentations of thiamine deficiency are also common, with only 16.5% of decedents with pathological diagnosis of Wernicke-Korsakoff syndrome exhibiting the classic three symptoms in one study—and 19% demonstrated no classic symptoms.[172]

Wernicke encephalopathy and Korsakoff syndrome are medical emergencies and should immediately be treated with parenteral thiamine. As the diagnosis is difficult to confirm and medical risks of undertreatment

Motivational interviewing and screening, brief intervention, and referral to treatment

The Screening, Brief Intervention, and Referral to Treatment (SBIRT) model has long been recommended for all substances in a variety of healthcare settings, both inpatient and outpatient. Screening is ideally performed on all patients admitted to hospital, with those screening positive being offered a brief intervention, which entails a motivational interviewing session around alcohol use to guide the conversation towards behaviour change.[193] Motivational interviewing is an evidence based approach to assist individuals in health behaviour change by utilising a patient centred, non-judgmental, empathic conversation to evoke and strengthen the individual's own motivation.[194] Motivational interviewing is commonly used for brief intervention, although there are other strategies available.[195] Regardless of the approach used, the key principle is to have a non-judgmental and empathic conversation targeting the unhealthy alcohol use. Individuals meeting criteria for an alcohol use disorder would then be referred to ongoing treatment in the community by the SBIRT provider, while those who do not meet the criteria only receive the brief intervention.

A robust evidence base now supports SBIRT as an effective approach for those with heavy or at-risk alcohol use.[193] In the US, the threshold for at-risk drinking is consuming five or more standard drinks on one occasion for men under 65 years old or four or more standard drinks on one occasion for women or men over 65 years old. These individuals benefit greatly from SBIRT, and the relatively low intensity treatment reduces drinking and improves other health outcomes, with an effect that persists for six months or more after discharge. For this reason, the American College of Surgeons mandates that all injured patients in Level 1 and 2 trauma centres be screened for alcohol use, and a brief intervention be provided to those who screen positive.[196]

However, for individuals meeting criteria for alcohol or other substance disorder, as opposed to heavy or at risk use, there is now sufficient evidence to also conclude that the SBIRT approach has not been effective in impacting outcomes.[197 198] In response, a growing body of evidence now points to the importance of initiating treatment during the general hospital admission, previous to referral to ongoing care.[199] Although this approach has been largely restricted to the initiation of drugs for opioid and tobacco use disorders using drugs such as buprenorphine and nicotine replacement therapies, there are also studies to show that a similar approach might be needed to improve the outcomes for those with alcohol use disorder by proactively initiating drugs while the patient is in the general hospital to prevent relapse.[192 200]

are high, clinicians should have a low index of suspicion to initiate treatment. As such, the National Institute for Health and Care Excellence recommends parenteral (intravenous or intramuscular) administration of thiamine for any hospitalised patient with heavy alcohol use, recognising that adverse reactions to high dose thiamine are extremely rare.[173 174] There is limited empiric evidence to support specific thiamine dosing regimens, although many suggest up to 500 mg intravenous thiamine three times daily administered for 3-7 days, typically followed by a course of lower intravenous or oral doses.[175 176] Thiamine has been traditionally given with or before receiving glucose, because of the concern that glucose metabolism could deplete thiamine stores, perhaps precipitating mammillary body infarction. More recent guidelines have cited a limited evidence base for this theory and highlight the importance of not delaying glucose in patients who are nutritionally compromised.[103] Correction of other nutritional deficiencies might be needed in individuals unable to maintain adequate oral intake, which is often sufficient for self-correction in patients resuming a normal diet.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two peer recovery specialists with lived experience of alcohol and other substance use disorders reviewed this manuscript and provided feedback about its content, the presentation of the article, and the use of language. The authors are grateful for their input, which has ensured that patient centred language has been used throughout the manuscript.

Guidelines

The alcohol withdrawal syndromes treatments outlined in this review align with those recommended for medically supervised alcohol withdrawal by the 2020 American Society for Addiction Medicine (ASAM) Clinical Practice Guideline. Additional applicable treatment guidelines have been published in 2010 by the National Institute for Health and Care Excellence, in 2012 by the World Health Organization, in 2015 by Substance Abuse and Mental Health Services, in 2017 by the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force, in 2019 by WFSBP and International Association for Women's Mental Health (for pregnant individuals), and in 2020 by the University of Michigan.

Treatment of underlying alcohol use disorder and relapse prevention

Treatment for the underlying alcohol use disorder is required to reduce the risk of relapse after discharge. Rates of relapse prevention drug initiation during inpatient admission are very low, with additional regional and racial disparities in initiation rates for drugs approved by the Food and Drug Administration (FDA).[177] Notably, specialty addiction consultation in the general hospital setting has been associated with increased initiation of medication for alcohol use disorder relapse prevention, with subsequent reduction in 30-day readmissions.[178] Further, psychosocial interventions aimed at referrals to ongoing treatment, including specialty programmes to treat alcohol use disorder and peer based support groups, have evidence supporting improvement in outcomes (box).[179 180]

Drugs for prevention of alcohol relapse

Current treatment guidelines for alcohol use disorder recommend initiation of drugs to prevent a relapse, including naltrexone or acamprosate, which have been approved by the FDA.[164] These drugs are evidence based, with a number needed to treat of 9-12 for return to any drinking across pooled studies.[181 182] Suggested alternatives for individuals not responding to the preferred drugs include topiramate, gabapentin, or (in carefully selected cases) disulfiram. Benzodiazepine drugs are not recommended outside of acute withdrawal management, because these have been associated with increased risk of relapse.[154 164]

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Living with the uncertainty of Parkinson's

CPD READING
0.5 HOURS

Ruth Herman shares her experience of Parkinson's disease and how health professionals can best support patients through the progression

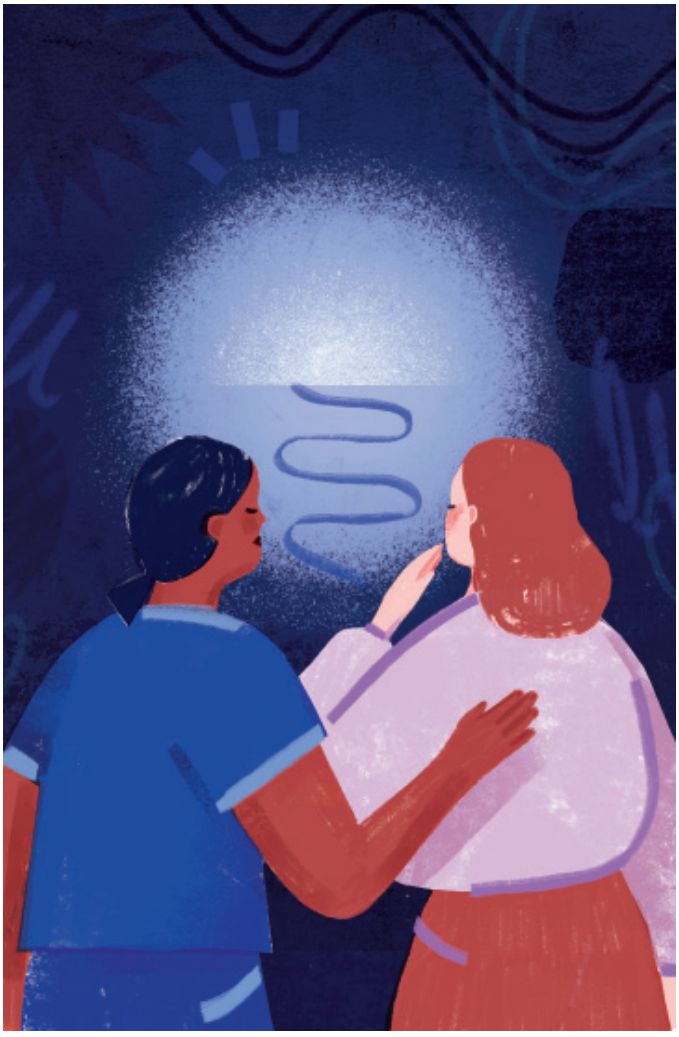
Just over 10 years ago I was diagnosed with Parkinson's disease. I had suffered for several years from strange bouts of cramp, stiffness, and a very painful back. A badly torn rotator cuff only confused the issue as I put much of my discomfort down to my shoulder or back problems. Before major back surgery the surgeon expressed doubts and quietly suggested a neurological rather than a musculoskeletal issue. Raising the possibility of a life changing condition with such non-alarmist tact was helpful.

A colleague along the corridor was more direct but equally careful. Not everybody would have appreciated this directness, but I was relieved. Knowing what I had gave me a better chance of dealing with it.

Facing the figures

Disease progression has been mercifully slow since my diagnosis. However, the intrinsic uncertainty in the condition breeds anxiety: another Parkinson's gift. A thoughtless remark could cause me to lose confidence, leading to isolation and depression. I was once told that within 10 years of diagnosis I would be wheelchair bound and have dementia. This brutal generalisation could have caused some people to give up the fight. I knew that those predictions could not be made, and luckily I am right.

Receiving the most effective drugs can be a challenge; from the patient's perspective, prescribing can look more like an art than a science. As an added complication, the patient may become less able to articulate their problems as the disease progresses. I have been very fortunate that the drugs prescribed for me work well, but this isn't the case for everyone. Patients need support when treatments do not deliver the expected results. I am fortunate as I am functioning well and need very little help, but I still need empathy and the reassurance that my healthcare team are doing the best they can. I want to believe that they will still be working with me even with the prospect of immobility and dementia.



ALISSA THALER

Building trust

Trust is a fragile creature which can be easily damaged. Parkinson's is a team game involving carers, family, and friends, but the patient is the only one who knows how it feels. When there is mutual trust and respect it is easier to tell the truth. Goodwill and openness engender respect. This is done by listening to each other. Health professionals have a key role in building trust with someone living with Parkinson's. Without this contact, the patient may turn to the internet or others living with Parkinson's for help. While support is good, there is a risk these sources may deliver mis- or disinformation.

Health professionals must trust the patient to do as they advise, and the patient must believe the healthcare team is doing their best. I find sending the medical team regular updates of my symptoms helps maintain a connection, provided there is a response. This dialogue brings our different viewpoints, understanding, and experience together. Everybody will learn something about Parkinson's while fostering mutual respect.

ruthherman145@gmail.com

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WHAT YOU NEED TO KNOW

- Be as honest, yet empathic as possible when delivering a life changing diagnosis
- Respond to questions about disease progression with as much information as you can, but explain that predictions are never certain

EDUCATION IN PRACTICE

- How could you ensure you deliver a life changing diagnosis with honesty and empathy?
- What information could you share with someone with Parkinson's to support them through the uncertainty they may face?
- How might you nurture a therapeutic relationship built on mutual respect?

CASE REVIEW

Soft tissue mass of the anterior upper arm

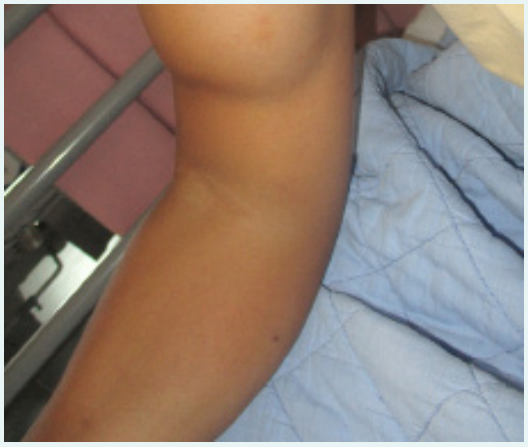
A man in his 30s presented with right anterior elbow pain after colliding with an opponent with his elbow in flexed position while playing basketball eight days previously. At the time of the collision he heard a pop. After the injury he noticed difficulty lifting heavy objects, turning a doorknob, opening bottles, or using a screwdriver, and he noticed a bulge on the arm. He did not seek medical care, however, because the pain began to improve. He reported no smoking or relevant medical history. He did not report any recent use of medications, including antibiotics and steroids.

On clinical examination, there was no bruising. Right elbow flexion and forearm supination strength were reduced, while elbow extension and forearm pronation strength were preserved. He had a soft tissue mass at the proximal part of the anterior arm (figure). The Hook test and the Ruland biceps squeeze test were performed. The right distal biceps tendon could not be hooked during the hook test and his right forearm did not supinate by the Ruland biceps squeeze test.

1 What is the most likely diagnosis?

2 What is the management?

3 What are the complications of this condition and its management?



Submitted by Tun Hing Lui, Amanda Mun Yee Slocum, Charles Churk Hang Li, and Yuen Ting Leung

Patient consent obtained.

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If you would like to write an Endgames article, please see our author guidelines at bit.ly/29HCBAL and submit online at bit.ly/29yyGSx

answers

CASE REVIEW **Soft tissue mass of the anterior upper arm**

1 What is the most likely diagnosis?

Complete rupture of the right distal biceps tendon. Distal biceps tendon rupture is uncommon (1.2–2.55/100 000) and can be partial or complete. In both cases, patients might present with sudden anterior elbow pain with an audible pop during the injury, bruising, swelling, and decreased range of motion.

In patients with complete rupture, the biceps muscle belly retracts proximally resulting in a bulge on the arm, sometimes called the reverse Popeye sign. With a partial rupture this reverse Popeye sign is not seen. In contrast, with proximal biceps tendon rupture, there is distal retraction of the muscle belly, known as Popeye sign.

2 What is the management?

Treatment of a complete distal biceps tendon rupture can be surgical or conservative.

Conservative management involves rest, non-steroidal anti-inflammatory drugs, taping and physiotherapy to manage pain and rebuild strength. Patients who are treated conservatively should be counselled that there is an expected 40% loss in forearm supination strength and 30% loss in elbow flexion strength. However, patients do not always report a subjective loss of strength even with a complete distal bicep tendon rupture.

Surgical repair is indicated in patients who are more active or involved in sports and who want to preserve function. The rate of postoperative complications for surgical repair is between 15% and 35%, with nerve injuries and tendon re-rupture post repair being common complications. Clinicians should advise patients of these risks and tailor management to the individual.

3 What are the complications of this condition and its management?

If the patient is treated conservatively, substantial loss of elbow flexion and forearm supination strength is expected. Surgical complications include heterotopic ossification, tendon re-rupture, and nerve injury—posterior interosseous nerve, median nerve, lateral antebrachial cutaneous nerve, superficial radial nerve.

LEARNING POINTS

- A distal biceps tendon rupture can be partial or complete with the reverse Popeye sign (proximal retraction of the muscle belly) seen in complete rupture.
- Risk factors for distal biceps tendon injury include ageing, smoking, obesity, hypertrophied bicipital tuberosity, overuse, quinolone, corticosteroids or anabolic steroids use, gout, diabetes, and renal disease.
- Management can be conservative or surgical based on the risk and benefit considerations of each approach for the individual.

PATIENT OUTCOME

The ruptured tendon was surgically repaired. At 18 months follow-up, the patient's elbow motion and strength had returned.

CPD READING 0.5 HOURS

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

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