education

FROM THE JOURNALS Edited highlights of weekly research reviews

PICCing the right line

When it comes to peripherally inserted lines for outpatient parenteral antimicrobial therapy (OPAT), where should one draw the line? Midline catheters, which end in peripheral veins, are thought to offer lower risks of infection and thromboembolism than peripherally inserted central catheters (PICCs).

A new cohort study supports this, finding that, for a device dwell of 14 days or less, midline catheters were associated with a lower risk of major complications (0.9% *v* 5.3%, adjusted hazard ratio 0.29 (95% CI 0.12 to 0.68)). However, the study design means that confounding by indication—whereby lower risk patients received a midline catheter—is hard to measure and exclude.

JAMA Intern Med doi:10.1001/jamainternmed.2024.5984

Prostate cancer in men with limited life expectancy

Don't wait until after prostate cancer diagnosis to consider life expectancy, advises an editorial in *JAMA*. This follows an observational study of veterans in the US that examined over-treatment of men with localised prostate cancer and limited life expectancy.

In men with low risk prostate cancer and a life expectancy of less than 10 years, rates of definitive treatment (surgery and radiotherapy) fell from 37.4% in 2000 to 14.7% in 2019, reflecting the introduction of new recommendations for active surveillance. In contrast, in those with higher risk disease, but where definitive treatment would still be classed as over-treatment due to a low life expectancy, rates of definitive treatment increased. For instance, 46.5% of men with high risk disease and a life expectancy of less than five years received definitive treatment in 2019 compared with only 17.3% in 2000.

JAMA Intern Med doi:10.1001/jamainternmed.2024.5994

Immunobridge over troubled water

Immunobridging methods used in the CANOPY trial of pemivibart have persuaded the US Food and Drug Administration (FDA) to grant emergency use authorisation for the monoclonal antibody as pre-exposure prophylaxis for covid-19 in adults and adolescents with moderate-to-severe immunocompromise. The primary efficacy outcome measure for the study is antibody titres to the currently circulating strain of covid-19, taken 28 days after receiving pemivibart.

The immunobridging method estimates the clinical effectiveness of pemivibart from antibody titres by linking these findings to neutralising antibody data for a previously effective monoclonal antibody—in this case adintrevimab against the delta variant of the SARS-CoV-2 virus.

N Engl J Med doi:10.1056/NEJMc24045

Tirzepatide for prediabetes

The SURMOUNT-1 trial included 1032 people with prediabetes and obesity who were allocated to take the new weight loss blockbuster tirzepatide or placebo. Rates of diabetes diagnosis were 93% lower in the tirzepatide group after three years of treatment, but, as ever, the absolute risk is important: progression to diabetes was not inevitable in the placebo group, occurring in just over one in 10 of the people (1.3% for tirzepatide, 13.3% for placebo; hazard ratio 0.07 (95% CI 0.0 to 0.1)).

The effect on patient-reported outcomes such as quality of life and physical functioning are also reported but hard to interpret, since the change in quality of life scores needed to make a noticeable difference to participants wasn't mentioned in the study or protocol.

N Engl J Med doi:10.1056/NEJMoa2410819

Winter is coming

We all know that multimorbidity is a risk factor for hospital admission and death in the winter months, but not all comorbidities are created equal and certain combinations of comorbidities are likely to come with a higher risk than others. A population based cohort study examined this in the UK in the winter of 2021-22. It found that the combination of cancer, chronic kidney disease, cardiovascular disease, and type 2 diabetes was associated with the highest risk of admission, with an adjusted incidence rate for hospital admission of 11 (95% CI 9.4 to 12.7) compared with no comorbidities.

The top 10 combinations of comorbidities for winter admission and death are listed—the authors hope that this approach can inform winter planning but warn against applying their findings directly to clinical practice.

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STATE OF THE ART REVIEW

Management of atrial fibrillation in older adults

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This is a summary of Clinical Review *Management of atrial fibrillation in older adults*. The full version can be read here: https://www.bmj.com/content/386/bmj-2023-076246

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Most people with atrial fibrillation are older adults, in whom atrial fibrillation co-occurs with other chronic conditions, polypharmacy, and geriatric syndromes such as frailty. Yet most randomised controlled trials (RCTs) and expert guidelines use an age agnostic approach. Given the heterogeneity of ageing, these data may not be universally applicable across the spectrum of older adults. This review synthesises the available evidence and applies rigorous principles of aging science. The full version of this summary, including a description of the methodology, is available on bmj.com.

Tailoring management for older adults

The figure shows a suggested approach to tailoring the management of atrial fibrillation in older adults according to multimorbidity, frailty, and prognosis.

Extrapolating guidelines

Simply extrapolating guideline recommendations on managing atrial fibrillation to all older adults is challenging because those with multimorbidity and frailty are under-represented in RCTs. Even trials that do include older adults may inadequately capture the heterogeneous health states of older adults, which then are not adequately covered in the guidelines.[32 33] Older adults' multimorbidity and associated treatment burden (for example, polypharmacy and drug-drug interactions) can negatively affect daily function and quality of life and increase the risk of harm from drugs and procedural therapy for atrial fibrillation.[4] Although preventing stroke and related morbidity and mortality remains an important goal, this benefit may be delayed or offset by treatment related adverse events.[2-36] Conversely, the paucity of data in older adults means that they may derive even greater benefit from treatment that has not yet been detected. Finally, older adults with multimorbidity and frailty often have competing health priorities and significant person-to-person variation in health goals.[5 37]

WHAT YOU NEED TO KNOW

- Atrial fibrillation predominantly affects older adults. Given the heterogeneous nature of ageing, disease focused randomised controlled trials and guidelines may not be applicable across the broad spectrum of this population
- To inform decision making, clinicians should assess an individual's level of function and frailty, and discuss their treatment goals, using evidence based shared decision making tools where available and appropriate
- Evidence needs strengthening to inform individualised care for the growing population of older adults with atrial fibrillation

Approaches to achieving individualised care

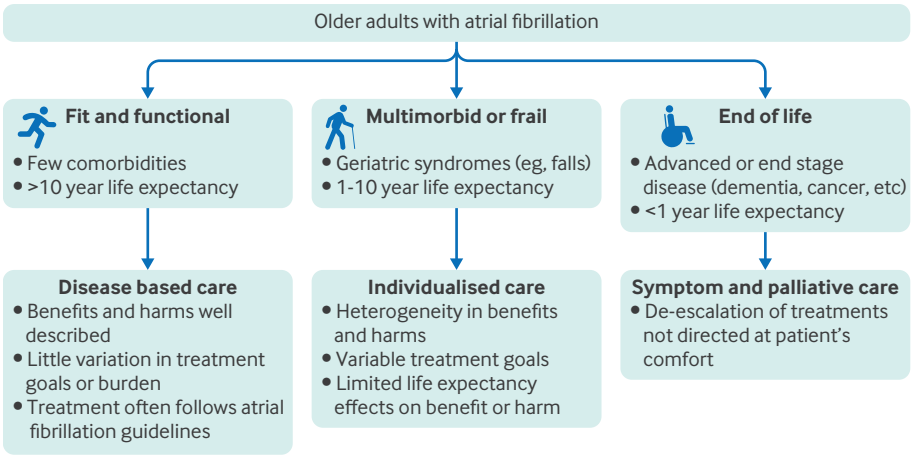
Clinicians should do an assessment of each patient's level of function and frailty. One practical means of assessing fitness and frailty is the Clinical Frailty Scale, which is a judgment based, nine point scale ranging from very fit to terminally ill.[39] The most in-depth method is comprehensive geriatric assessment, an interdisciplinary, multidimensional assessment of an older person's medical, psychological, and functional capacity.[40] Estimating prognosis is notoriously difficult, but validated prognostic indices may be helpful for improving assumptions that influence clinical decisions. ePrognosis (https://eprognosis.ucsf.edu/).

Treatment de-escalation

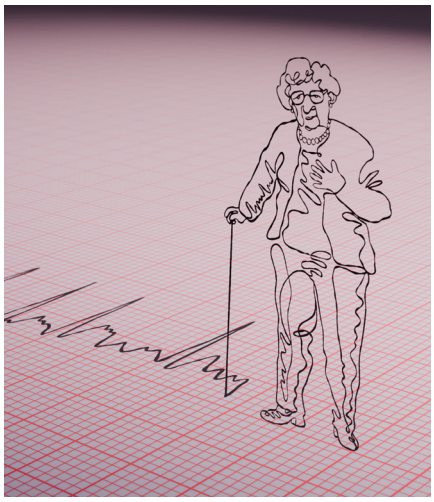
For older adults with atrial fibrillation nearing the end of life (that is, remaining life expectancy less than one year), palliative care focusing on symptoms (for example, palpitations and shortness of breath), quality of life, and comfort is appropriate. De-escalation of care should be considered when the risk of treatment related adverse events is deemed to outweigh the benefit or when the benefit is uncertain in the setting of advanced illness. The decision to stop anticoagulation should be individualised after consideration of the patient's prognosis (for example, terminal illness), risk of major bleeding versus stroke within the remaining lifespan, factors influencing quality of life (for example, laboratory monitoring), and the patient's and family's preference.

Population level systematic screening

Given its high prevalence in older adults, a concerted effort has been made to determine the value of screening for atrial fibrillation. Although the case for screening



Proposed approach to tailor clinical management of atrial fibrillation (AF) to older adults



MALCOLM WILLETT

following a stroke or transient ischaemic attack is clear, the evidence for primary screening is unclear. RCTs have shown that screening can increase the rate of diagnosis of atrial fibrillation. Whether this translates into fewer strokes and better health has not been demonstrated.[43]

Lifestyle intervention for secondary prevention

Obesity is a well established risk factor for development of atrial fibrillation. Observational studies that enrolled primarily older adults with atrial fibrillation in a supervised weight loss programme suggest a dose dependent effect of weight loss on reversal of atrial fibrillation from persistent to either paroxysmal or no atrial fibrillation.[53 54]

The relation between physical activity and incident atrial fibrillation is more complex.[55-60] A prospective study of older adults examining the association of exercise patterns and incidence of atrial fibrillation showed a U-shaped relation: although light and moderate intensity exercise was protective against development of atrial fibrillation, both inactivity and high intensity exercise were associated with increased incident atrial fibrillation.[61] The Systolic Blood Pressure Intervention Trial (SPRINT), an RCT randomising 8022 older adults at high risk of cardiovascular disease, showed that achieving systolic blood pressure <120 mm Hg led to a 26% lower risk of development of atrial fibrillation compared with targeting a goal of <140 mm Hg (hazard ratio 0.74, 95% confidence interval (CI) 0.56 to 0.98).[62] Among adults of all ages, alcohol consumption has been confirmed as a trigger of atrial fibrillation, whereas caffeine does not seem to have an effect.[63-66]

Symptoms and clinical manifestations of atrial fibrillation

Symptoms of atrial fibrillation can be non-specific and intermittent and may manifest differently in older compared with younger adults. Older adults are more likely to experience fatigue or generalised weakness as their main concern.[67] Syncope is uncommon in the absence of additional conduction disease, such as significant conversion pauses or rapidly conducting accessory pathways. Attributing any of these symptoms to atrial fibrillation may be more complex in older adults with multiple comorbidities, as concurrent lung disease, heart failure, other arrhythmias, or medication effects may confound attribution to specific causes.

Rate and rhythm control

The recently published 2023 American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society (ACC/AHA/ACCP/HRS) guidelines for the diagnosis and management of atrial fibrillation recommended a substantial shift toward greater and earlier use of rhythm control over rate control in both paroxysmal and persistent atrial fibrillation compared with earlier guidelines.[72] In the trials informing these guidelines, rhythm control improved a range of clinical outcomes with reassuring safety data, and older adults were relatively well represented, although the generalisability to the frail, multimorbid population remains a concern.

These guidelines give a strong recommendation for rhythm control in patients with heart failure and a moderate recommendation in symptomatic atrial fibrillation and in the first year after diagnosis of atrial fibrillation, among other groups. The guidelines draw on rigorous clinical trials, such as Early Rhythm-Control Therapy in Patients with Atrial Fibrillation (EAST-AFNET4), which found that patients randomised to early rhythm control experiencing a significantly lower rate of death from cardiovascular causes, stroke, or admission to hospital for worsening of heart failure or acute coronary syndromes.[72]

While EAST-AFNET4 included both anti-arrhythmic drugs and ablation as treatment strategies, selected at the investigator's discretion, other clinical trials have established that catheter ablation is superior to drug treatment in the maintenance of sinus rhythm and has low procedural complication rates.[73] Safety data

from these trials inform the risk-benefit discussion, as both clinicians and patients may be wary of ablation owing to perceived risk of complications and recovery time. Cardiac tamponade occurred in 0.8% of patients undergoing catheter ablation. Minor haematomas (2.3%) and pseudoaneurysms (1.1%) were the most common adverse events.

Early data suggest that catheter ablation may improve cognition in older adults with atrial fibrillation. Observational studies have associated atrial fibrillation with reduced brain volume, lower cognitive function, and greater risk of dementia.[77 78]

Heart failure and atrial fibrillation

Management of atrial fibrillation in heart failure requires special consideration because a bidirectional relation exists between atrial fibrillation and heart failure, wherein heart failure increases the risk of incident atrial fibrillation and atrial fibrillation worsens heart failure outcomes. Atrial fibrillation and heart failure often coexist,[29 82] and this may lead to compounded symptom burden, worsened quality of life, and mortality. Treatment recommendations in this setting are primarily extrapolated from data in younger populations. Presence of coexisting heart failure with reduced ejection fraction favours early rhythm control to maintain sinus rhythm, and catheter ablation should be considered over long term anti-arrhythmic therapy.[31 83]

Risks and benefits of oral anticoagulants for thromboprophylaxis

Current consensus guidelines consider all patients aged 75 years and older as being at high risk for atrial fibrillation related stroke and recommend anticoagulation.[27-72] However, the recently released European Society of Cardiology guidelines explicitly state that, "Not enough evidence is available for oral anticoagulants (OAC) in elderly patients, frail polypharmacy patients, those with cognitive impairment/dementia…."[27]. Importantly, the 2023 ACC/AHA/ACCP/HRS guidelines explicitly recommend against using bleeding risk prediction scores (for example, HAS-BLED, HEMORR2HAGES, ATRIA) because they poorly discriminate between people who develop bleeding and those who do not, and instead suggest mitigating reversible risk factors for bleeding.[72] Guidelines generally recommend direct oral anticoagulants (DOACs) over warfarin because of similar efficacy, generally lower bleeding rates, fewer drug-drug interactions, and less need for monitoring.[27-72]

Chronic kidney disease

Anticoagulation with DOACs for patients with mild or moderate chronic kidney disease (estimated glomerular filtration rate 30-59 mL/min or stage 3a and 3b) may be beneficial.[108] For patients with atrial fibrillation and end stage kidney disease, no RCT has shown net benefit from anticoagulation.[109-111] The use of anticoagulants in dialysis is associated with high bleeding rates and mortality.

HOW PATIENTS WERE INVOLVED IN CREATION OF THIS ARTICLE

A patient advocate and frequent research collaborator from the non-profit Arrhythmia Alliance (www.heartrhythmalliance.org) reviewed a draft of this review. They offered their perspective on aspects of atrial fibrillation that are of particular concern to older adults. In particular, they emphasised the need to distinguish between interventions for atrial fibrillation that treat symptoms (for example, ablation) and those that are preventive (for example, anticoagulation). They also highlighted ways to engage patients with scientific literature. Their suggested edits were incorporated into the final version where applicable.

Anticoagulant associated haemorrhage

One intervention that can reduce the bleeding risk associated with anticoagulants is de-prescribing antiplatelet agents, which confer a 1.5-fold to twofold increased bleeding risk without reducing thrombosis.[116-118] Expert consensus guidance on concurrent antiplatelet and anticoagulant medications recommends avoiding aspirin for primary prevention of cardiovascular disease, avoiding "triple therapy" (dual antiplatelet therapy plus anticoagulation) except very short duration in high risk clinical circumstances (for example, recent percutaneous coronary intervention), anticoagulation monotherapy for long term treatment of patients with an indication for antiplatelet therapy and anticoagulation (for example, stable ischaemic heart disease and six to 12 months after acute coronary syndrome or percutaneous coronary intervention), and anticoagulation monotherapy for patients with cerebrovascular disease without carotid stenting.[119]

Guidelines

Clinicians have multiple guidance statements covering management of atrial fibrillation to choose from. During the editorial process for this review, the ESC guidelines were updated in August 2024.[27] These guidelines offer dedicated sections on anticoagulation management in older adults and those with cognitive dysfunction and are largely concordant with evidence and guidance we report. The 2024 ESC guidance newly emphasises the lack of evidence to support anticoagulation in frail, multimorbid older adults, including those with dementia. The 2023 update to the ACC/AHA/ACCP/HRS guidelines for the diagnosis and management of atrial fibrillation incorporates a brief discussion of shared decision making, but mainly to highlight lack of data on improvement in clinical outcomes.[72] Guidance from the National Institute for Health and Care Excellence, from the UK and updated in 2021, calls for a "personalised package of care," including psychological and social support, contact information, and educational information.[30] Finally, the Canadian Cardiology Society guidance released in 2020 also promotes a multidisciplinary model of care for atrial fibrillation.[28]

Competing interests: None declared.

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Proactive therapeutic drug monitoring of biologic drugs in patients with immune mediated inflammatory disease: a clinical practice guideline

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Clinical question

In adult patients with inflammatory bowel disease, inflammatory arthritis (rheumatoid arthritis, spondyloarthritis, psoriatic arthritis), or psoriasis taking biologic drugs, does proactive therapeutic drug monitoring (TDM) improve outcomes as compared with standard care?

Context and current practice

Standard care for immune mediated inflammatory diseases includes prescribing biologic drugs at pre-determined doses. Dosing may be adjusted reactively, for example with increased disease activity. In proactive TDM, serum drug levels and anti-drug antibodies are measured irrespective of disease activity, and the drug dosing is adjusted to achieve target serum drug levels, usually within pre-specified therapeutic ranges. The role of proactive TDM in clinical practice remains unclear, with conflicting guideline recommendations and emerging evidence from randomised controlled trials.

The evidence

Linked systematic review and pairwise meta-analysis which identified 10 trials including 2383 participants. Inflammatory bowel disease, inflammatory arthritis, and psoriasis were grouped together as best current research evidence on proactive TDM did not suggest heterogeneity of effects on outcomes of interest. Proactive TDM of intravenous infliximab during maintenance treatment may increase the proportion of patients who experience sustained disease control or sustained remission without considerable additional harm. For adalimumab, it remains unclear if proactive TDM during maintenance treatment has an effect on sustained disease control or sustained remission. At induction (start) of treatment, proactive TDM of intravenous infliximab may have little or no effect on achieving remission. No eligible trial evidence was available for proactive TDM of adalimumab at induction (start) of treatment. No eligible trial evidence was available for proactive TDM of other biologic drugs in maintenance or at induction (start) of treatment.

Recommendations

The guideline panel issued the following recommendations for patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis:1. A weak recommendation in favour of proactive TDM for intravenous infliximab during maintenance treatment 2. A weak recommendation against proactive TDM for adalimumab and other biologic drugs during maintenance treatment 3. A weak recommendation against proactive TDM for intravenous infliximab, adalimumab, and other biologic drugs during induction (start) of treatment.

Understanding the recommendations

When considering proactive TDM, clinicians and patients should engage in shared decision making to ensure patients make choices that reflect their values and preferences. The availability of laboratory assays to implement proactive TDM should also be considered. Further research is warranted and may alter recommendations in the future.

How this guideline was created

An international panel including patient partners, clinicians, and methodologists produced these recommendations based on a linked systematic review and pairwise meta-analysis which identified 10 trials including 2383 participants. The panel followed standards for trustworthy guidelines and used the GRADE approach, explicitly considering the balance of benefits and harms and burdens of treatment from an individual patient perspective.

Why is the guideline needed?

Inflammatory bowel disease, inflammatory arthritis (rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis), and psoriasis are chronic immune mediated inflammatory diseases with a high burden on patients' health, quality of life, and use of healthcare resources.[1-7] Emerging treatment options for these conditions have improved patient outcomes over the past two decades, especially after the introduction of biologic drugs such as tumour necrosis factor inhibitors (TNFi).[3-10] Biologic drugs are used by a substantial proportion of patient populations worldwide, with usage varying with disease and geographical location.[11-16]

Despite these advances, some patients do not reach disease remission and/or disease control.[3-7] Biologic

Visual summary of recommendation

Population

These recommendations apply only to people with these characteristics:

Adults with immune-mediated inflammatory diseases

Being treated with or starting treatment with infliximab, adalimumab, or other biologic drugs

- ✔ Inflammatory bowel disease
- ✔ Inflammatory arthritis
  - Rheumatoid arthritis
  - Spondyloarthritis
  - Psoriatic arthritis
- ✔ Psoriasis

May or may not apply to: ? Other immune-mediated inflammatory diseases

Does not apply to: ✖ Inflammatory diseases that are not immune-mediated

See an interactive version of this graphic online

https://bit.ly/bmj-rr-bio

Recommendations

1

Standard care (Reactive or no monitoring)		Proactive monitoring	
Strong	Weak	**Weak**	Strong

Adults receiving maintenance therapy with infliximab

> We suggest proactive therapeutic drug monitoring

2

Standard care (Reactive or no monitoring)		Proactive monitoring	
Strong	**Weak**	Weak	Strong

Adults receiving maintenance therapy with adalimumab and other biologics

> We suggest not using proactive therapeutic drug monitoring

3

Standard care (Reactive or no monitoring)		Proactive monitoring	
Strong	**Weak**	Weak	Strong

Adults starting therapy with infliximab, adalimumab, and other biologics

> We suggest not using proactive therapeutic drug monitoring

Key practical issues

Recommendation 1

- Requires access to laboratory with validated analyses of infliximab serum drug levels and anti-drug antibodies
- Drug dosing is adjusted to keep serum drug levels in a defined therapeutic range, typically by using an algorithm
- There is little evidence on how often proactive monitoring should be done to be beneficial

Recommendations 2 and 3

- Proactive therapeutic drug monitoring involves regularly measuring serum drug levels and anti-drug antibodies

Values and preferences

There was no evidence about how individuals with an immune mediated inflammatory disease would judge the success of proactive monitoring.

Recommendation 1

An assumption was made that most patients would value proactive monitoring if it increased sustained disease control, sustained remission, or both by 5% without causing additional serious harm

Recommendations 2 and 3

An assumption was made that most patients would prefer standard care, given the very low certainty of the evidence informing this recommendation

Linked resources in these BMJ Rapid Recommendations

- Zeraatkar D, Pitre T, Kirsh S, et al. Proactive therapeutic drug monitoring of biologic drugs in patients with inflammatory bowel disease, inflammatory arthritis, and psoriasis: systematic review and meta-analysis. *BMJMED* 2024;3:e000998.
- MAGICapp. An expanded version of the guideline with multi-layered recommendations, evidence summaries, and decision aids for use on all electronic devices. https://app.magicapp.org/#/guideline/nBAezL.

drugs are usually dosed according to body mass and/or fixed dosing to all patients, and large variations in patient serum drug levels are seen even among patients on the same dose. For several of these drugs (including infliximab and adalimumab), higher serum drug levels are associated with treatment effectiveness.[17 18] A proportion of patients develop anti-drug antibodies, which can block the action of the drug and increase drug clearance, reducing the effectiveness of the treatment.[19-22]

Therapeutic drug monitoring (TDM) of biologic drugs is being investigated as a method to optimise treatment to improve effectiveness and reduce side effects.[23] TDM may be proactive or reactive. Proactive TDM is the measurement of drug concentrations and anti-drug antibodies at timed intervals irrespective of disease control. Reactive TDM is the measurement of drug concentrations and anti-drug antibodies triggered by a clinical event (a disease flare, for example). Both proactive and reactive TDM aim to optimise individual patient dosage regimens and therefore improve outcomes. Proactive TDM has the additional aim of preventing disease flares.[24] With proactive TDM, individual patient drug doses are adjusted based on the results of periodic measurements to avoid patients falling outside the target serum drug levels.[17] Practical information on serum drug and anti-drug antibody measurements can be found on MAGICapp: https://app.magicapp.org/#/guideline/7735/section/146829.

Despite randomised controlled trials (RCTs) showing promising results with proactive TDM of biologic drugs, current guideline recommendations diverge concerning whether to use this novel approach, when to use it, and for what diseases.[6-27] Surveys among US, UK, Indian, and Scandinavian gastroenterologists show that proactive TDM of TNFi has been variably adopted in clinical practice (20-60%), reflecting the diverging guidelines.[28-31] We have not identified any guideline applying appropriate standards and methods that includes the most recent trial evidence. Our guideline was triggered by a RCT investigating the use of proactive TDM in the maintenance treatment of inflammatory arthritis, inflammatory bowel disease, and psoriasis with intravenous infliximab.[24] This trial reported a benefit with proactive TDM across inflammatory bowel disease and inflammatory arthritis, with no associated harm.

About this guideline

This guideline contributes to the BMJ Rapid Recommendations series—a collaborative effort between MAGIC Evidence Ecosystem Foundation and *TheBMJ*—which is focused on providing clinicians with trustworthy recommendations for potentially practice changing evidence. The box gives linked resources for this guideline, including a systematic review and meta-analysis evaluating proactive TDM of biologic drugs in immune mediated inflammatory diseases.[32] This systematic review synthesised findings from 10 randomised controlled trials, with a total of 2383 patients.[32]

An international panel that included patients, healthcare professionals, and methodologists created these recommendations following globally accepted standards for trustworthy guidelines and using the GRADE approach.[33] No panel member reported financial conflicts of interest. Intellectual and professional conflicts were minimised and managed. For more information on how this guideline was created please see MAGICapp (https://app.magicapp.org/#/guideline/nBAezL). Briefly, the recommendations synthesise the best available evidence on benefits and harms, the expertise and experience of the guideline panel (which also included patient representatives), and what we understood about the values and preferences of patients living with inflammatory bowel disease, inflammatory arthritis, or psoriasis.

The recommendations also take into account practical issues, geographical variation in practice, implementability, and patient burden. The recommendations do not explicitly take into account cost effectiveness or other healthcare system factors as we take an individual patient perspective.

The recommendations

Recommendation 1: For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis receiving treatment (maintenance) with intravenous infliximab we suggest proactive TDM rather than reactive TDM or no TDM

Understanding the recommendation—When making a weak recommendation for the use of proactive TDM in patients taking intravenous infliximab as maintenance treatment, we recognised the potentially important benefit of an absolute 14% rate increase (ranging from 8% to 22% increase) in sustained disease remission and/or disease control as compared with standard care (no TDM or reactive TDM) with no evidence of harm. We assumed that most patients would value proactive TDM if it increased sustained disease control and/or sustained remission by 5% without causing additional serious harm. As the lower bound of the 95% confidence interval is 8%, we considered it a significant benefit compared with standard care.

Nevertheless, the anticipated benefits and harms were informed by low to very low certainty evidence from four RCTs with a total of 872 patients identified in

the systematic review.[32] This uncertainty precluded us from making a strong recommendation for the use of TDM in these patients. The low certainty evidence rating stemmed from the risk of bias in the RCTs (owing to lack of blinding), indirectness in the body of evidence owing to grouping different diseases together (box 2, bmj.com), and limited follow-up of patients.

Finally, a key element leading to a weak (instead of a strong) recommendation was the concern about the influence of disease specific factors such as a lower risk of flare consequences in psoriasis and inflammatory arthritis, and a higher risk of flare consequences in inflammatory bowel disease (need of hospital admission, surgical intervention).

Recommendation 2: For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis receiving treatment (maintenance) with adalimumab or other biologic drugs we suggest not using proactive TDM

Understanding the recommendation—In agreeing on a weak recommendation against the use of adalimumab, we were mostly concerned about the very low certainty evidence for use of proactive TDM during maintenance treatment: the only evidence available informing critical outcomes (sustained remission and/or sustained disease control) was a small trial with 78 children and adolescents, a group outside the scope of this guidance.[37] A larger body of evidence (three studies, 633 patients) was available for the outcome remission (measured at the end of the follow-up period) but this estimate was imprecise, ranging from a reduction of 9% remission events to an increase of 30% in absolute terms. The very low certainty of the evidence combined with our decision to place a high value on avoiding a patient burden of potential extra clinic visits for blood sampling (as adalimumab is most often self-administered subcutaneously at home), resulted in a weak recommendation against proactive TDM for adalimumab, while waiting for better trial evidence to become available.

For other biologic drugs, no trial evidence was available for proactive TDM, leading to a weak recommendation against proactive TDM with other biologics.[32] A strong recommendation against proactive TDM during maintenance treatment with adalimumab or other biologic drugs was deemed inappropriate given the uncertainty in the evidence added to the biological plausibility of a possible beneficial effect, especially for adalimumab. In this context, on a case-by-case basis, depending on values or preferences (ie, higher value placed on avoiding disease flares), some patients—such as those at highest risk of disease flares with major consequences—may prefer to receive the intervention.

A "weak recommendation against" may still offer room for the use of proactive TDM on an individual basis. In general, patients at the highest risk of disease flares will benefit most from proactive TDM (box 2, bmj.com).

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Our panel included two patients living with inflammatory bowel disease and inflammatory arthritis. Their perspectives helped the panel to consider better the values and preferences associated with decision making related to proactive TDM of biologic drugs.

Our patient partners have contributed in various ways, including but not limited to: collaborating in the identification of priority areas, drawing from their own experiences and those of the broader patient community; participating in guideline development meetings, where their perspectives were integral in crafting recommendations that resonate with the needs and preferences of patients; reviewing draft versions of the guideline, offering feedback from a patient's viewpoint to enhance clarity, accessibility, and relevance; and validating the final recommendations to ensure they are truly reflective of patient values, preferences, and experiences.

Recommendation 3: For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis starting treatment with intravenous infliximab, adalimumab, and other biologic drugs we suggest not using proactive TDM

Understanding the recommendation—The weak recommendation against proactive TDM of intravenous infliximab at the start of treatment (induction scenario) is supported by the lack of benefit observed in one study with 398 patients.[38] The effect of proactive TDM of intravenous infliximab could vary from a reduction of 8% remission events to an increase of 11% in absolute terms. Additionally, the certainty of the evidence was very low owing to the risk of bias, imprecision, and indirectness. We felt it inappropriate to extrapolate indirect evidence from maintenance to the induction (start of treatment) scenario given the differences in the induction scenario (when patients are experiencing a flare), and drug dosing may be greater than during maintenance treatment, thus limiting the effect of dose adjustments and reducing the risk of generating anti-drug antibodies. This reduces the benefit of proactive TDM.[19]

The weak recommendation against proactive TDM for induction with adalimumab and other biologics was because of the lack of eligible evidence (RCTs). In the absence of evidence, we agreed that most well informed patients would prefer not to have the intervention. We also judged it inappropriate to extrapolate data on intravenous infliximab to adalimumab and to other biologics. Infliximab is expected to be more immunogenic than other biologics, which increases the risk of anti-drug antibodies and consequently the benefit from proactive TDM. Patient burden is also different between infliximab, which is given intravenously, and adalimumab, which is self-administered subcutaneously.

Competing interests: None declared.

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Find the full version with references at doi: 10.1136/bmj-2024-079830

CASE REVIEW

Acral and periorificial scaly erythematous plaques in a child

A 7 year old girl presented with a six year history of pruritic erythema on her face and extremities. She had been breastfed after birth, introduced to solid foods gradually, and completely weaned at 1 year of age. Symptoms began after weaning. Eczema and atopic dermatitis were repeatedly diagnosed, but symptoms did not improve with use of oral antihistamines, topical corticosteroids, and emollients. The patient also experienced diffuse hair thinning, intermittent diarrhoea, and lack of energy. There were no developmental concerns. The patient had no additional symptoms and no relevant medical history, but a younger brother had similar albeit milder symptoms. On examination, scaly erythematous plaques were observed predominantly involving the fingers and toes, inner canthus and perioral, perinasal, and perianal areas (figure). Results of laboratory tests showed decreased levels of alkaline phosphatase (ALP) (25 U/L, normal range 30-100 U/L) and zinc (3.58 mg/L, normal range 3.7-20.0 mg/L). Other laboratory test results, including full blood count, biotin, and IgE levels were within normal limits.

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

Submitted by Jiaping Zhu, Ran Mo, and Yiqun Jiang

Patient consent obtained.

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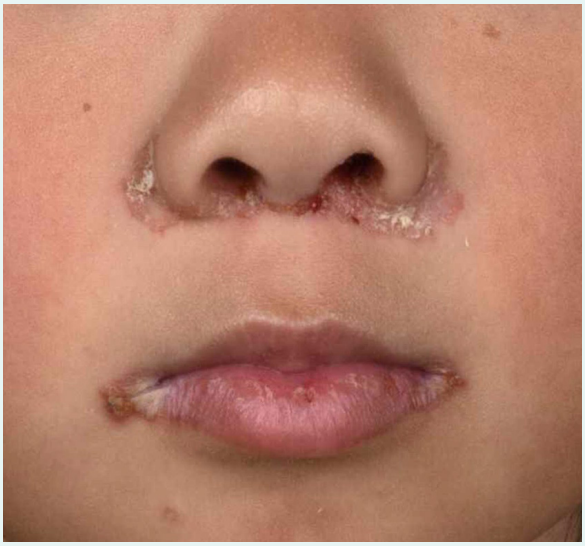

Scaly erythematous lesions around the mouth and perinasal skin-mucosal junction

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answers

CASE REVIEW **Acral and periorificial scaly erythematous plaques in a child**

1 What are the differential diagnoses?

Differential diagnoses include atopic dermatitis, psoriasis, and zinc deficiency. Other nutritional deficiencies can present similarly—in particular, both biotin and zinc deficiencies can result in periorificial dermatitis and alopecia. Biotin and zinc deficiencies might be inherited or nutritional (acquired) and would show as low serum levels. See table on bmj.com for full details.

2 What is the most likely diagnosis?

Acrodermatitis enteropathica—an inherited zinc deficiency disorder. This condition has a global incidence of about one in 500 000, with no racial predisposition reported. Typical clinical manifestations are acral and periorificial dermatitis, diarrhoea, and alopecia, but only 20% of patients exhibit this classic triad simultaneously. Other possible manifestations include mood and psychiatric symptoms and, in severe cases, growth problems and secondary infections. Inherited and nutritional zinc deficiencies have similar clinical presentations; however, in inherited deficiencies, the symptoms tend to occur after weaning, whereas nutritional zinc deficiency in newborns typically occurs during periods of exclusive breastfeeding. Low zinc and ALP levels strongly support a diagnosis of zinc deficiency. Genetic testing will confirm the diagnosis of inherited acrodermatitis enteropathica.

3 How would you manage this patient?

Treatment for acrodermatitis enteropathica usually begins with high dose oral zinc supplementation (3 mg/kg/day of elemental zinc) and monitoring of response and serum zinc levels, followed by individualised adjustment. Lifelong treatment is necessary, with regular monitoring of serum zinc and zinc dependent enzyme ALP, and of copper levels, as zinc can competitively inhibit copper absorption.

LEARNING POINTS

- Consider zinc deficiency in patients with chronic dermatitis localised to the acral and periorificial areas.
- Acrodermatitis enteropathica is an autosomal recessive genetic disorder, with a clinical presentation that might include some or all the classic triad of dermatitis, diarrhoea, and alopecia.
- Zinc supplementation can rapidly relieve the symptoms of acrodermatitis enteropathica, but lifelong treatment is necessary.

PATIENT OUTCOME

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LEARNING MODULE

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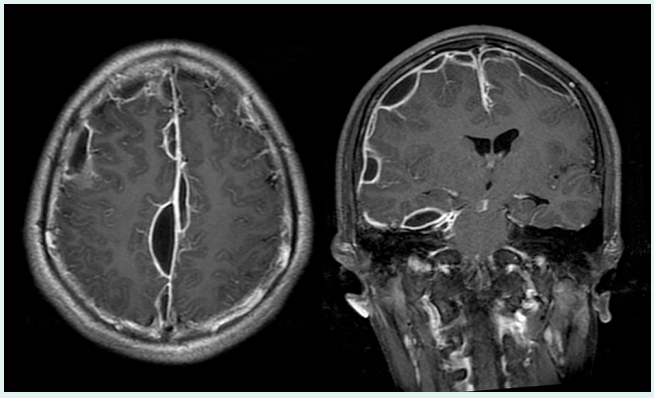
Multiple contrast enhancing subdural lesions

This previously well teenager presented with a three week history of fever, headache, and a single episode of tonic-clonic seizure. On examination, he responded slowly to verbal commands and motor stimuli, and muscle strength in all four limbs was decreased (graded 4/5 on the Medical Research Council scale). Brain magnetic resonance imaging (MRI) showed multiple contrast enhancing subdural lesions. Based on the MRI finding, differential diagnoses included empyema, tuberculosis, neurocysticercosis, and neoplasm.

Brain biopsy, metagenomic next generation sequencing, and polymerase chain reaction assay identified empyema caused by *Porphyromonas endodontalis*. This Gram negative anaerobic bacterium is typically found in infected dental root canals and submucosal dental abscesses, and is not often detected beyond the oral cavity. Notably, the patient did not report any signs or symptoms of oral disease. Symptoms resolved completely after surgical drainage and intravenous antibiotics for eight weeks. Owing to the severity of the presentation, the patient was screened for immunodeficiencies. Results of complete blood count, quantitative immunoglobulins, and HIV screening were within normal limits.



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Adverse pregnancy outcomes in women with epilepsy

A large multinational study in the Nordic countries which compared pregnancy outcomes of women with epilepsy with those of women without epilepsy finds that the risk of a range of serious complications including pre-eclampsia, embolism, disseminated intravascular coagulation, cerebrovascular events, and mental health conditions is substantially raised (*JAMA Neurol* doi:10.1001/jamaneurol.2024.2375). Women with epilepsy also had a higher risk of death in childbirth than women without epilepsy.

Sensor detected hypoglycaemia

At least half of the hypoglycaemic episodes experienced by people using insulin for type 1 or 2 diabetes are asymptomatic, even at levels below 3.0 mmol/L. On the other hand, many reported symptomatic episodes of hypoglycaemia occur at levels above 3.9 mmol/L. These findings come from 600 people who wore a continuous glucose monitoring sensor for 10 weeks while recording hypoglycaemic episodes on a smartphone app (*Diabetes Care* doi:10.2337/dc23-2332).

Hearing loss and incident Parkinson's disease

Earlier this year, Minerva noted a study from the US showing that mortality in people with hearing loss was raised but mitigated by wearing hearing aids (*Lancet Healthy Longev* doi:10.1016/S2666-7568(23)00232-5). Electronic health records of more than three million US veterans suggest that something similar is true for Parkinson's disease (*JAMA Neurol* doi:10.1001/jamaneurol.2024.3568). In the 10 years after a baseline audiogram, cases of Parkinson's disease were commoner in those with hearing loss than in those with normal hearing. The increase in risk was attenuated in those who had hearing aids.

Cardiovascular disease mortality in the United States

Since 2010, the trends in cardiovascular disease in the US have stagnated. After decades of improvement, the declining mortality from cardiovascular disease at both midlife (ages 40-64) and old age (ages 65-84) has flattened out. A geographical analysis finds that this applies in nearly every state and at all income levels, even the wealthiest states (*Am J Epidimiol* doi:10.1093/aje/kwae414).

Screening for tuberculosis

Historical data from Glasgow, Scotland, allowed a reassessment of the impact of a mass screening campaign which took place over four weeks in 1957 (*PLoS Med* doi:10.1371/journal.pmed.1004448). The campaign succeeded in screening three quarters of the adult population of the city using miniature chest radiography. More than 2000 people were diagnosed with pulmonary tuberculosis. Over the next few years, numbers of new cases of tuberculosis declined sharply. Active case finding, with new screening tools and technologies, might be worth considering today in locations where the burden of tuberculosis is as high as it was in Glasgow 70 years ago.

Types of curiosity

According to an analysis of anonymised browsing data from half a million users of Wikipedia, humans fall into three broad categories when they search for information (*Sci Adv* doi:10.1126/sciadv.adn3268). The busybody scouts for loose threads of novelty, the hunter follows a linear path pursuing specific answers, and the dancer leaps creatively across eclectic areas of knowledge. One conclusion is that individuals vary in their styles of curiosity and that understanding this diversity might be important when building creative teams.

Delayed consequences of violence

A register study from Finland and Sweden identified 130 000 people who had been victims of violence severe enough to require medical treatment for their injuries (*PLoS Med* doi:10.1371/journal.pmed.1004410). In comparison with both age and sex matched population controls and their unaffected siblings, they were at least twice as likely to develop a psychiatric disorder, engage in suicidal behaviours, or die prematurely. These increased risks persisted for two years after the violent event.

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