education

FROM THE JOURNALS Edited highlights of weekly research reviews

Waiting for thrombolysis

One of the many terrifying aspects of our healthcare system that we seem to accept is ambulance response times. In England last December the median response time for a category 2 emergency call—which includes stroke—was 45 minutes, compared with a target of 18 minutes. Of the callouts, 10% had a wait time of 1 hour 40 minutes or longer.

For those unlucky people who are waiting this long and have had a stroke amenable to intravenous thrombolysis (IVT) followed by thrombectomy, the time for any added benefit from IVT and thrombectomy versus thrombectomy alone is nearly up before the ambulance arrives, according to a new meta-analysis. The study looked at individual patient data from six randomised controlled trials, assessing levels of disability at 90 days. Benefits of IVT plus thrombectomy versus thrombectomy alone were greater the sooner after symptom onset that treatment was received, and by 2 hours 20 minutes no statistically significant difference between the two interventions was found.

JAMA doi:10.1001/jama.2024.0589

Testing times

One of the many lessons from the story of Theranos—the healthcare startup whose founder, Elizabeth Holmes, is now serving an 11 year prison sentence for fraud and conspiracy—is that people love the idea of rapid testing. Investors loved it so much they pumped in $700m despite the fact that the rapid blood testing technology didn't work. But even if the tests had worked, would they have been a game changer?

A systematic review and meta-analysis looked at randomised clinical trials of people in emergency departments having rapid viral testing. Researchers measured the impact of rapid viral tests on antibiotic prescribing and found that testing made no difference. But I'm not sure that will stop tests being used. To test is best, right?

JAMA Intern Med doi:10.1001/jamainternmed.2024.0037

Central line complications

On a harrowing night as an out-of-my-depth F2 on-call doctor for a renal ward, I asked for help from a registrar. "Put a central line in" was their advice. When I told them I couldn't, they shamed and bullied me for the rest of the night.

This all came flooding back to me while reading a systematic review and meta-analysis of central venous catheters. It found that serious complications occur 30 times for every 1000 catheters placed—including arterial cannulation (3 per 1000), arterial puncture (16 per 1000), and pneumothorax (4 per 1000). Ultrasound guidance reduced the risk of arterial puncture and pneumothorax by around 80% and 75%, respectively. That night put me off hospital medicine, but I'm still glad I didn't do as I was told.

JAMA Intern Med doi:10.1001/jamainternmed.2023.8232

Plastic people

Expect to hear a lot more about microplastics and nanoplastics (MNPs). A prospective observational study in the *New England Journal of Medicine* has two remarkable and troubling findings: first, the researchers found that 150 people out of 257 who underwent carotid endarterectomy for asymptomatic carotid artery disease had the microplastic polyethylene in their carotid artery plaque. Second, those with MNPs within their plaques were far more likely to reach the primary endpoint of myocardial infarction, stroke, or death from any cause at 35 weeks' follow-up (hazard ratio 4.53 (95% confidence interval 2.00 to 10.27), P<0.001).

However, this observational study doesn't prove causality and didn't adjust for common confounding factors such as socioeconomic status.

N Engl J Med doi:10.1056/NEJMoa2309822

Covid and autoimmune inflammatory disease

Can covid-19 trigger autoimmune inflammatory rheumatic diseases (AIRDs)? Investigators looked at data from over 20 000 000 people in Japan and South Korea. During the 2020/21 study period an AIRD diagnosis was more likely in the 30 days after covid-19 than in the 30 days after flu (both defined as a positive PCR test result, adjusted hazard ratio, 1.30 (95% confidence interval, 1.02 to 1.59)).

However, a response to the research paper in *Annals of Internal Medicine* is sceptical of any causal link: symptoms of AIRDs such as rheumatoid arthritis, myositis, polyarteritis nodosa, and lupus often take months, or sometimes years, to be recognised and even once suspected the investigations required to make a diagnosis can take several weeks (or months if you're in the UK) to arrange. The response suggests the results may be explained by ascertainment bias, owing to higher levels of scrutiny in people diagnosed with covid-19 than those with flu.

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PRACTICE POINTER

Advance and future care planning

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CPD READING
0.5 HOURS

WHAT YOU NEED TO KNOW

- Advance (or future or anticipatory) care planning is an umbrella term for many documents and guidelines in use in the UK today such as DNACPRs (do not attempt cardiopulmonary resuscitation), treatment escalation plans, advance directives, and ReSPECT forms
- Advance care planning often involves a multidisciplinary team approach with many conversations occurring between patient, clinician, and next of kin at various points in the patient's life
- Recommendations made in advance care plans are often multifaceted and require a careful and considered approach, especially as they can carry legal significance

Patients, relatives, and healthcare professionals recognise the value of pre-emptive consideration and documentation of what treatments might be wanted and beneficial in an emergency. In the past, the most common advance planning documentation was a "do not attempt cardiopulmonary resuscitation" (DNACPR) notice. These communicate that one specific treatment—cardiopulmonary resuscitation (CPR)—should not be attempted,[1] often without contextualising this decision within overall goals of care.[2] A growing recognition of the importance of respecting patient autonomy[3] has contributed to a shift towards more patient centred conversations and increasing integration of patient values and wishes into the decision making process.[2 4] However, this process of shared decision making continues to be often initiated only at the point of serious illness and focused on specific treatments.[1]

Patients and healthcare professionals can use many different tools to make sure that future treatment aligns with a patient's wishes. All these tools fall under the umbrella of advance (or future or anticipatory) care planning[5] but vary in who leads them and whether they focus on specific treatments or goals of care. These tools are summarised in the table. This article outlines the different forms of advance care planning available to patients and clinicians and answers many of the common questions that arise around advance decision making.

When is the best time to discuss goals of care and treatment recommendations?

Early, detailed, and person centred discussions facilitate the alignment of treatment decisions and a patient's values in future situations when they may not have the capacity to engage in meaningful conversations.[15-17] Specific triggers for starting these conversations might include admission into a care home or hospital, planning major surgery, or an appointment for chronic conditions such as chronic obstructive pulmonary disease or heart failure. Clinicians should consider starting conversations and instigating necessary documentation if an individual feels strongly about treatments or outcomes or a clinician thinks physical deterioration is likely. Often more than one conversation will be needed, and recommendations and documentation surrounding advance care planning should be reviewed regularly. These conversations should first establish a shared understanding of the patient's condition and what outcomes they value before making recommendations about treatments (including attempted CPR) that you think they would and would not benefit from.

How do patients feel about discussing advance care planning?

Every patient and situation is different. A systematic review in 2018[18] suggests that even though many patients experience ambivalent feelings about advance care planning, most are comfortable being open about their goals and preferences for future care and many report benefits of having advance care planning conversations. Having this conversation is ultimately driven by a desire to respect an individual's autonomy and should not be done against a patient's will. If an individual seems uncomfortable having a conversation, then they should be given the opportunity to return to the topic at a later date, perhaps with a family member, or having had time to learn more about advance care planning.

Advance care planning perioperatively and intraoperatively

1 *Advance decisions to refuse treatment (ADRT) are legally binding*—If a person has an ADRT stating they would not want CPR, the surgeon and/or anaesthetist should explain that some elements of CPR may be needed intraoperatively or perioperatively, and the ADRT may need to be suspended temporarily. Full advice has been published by the Association of Anaesthetists.[21]

2 *All other advance care planning documents are recommendations and are not legally binding*—During an operation, all treatments (including CPR) should be given to treat potentially rapidly reversible problems. This should be explained to the patient, who may be concerned about what will and will not be done.

3 *A DNACPR or treatment escalation plan is not a contraindication to having surgery*—These forms are automatically suspended during the operation. In discussing the situation, the clinician should inform the patient of possible intraoperative or perioperative complications that may occur (including where their care will be provided afterwards such as the intensive care unit). Since the anticipated prognosis can change over time, a DNACPR or treatment escalation plan (TEP) should be rediscussed postoperatively.[21]

Different forms of advance care planning

Who initiates the plan?	Treatment or goal oriented	Comments
Do not attempt cardiopulmonary resuscitation (DNACPR) notices		
Clinician led	Treatment specific	Clinicians write DNACPR recommendations when a person's organ function, frailty, or irreversible disease indicates that attempting CPR would not be successful[2 6] or at the person's own request. They are not legally binding and so do not need to be rescinded perioperatively or intraoperatively. A DNACPR form only refers to withholding resuscitation in the event of cardiac arrest; all other aspects of care should continue.[7] DNACPR notices are utilised across various healthcare settings, spanning community, secondary, and tertiary care. Also known as "Not for resuscitation" (NFR), such as in Australia.
Treatment escalation plans		
Clinician led	Treatment specific	Treatment escalation plans (TEPs) are plans which record medical interventions unlikely to be beneficial to a patient or contrary to their wishes. Some TEPs can record specific treatments that should be considered.[2] They can also incorporate a DNACPR notice section. TEPs are most often written in hospitals in response to the deteriorating patient[8 9] and are initiated by clinicians. They should be clearly recorded, reviewed regularly, and be made easily accessible for emergency situations. They are known as Medical Orders for Scope of Treatment in Canada.
Advance decisions to refuse treatment (ADRT)		
Patient led	Treatment specific	This is a patient initiated legally binding document explicitly delineating what treatments they would not want in the future. These can be written to ensure that a person's healthcare wishes and values are to be respected and followed when they no longer have capacity to actively participate in decision making about their care. Advance decisions to refuse treatment (ADRT) in England and Wales and "Living will"[10] in the US are two examples of legally binding documents: If a clinician ignores the directions on these forms they could face criminal prosecution or civil liability.[11 12] In general, clinicians do not need to be involved in the writing these. In England and Wales, the patient must have mental capacity under the 2005 Mental Capacity Act to articulate these preferences, and they must be witnessed, signed, and dated. The treatment refusal decisions expressed in an ADRT are legally equivalent to preferences or decisions expressed by a patient with capacity. It is recommended that patients regularly review their ADRT as treatment decisions made a long time ago may raise doubts of continued validity, particularly if the patient develops a new condition or medical advances in treatments occur. In cases of disagreement about the existence, validity, or applicability of an advance decision, the Court of Protection in England and Wales can review the case and reach a verdict. While the court makes this decision, a clinician can legally continue to provide active treatment.
Goals of care document (eg, ReSPECT forms)		
Co-created by patient and clinician	Outcome focused. Can include details of specific treatments	Goals of care documents provide guidance to clinicians about which treatments would or wouldn't be wanted in an emergency in the event of a patient not having capacity to make decisions for themselves. The *Recommended Summary Plan for Emergency Care and Treatment (ReSPECT)* is one example of this. The process involves establishing a shared understanding of: 1. The person's diagnoses, prognosis, and quality of life 2. Outcomes that the person values and fears 3. What treatments would or wouldn't be likely to result in the outcomes which are valued by the person 4. Which treatments, including CPR, are or are not recommended by the clinician in this context. The ReSPECT discussions are summarised on a two page proforma held by the person and on digital records. It is recognised and respected in the community through to secondary care and is currently being adopted in England, Scotland, and Northern Ireland.[13 14] It is reviewed frequently to ensure that the form complies with the individual's wishes while their disease or illness progresses or changes. "Shared goals of care" in New Zealand offers a similar approach.

How senior do you have to be to have an advance care planning discussion?

It's not about seniority, it's about competency. Any clinician can open a discussion with a patient about what health outcomes they value and fear. A patient with a complex clinical condition may need a specialist consultant to advise on, for example, whether and in what circumstances they would benefit from intensive care. For other patients, early career doctors, or specialist nurses will have enough expertise to make appropriate recommendations. In all situations, the recommendations made should be discussed, agreed, and documented with a senior responsible clinician at the earliest opportunity.

How would you approach a family that disagrees with the advance care plan?

Conversations with families surrounding advance care planning requires establishing a shared understanding of the person's diagnosis and prognosis and understanding what the person values and fears. This information can be used to recommend treatments that would be of benefit to them, and to explain why some would not be of benefit. If the family disagrees with recommendations in the first instance, check their understanding, let them know that their views are important, and then offer them a second opinion. If they still disagree, then it is wise to seek legal advice. In the UK, neither a patient nor those close to them can demand a treatment from the clinician responsible for their care if the clinician believes it would not benefit the patient.[3 19] However, it is important to ensure that patients' and relatives' rights are being respected and that you are acting within the law in the setting in which you are working.

Conversations should first establish a shared understanding of the patient's condition and what outcomes they value before making recommendations about treatments

EDUCATION INTO PRACTICE

- Recall the different types of advance care planning documentation encountered locally and globally. Understand the rationale behind the applications of these in different settings
- Consider situations relating to discussions about CPR where you must be careful to understand legislation or case law: how will your practise change?
- How will this article influence and modify the way you have discussions about CPR with patients or their relatives?

What should you do if you disagree with a senior doctor's decision regarding advance care planning?

Disagreeing with your senior's decision can be challenging. Be honest with them, explain your concerns, and ask them to explain their reasoning. This may prompt a discussion about the patient's condition and prognosis and address any assumptions or biases that are present. It can be a good starting point for reviewing an advance care plan.

What are common misconceptions about DNACPRs?

A lot of misunderstanding still surrounds DNACPRs, with both patients and clinicians wrongly interpreting them as meaning that other treatments, in addition to CPR, are to be stopped or withheld.[20] It is important to address this directly with patients, family members, and colleagues by discussing overall goals of care and clarifying which treatments are still recommended. You can emphasise that, while there may be treatments that are not recommended, there is no limit to the care that clinicians will give (so try to avoid phrases such as "ward based ceiling of care"). Another common misunderstanding is that a DNACPR is legally binding and needs to be rescinded during surgery. DNACPRs are not legally binding, and act only as a recommendation that a clinician will follow according to the clinical scenario. If there is a readily reversible cause for the cardiac arrest (which is often the case perioperatively, or if the patient is choking for example) then CPR should be attempted. See the box for more detail about advance care planning and surgery.

With whom must you legally discuss a recommendation regarding CPR?

This varies from country to country. In the UK, you must discuss a DNACPR recommendation with the patient unless you think it would cause psychological or physical harm. If they lack the capacity to have this discussion, you should discuss it with those close to them unless it is not practicable to do so. Box 2 (bmj.com) summarises two UK legal cases informing current lawful practice.[6-24] If a DNACPR is filled out in hospital, this information should be shared with the patient's general practitioner on discharge.

Competing interests: ZF declares that she chairs the ReSPECT subcommittee for Resuscitation council UK

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CLINICAL UPDATE

Identification and management of co-infections in people with malaria

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CPD READING

0.5 HOURS

In patients who have evidence of acute or recent malaria infection, co-infections with other pathogens occur commonly.[3] In this article, we consider the challenges of diagnosing bacterial, viral, and parasitic co-infection in patients who have malaria, and the related challenge of attributing illness to malaria in endemic countries. We focus on how to assess and manage co-infection in children with severe *P falciparum* malaria in sub-Saharan Africa (who account for most deaths from malaria globally) and in travellers of all ages with imported malaria who present in non-endemic countries (where all age groups are at risk of severe illness). We do not focus on malaria endemic countries outside Africa, or non-falciparum malaria.

Does detection of malaria parasites always indicate a diagnosis of malaria?

Individuals living in malaria endemic areas can acquire "clinical immunity" to malaria through repeated infections, enabling persistent asymptomatic parasitaemia.[4] The age at which this tolerance is acquired depends on the frequency of exposure. In some African countries with high malaria transmission, asymptomatic *P falciparum* parasitaemia can be found in up to 80% of school age children[2] and symptomatic malaria is uncommon in adults. It is likely, therefore, that co-infection with non-malarial illnesses in these populations will be accompanied by incidental malaria parasitaemia.

WHAT YOU NEED TO KNOW

- Co-infections with malaria affect up to half of children in endemic countries and around one in seven travellers with malaria
- A positive diagnostic test does not mean malaria is the only, or even a contributing, cause of current illness
- In settings where resources are constrained, limited diagnostic capacity can influence the diagnosis of co-infections, so vigilance is required for clinical features atypical for malaria

Features in history that may suggest co-infection with other pathogens

Symptoms

- Insidious onset, gradual weight loss
- Prolonged fever (>7 days)
- Profuse vomiting, diarrhoea (including presence of blood or mucus)
- Coryza, conjunctivitis, sore throat, stridor, prominent/productive/whooping cough
- Focal musculoskeletal symptoms
- Rash, skin or mucosal lesions
- Strong or foul smelling urine, dysuria

Risk factors

- Recent exposure to others with transmissible infections
- Presence of HIV, other immunodeficiencies, or immunosuppression
- Malnourished state
- Presence of sickle cell disease
- Congenital or acquired heart disease
- Pregnancy
- Close contact with animals
- Positive travel history (including within malaria endemic countries)
- Presence of indwelling medical devices (eg, catheters, ventriculoperitoneal shunts) or recent surgery

Drug history (which may modify risk or influence diagnostic test results)

- Recent use of antibiotics and antimalarials
- Vaccinations
- Immunosuppressive medication

How common are co-infections?

Although comprehensive data are lacking, co-infections are probably very common.[3] Prevalence is higher in populations living in malaria endemic countries than in those where malaria is imported, but estimates depend on how intensively co-infections are sought and availability of diagnostics. In one large observational study of outpatient children in Tanzania undergoing extensive diagnostic evaluation for a spectrum of causes of fever, half of patients with malaria had at least one co-infection.[5]

Bacteraemia

Risk of bacteraemic co-infection has been studied extensively. Malaria is thought to increase susceptibility to bacteraemia by impairment of gastrointestinal barrier defences and impairment of immune responses.[9 10] The most commonly reported bacterial co-infections are enteric Gram negative organisms (eg, *Salmonella* species, particularly non-typhoidal salmonella in African children) and *Staphylococcus aureus*.[11 12]

A large epidemiological study that used mendelian randomisation with malaria protective sickle cell trait to establish causality, provided strong evidence that malaria increases the risk of bacteraemia in Kenyan children, explaining 62% of cases when malaria prevalence was highest.[13]

Epidemiology of malaria transmission overlaps with areas of high prevalence of HIV and chronic hepatitis viruses

Large observational studies suggest the prevalence of bacteraemic co-infection is lower in those who do not reside in high malaria transmission settings. Bacteraemia was present in 1% (95% CI 0.4% to 1.8%) of Vietnamese adults with severe malaria,[14] 1.4% (3/219) of adult patients with imported malaria at a German university hospital,[8] and 0.3% (2/417) of imported malaria cases in Sweden.[15]

Viral

Acute viral co-infections are likely more common than bacterial co-infections, but they are frequently undocumented because of limited diagnostic testing capacity in malaria endemic countries. In outpatient children in Tanzania with malaria, about one third had concomitant viral upper respiratory tract infections or a systemic viral illness.[5] In Malawian children with a clinical diagnosis of cerebral malaria, 35% (27/78) also had a central nervous system viral infection.[17] Conversely, only 5% (14/264) of adults with imported malaria at a German university hospital were found to have a viral co-infection.[8]

The overlapping epidemiology of malaria transmission with areas of high prevalence of HIV and chronic hepatitis viruses means that these will also be common viral co-infections. A large cross sectional study in Mozambique, a country with high HIV prevalence and high malaria transmission, found malaria parasites in 33% of adult patients with HIV.[18] Viral haemorrhagic fevers are rare co-infections compared with respiratory viruses and bacteraemia, but can be more common in endemic areas and outbreaks. In an area of Nigeria where Lassa fever is endemic, Lassa virus was identified in 4.6% (4/87) of febrile children with malaria parasitaemia.[19]

Parasites

Mixed infections of *P falciparum* and non-*P falciparum* malaria parasites are a common finding in sub-Saharan Africa, particularly when sensitive molecular techniques are used for the detection of non-*P falciparum* species. One recent study reported mixed infection in 25.8% (523/2027) of outpatients with malaria in Kenya.[20] Helminths (eg, hookworm, roundworm, *Schistosoma*) are widely distributed and also common co-infections in many malaria endemic regions, with a pooled prevalence of 17.7% (95% CI 12.7% to 23.2%) in a recent systematic review.[21] Many countries where malaria is endemic are also endemic for systemic parasitic diseases, with clinical features overlapping those of malaria (eg, visceral leishmaniasis, human African trypanosomiasis), and co-infections are well documented in populations with a high overlapping incidence.[22 23]

Fungi

Few data are available on malaria and fungal co-infections, but several case reports documented disseminated aspergillosis following malaria in individuals who were previously healthy, possibly as a result of immune dysfunction related to malaria.[24]

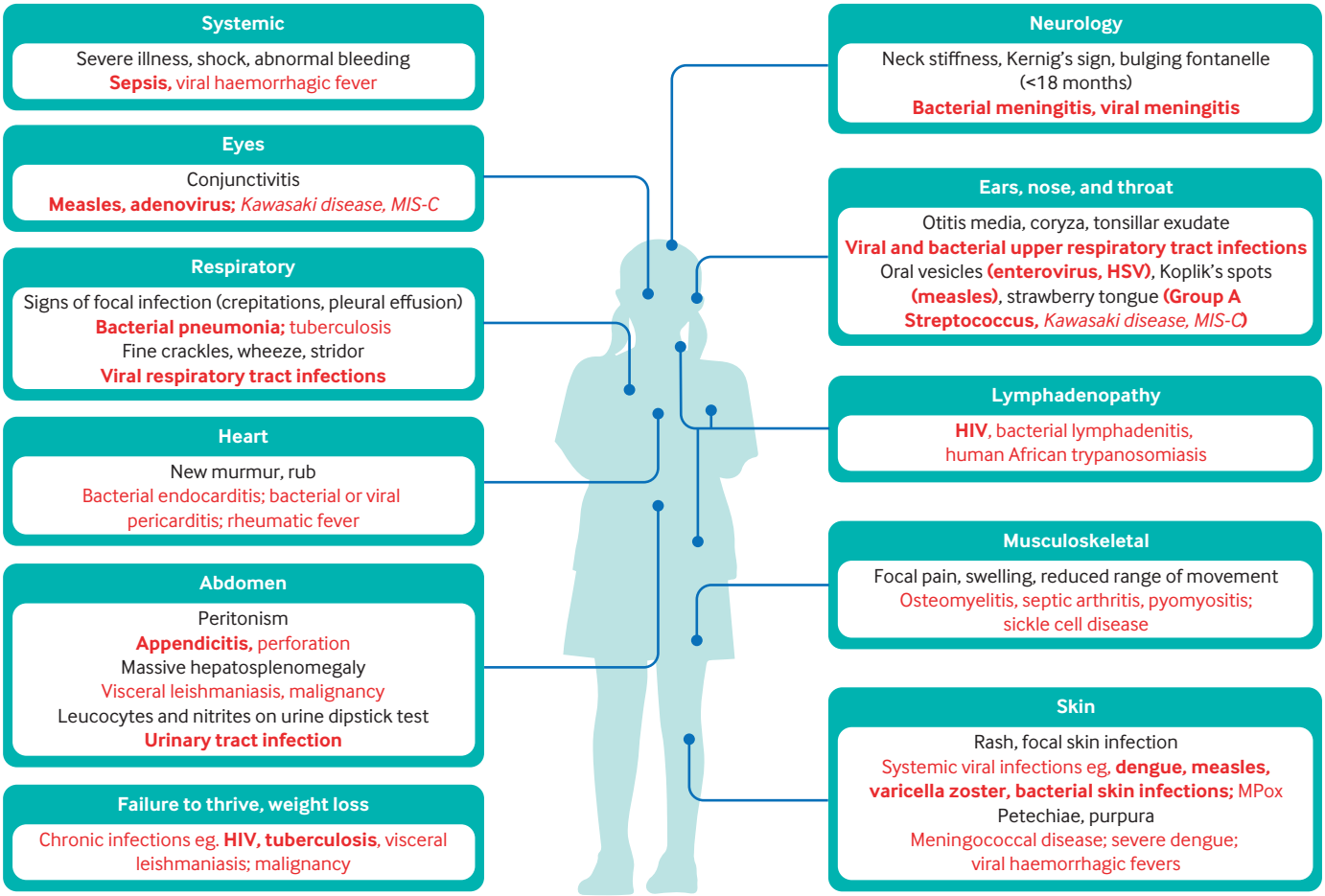

Fig 1 | **Features on physical examination that may suggest malaria is not the only cause of illness. Example non-malarial causes are provided under respective clinical features (in red text). Those in bold are most common. Those in *italics* are specific to children. MIS-C=multisystem inflammatory syndrome in children**

Do co-infections influence severity of illness?

The implication of assuming the diagnosis is *only* malaria can range from insignificant, usually for self-resolving viral co-infections, to severe and life threatening, for treatable invasive bacterial co-infections or viral haemorrhagic fevers.

Bacteraemia

A systematic review of studies in African children reported a higher pooled case fatality rate (24.1%) in severe malaria with invasive bacterial co-infection than in severe malaria alone (10.2%).[11] Another systematic review reported a mortality rate of 15% (95% CI 8.0% to 23.0%) across all patients with malaria and bacteraemic co-infection.[12] Bacterial co-infection was more common in fatal cases (40%, 4/10) of imported severe malaria than non-fatal cases (11%, 9/83) in a European intensive care unit.[16]

Viral

Most acute viral co-infections are self-limiting, but incorrect diagnosis can result in missed opportunities to detect, treat, and prevent transmission of more significant viral diseases such as dengue, viral haemorrhagic fevers, or covid-19. The clinical consequences of viral co-infections in individuals with severe malaria and, conversely, of malaria co-infection in individuals with severe viral diseases, are less well established. In Malawian children with suspected central nervous system infection, mortality was higher (38%, odds ratio 3.6 (95% CI 1.6 to 8.0)) for children with *P falciparum* parasitaemia and central nervous system viral infection than in those with parasitaemia alone (14%).[17] Conclusive data for the most common or severe viral infections, including Ebola virus[26] and SARS-CoV-2, are lacking.[27 28]

Parasites

Data on the impact of malaria and co-infections with *Leishmania* or *Trypanosoma* on severity of illness and survival are inconclusive.[22 23] Helminths transmitted in soil may contribute to the severity of anaemia associated with malaria.[21]

What are the challenges for diagnosing malaria and co-infections?

Presentation

Malaria usually presents as an acute febrile illness with systemic symptoms such as chills, headache, and body aches.[29] Most clinical features of the disease are

indistinguishable from many other systemic febrile illnesses (table 1, bmj.com), including some non-infectious causes. Only one clinical finding, malarial retinopathy, is highly specific for malaria (up to 100% specificity for diagnosis of cerebral malaria[30]), but it does not exclude co-infection with other pathogens.[17]

In the box and figure, we outline features of other infections (and selected non-infectious febrile illnesses) which do not usually occur in malaria. Focal symptoms and signs, such as lymphadenitis or unilateral lung crepitations, are not typical of malaria and should prompt consideration of an additional cause. In a setting with low resource healthcare, WHO's Integrated Management of Childhood Illness guidelines recommend assessing for stiff neck, runny nose, localised tenderness, oral sores, refusal to use a limb, hot tender swelling, red tender skin or boils, lower abdominal pain, pain on passing urine, and signs of measles, which may suggest a diagnosis other than malaria.[31]

Testing

Malaria must be confirmed by diagnostic testing, most commonly microscopy for parasites within red blood cells and/or the detection of one or more parasite antigens in blood using lateral flow rapid diagnostic tests (RDTs).[29] A full blood count is also helpful, with thrombocytopenia being a typical finding in malaria. In Africa, common RDTs based on the detection of the parasite antigen PfHRP2 are around 95% sensitive and 95% specific for symptomatic *P falciparum* malaria,[32] but with caveats:

- Sensitivity is diminished in low parasitaemia asymptomatic infections[33]
- Results from PfHRP2 RDTs can remain positive for several weeks after successful treatment of malaria[29 33]:
  - They can detect malaria even if treatment was given before testing in the current illness
  - A false positive test may arise from a previous malaria infection, especially in settings with high transmission rates
- Increasingly, false negative PfHRP2 RDT results occur because of deletions of the parasite PfHRP2/3 genes.[33]

Current RDTs for malaria have lower sensitivity for non-falciparum parasite species, and their detection by microscopy may be challenging because parasitaemia is often lower than that of *P falciparum*.[34]

Rapid multiplex molecular assays for efficient syndromic testing (table 2) are increasingly available in resource rich settings,[35] but diagnostics for infections other than malaria can be scarce in resource limited settings.[36] Diagnostics for bacterial co-infection usually require the culture of bacteria from sterile site samples before starting antimicrobial therapy.

Presenting features and patient age determine appropriate microbiological samples, which can generally be performed in line with context appropriate guidelines for management of fever or sepsis (eg, guidance from WHO[37] or the National Institute for Health and Care Excellence[38]).

Most clinical features of malaria are indistinguishable from other systemic febrile illnesses

Assessing risk of clinically significant co-infection

To our knowledge, there are no validated prediction rules or prospective studies of risk stratification for clinically significant co-infection in patients with malaria. In a retrospective study of adult patients with imported malaria in Germany, multivariate analysis showed that clinical evidence of an alternative focus of infection was associated with an odds ratio of 3.9 (1.5 to 11.5) for bacterial co-infection, while C reactive protein was not significantly different in those with and without bacterial co-infection.[8]

Bacteraemia

Some risk stratification may be possible based on patient and clinical factors. One large systematic review identified bacteraemia as most common in high transmission settings, in younger children, and in those with severe malarial anaemia.[11] However, retrospective observational studies indicate that laboratory measurements can help to identify two groups of patients who appear to have severe malaria and are at highest risk of bacterial co-infection (fig 2, bmj.com):

- Individuals who have incidental parasitaemia and another cause of severe illness, characterised by low parasite load and absence of polymorphonuclear leucocytes containing malaria pigment (determined by microscopy), high white cell count for age, and normal platelet count[39-41]
- Individuals who have true severe malaria with very high parasite load,[42] low platelet count, lower white cell counts,[40] and often >5% of polymorphonuclear leucocytes contain malaria pigment,[39] at increased risk of bacterial co-infection as a direct consequence of their malaria infection.

Malaria parasitaemia is quantified as the percentage of infected red blood cells. Parasitaemia is lowest in asymptomatic infections, intermediate in uncomplicated malaria, and highest in severe malaria, but the groups overlap considerably.[2] In severe *P falciparum* malaria, many parasites are sequestered in the microvasculature and not visible on blood film. Research studies quantify the total parasite load of circulating and sequestered parasites by using plasma or serum PfHRP2 concentration, which discriminates better between asymptomatic, uncomplicated, and severe groups,[41 42] but these are not available in routine clinical practice. Parasitaemia and PfHRP2 concentrations are only moderately correlated, and their relations with symptomatic or severe disease can vary with age and endemicity, making it challenging to set generalisable risk thresholds.

Prolonged fever, recurrence of fever, or deterioration after starting antimalarial treatment, warrant evaluation for bacterial infection and antibiotic treatment, as well as consideration of antimalarial resistance.

Viral

Consider the potential for viral haemorrhagic fever co-infection in patients from areas where such diseases are endemic (eg, Lassa fever in West Africa) or when

Table 2 | Examples of diagnostic tests for co-infections with clinical features overlapping those of malaria

Test category (example)	Gold standard diagnostic	Recommended tests for different levels of care		
		Community or health facility without a laboratory (LMIC)	Facility with a clinical laboratory (LMIC)	Facility with an advanced laboratory
Invasive bacterial infections (non-typhoid Salmonella bacteraemia)	Culture based detection from sterile site	Usually none	Staining procedures (eg, Gram stain) *Culture based methods.* *Antimicrobial susceptibility*	Culture based detection and bacterial identification from many specimen types. Antimicrobial sensitivity. Molecular diagnostics (eg, PCR)
Parasitic infection (malaria, visceral leishmaniasis)	Microscopy	Malaria RDT.*Visceral leishmaniasis (rK39) RDT*	Malaria RDT and microscopy. *Visceral leishmaniasis (microscopy, direct agglutination)*	Malaria RDT and microscopy, visceral leishmania (microscopy, serology, PCR)
Viral infection	NATs (+/- antigen based tests). Serological assays	*HIV (RDT), Influenza (RDT) SARS-CoV-2 (RDT)*	*Viral NAT: SARS-CoV-2, influenza, dengue virus, measles, HIV.* RDT: HIV, *dengue* Serological immunoassay: HIV, measles, rubella	NATs for many viruses, often in multiplex syndromic panels; antigen tests; serological assays
Mycobacterium tuberculosis	Culture based detection	*Urinary Lipoarabinomannan RDT (in patients with HIV)*	Microscopy, *culture, NAT (eg, gene expert), drug susceptibility testing*	Microscopy, culture, NAT. Drug susceptibility testing
Severity assessment	Clinical chemistry and haematology tests	*Haemoglobin (haemoglobinometer); glucose (glucometer); urinalysis (dipstick)*	Complete blood count (automated analyser). *Liver function, renal function, electrolytes (semi-automated or automated analyser)* *Blood gas/pH/lactate/ glucose (portable analyser)* *CRP (RDT, immunoassay)*	Extensive range of automated analysers for haematology and biochemistry

Tests shown in italics vary in availability, meaning that they will often not be available at a health facility. LMIC=low and middle income countries; RDT=rapid diagnostic test; NAT=nucleic acid test; PCR=polymerase chain reaction

outbreaks occur. Test patients with suspected viral haemorrhagic fever for malaria to rule out a treatable co-infection, and consider viral haemorrhagic fever co-infection in patients with malaria to enable appropriate measures of infection control. Risk of viral haemorrhagic fever can be stratified by a detailed travel history, including dates of travel to endemic areas (most have an incubation period under 21 days), exposures, and contacts (box 'Guidelines', bmj.com). In areas with a high prevalence of HIV, it may be appropriate to screen all individuals with severe malaria for HIV.

Parasitic and fungal

Consider significant parasitic or fungal co-infections when the patient has a high risk of exposure or clinical features that are atypical for malaria (figure) or which fail to respond fully to antimalarial treatment.

How to manage possible co-infection

Bacteraemia

In children with malaria in an endemic country:

- Initiate antimalarial treatment
- Examine and investigate, if possible, for focal bacterial co-infection
- Commence broad spectrum antibiotic treatment in all children with severe malaria.

In returning travellers:

- Initiate antimalarial treatment
- Examine and investigate for focal bacterial co-infection
- Commence broad spectrum antibiotic treatment in all severely ill children and in adults with signs of shock or respiratory failure.

Consider empirical treatment also for patients with severe illness who have inconsistent clinical or laboratory findings, and those with very high parasitaemia (>20%). Some national guidelines recommend more restrictive approaches to empirical antibiotic treatment, focusing on patients with circulatory shock, respiratory failure, very high lactate.[46-48]

Treatment with a third generation cephalosporin (eg, ceftriaxone) is likely to be effective against the most common bacterial co-infections, non-typhoidal *Salmonella* and *S aureus*, but this may not be feasible for every child with severe malaria in endemic countries because of cost and limited availability. Alternative empirical treatment regimens using gentamicin plus narrower spectrum β lactam antibiotics may not provide adequate cover. Even third generation cephalosporins may sometimes be inadequate because of increasing prevalence of resistant organisms.[43]

Viral

Diagnostics and specific treatments for many viral infections are rarely available outside advanced healthcare facilities. If viral co-infections of public health importance are suspected, such as measles or a viral haemorrhagic fever, take available infection control precautions, and notify appropriate authorities according to local and national procedures. Post-exposure vaccination or immunoglobulin may protect and prevent further spread for specific infections.[51]

After stratifying risk for viral haemorrhagic fevers and other transmissible infections, follow standard local infection control policies for patients at low risk.

Parasitic and fungal

Treatment of specific parasitic and fungal co-infections depends on the organism. Empirical treatment with albendazole or mebendazole may be given to anaemic children with malaria, if not received in the last six months, to treat soil transmitted helminths.

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Patient involvement: Patients were not directly involved in in the writing of this article, but a representative patient story has been included (bmj.com).

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CASE REVIEW

Unilateral skin eruptions

A woman in her 40s, with a history of asthma and hypertension, presented with a seven day history of sudden onset bullous skin lesions, associated with itching and a burning sensation (fig 1). She had no personal or family history of bleeding disorders. The lesions initially appeared on her right foot, progressed to the right thigh, and then evolved to hyperpigmented macules within seven days (fig 2). She reported no history of fever, mucosal ulcers or lesions, dermatomal distribution of the rash, malaise, or joint pains. Four days before the onset of the lesions the patient had been prescribed levofloxacin for acute gastroenteritis. On examination, she had multiple hyperpigmented, non-tender, and non-indurated macular lesions over her right leg and both thighs.

1 What are the differential diagnoses?

2 What is the most likely diagnosis?

3 How would you manage this condition?

Submitted by Karun Saathveeg Sam, Pooja Khosla, Vinus Taneja, and Rishikesh Dessai

Patient consent obtained.

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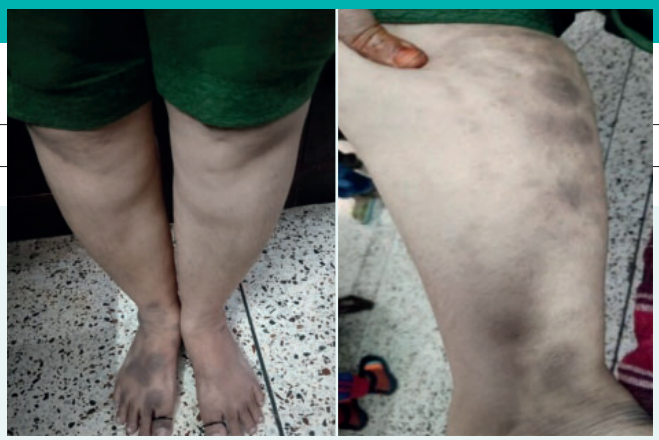

Fig 1 | Right foot and leg lesions on presentation

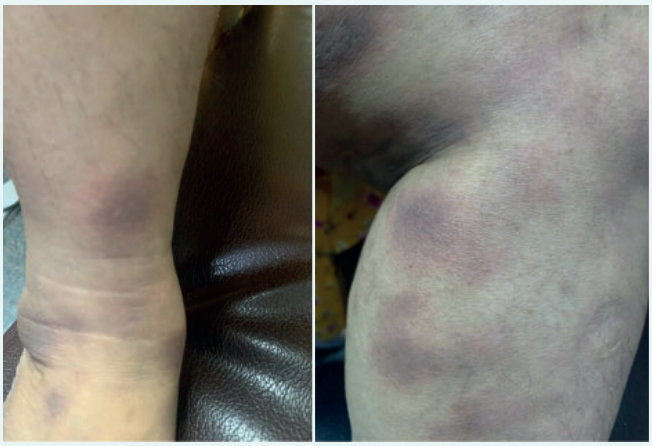

Fig 2 | Erythematous rim around hyperpigmented macules

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answers

CASE REVIEW **Unilateral skin eruptions**

1 What are the differential diagnoses?

Differential diagnoses include erythema multiforme, bullous pemphigoid, pemphigus vulgaris, fixed drug eruption, herpes zoster, and Stevens-Johnson syndrome. Immunobullous diseases and Stevens-Johnson syndrome would typically present with extensive involvement and systemic symptoms. The lack of dermatomal distribution and the pattern of the rash made herpes zoster less likely. The lesions were not characteristic of those seen in erythema multiforme, which are typically target-shaped and do not recur at the same site. A bleeding disorder was unlikely since the patient had no personal or family history of spontaneous bleeding episodes.

2 What is the most likely diagnosis?

Fixed drug eruption—this patient most likely had a bullous fixed drug eruption secondary to use of a quinolone antibiotic. Fixed drug eruptions are uncommon immune mediated lesions, which can be localised or generalised secondary to a specific drug. They appear as well demarcated, dusky red lesions, but can present with varying morphology, such as bullous, linear, or non-pigmented lesions. The lesions heal with scarring or hyperpigmentation and may recur at the same site on re-exposure, with an increase in the hyperpigmentation Diagnosis is clinical and a skin biopsy is not necessary unless uncertainty remains.

3 How would you manage this condition?

Fixed drug eruptions are typically managed by discontinuing the responsible drug. Topical or systemic steroids are given depending on the severity of the disease. Symptomatic treatment for pain, itching, and scarring might also be considered. Patients should be educated to avoid a particular drug class.

LEARNING POINTS

- Fixed drug eruptions are an immune mediated condition secondary to a specific drug.
- Typical presentations are usually unilateral and of varying morphology.
- Discontinuing the responsible drug remains the cornerstone of treatment, but steroids might be required for management depending on the severity of the presentation.

PATIENT OUTCOME

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MINERVA

A parrot's beak in the lumbar spine

This computed tomography (CT) scan shows the spine of a man in his 50s who presented to hospital with low back pain and limited mobility of the lumbar spine for four months.

Lumbar radiographs showed worm eaten bone destruction with sclerosis of the peripheral bone. The CT scan showed anterior osteophytes (small hook shaped bone growths, shaped like a parrot's beak, around the intervertebral disc, "parrot's beak sign") (arrow). A brucellosis antibody test showed positive results in the tiger red plate agglutination test and tube agglutination test (titre, 1:400), confirming a diagnosis of brucella spondylitis.

Brucella spondylitis is a complication of spinal arthritis caused by brucellosis infection. Risk factors for brucellosis include living in or travelling to endemic countries, consumption of unpasteurised dairy products or raw meat products, occupational exposure, and hunting. Despite four months of regular anti-brucellosis treatment, the lower back pain and intermittent claudication worsened, and he required a laminectomy and decompression, debridement, and percutaneous spine internal fixation. The patient's symptoms had completely resolved when he was seen at a postoperative review one year later.

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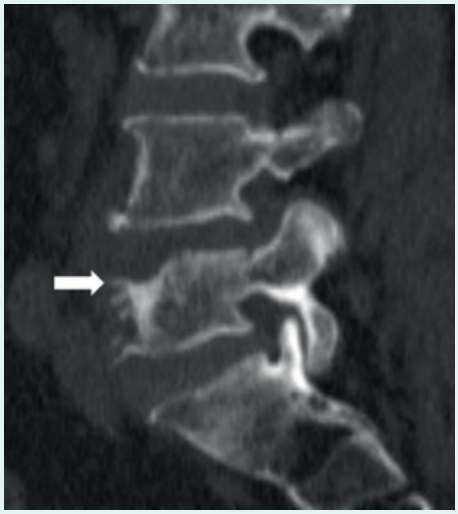

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Subclinical hypothyroidism

Don't be in a hurry to diagnose or treat older adults suspected of having subclinical hypothyroidism. That's the message from an analysis of pooled data from two randomised trials. Two thousand people with biochemical subclinical hypothyroidism (defined as an elevated thyroid stimulating hormone (TSH) measurement combined with a free thyroxine level within the laboratory reference range) were assessed for eligibility for trials of thyroid replacement. During the pre-trial phase, TSH levels became normal in more than half of the participants (*J Clin Endocrinol Metabol* doi:10.1210/clinem/dgad623).

Anaesthesia for hip fracture surgery

Long term outcomes in a comparison of spinal anaesthesia with general anaesthesia for hip fracture surgery didn't differ between either. A large trial in 46 hospitals in the US and Canada randomised patients requiring surgery for hip fracture repair either to spinal or to general anaesthesia (*N Engl J Med* doi:10.1056/NEJMoa2113514). Sixty days after surgery, survival and recovery of ambulation were the same in both treatment arms. The investigators now report that survival, ambulation, and need for nursing home care remain similar after a year (*Anaesthesiology* doi:10.1097/ALN.0000000000004807).

Outcomes for patients undergoing hip fracture surgery were the same, whether they had spinal or general anesthesia

Transcatheter versus surgical aortic valve replacement

Evaluated 10 years after the procedure, there's little to choose between different approaches to aortic valve replacement. The Nordic Aortic Valve Intervention trial randomised 280 patients, mean age 79, either to transcatheter or to surgical replacement. After 10 years, the cumulative risk of the composite outcome (death from any cause, stroke, or myocardial infarction) was 65.5% in both groups, with no differences in individual outcomes (*Eur Heart J* doi:10.1093/eurheartj/ehae043).

Suicide rates among members of the UK armed forces

Suicide rates have been decreasing in the Royal Air Force since the 1950s, in the Royal Navy since the 1970s, and in the army since the 1980s. Since the 1950s, suicide rates among members of the armed forces have been lower than in the population generally, and the difference has widened in recent decades. A policy change in the mid 1990s that led to restricted access to weapons coincided with a fall in the suicide rate by firearms and explosives (*BMJ Mil Health* doi:10.1136/military-2022-002309).

Seizures in multiple sclerosis

Data from 54 000 patients with multiple sclerosis who were taking part in treatment trials contained 120 seizure events over two years' observation. This puts the incidence of seizures at 68 per 100 000 patient years, which is about twice as high as in the population generally. Most seizures were generalised tonic-clonic seizures. Seizures were commoner in people with rapid progression of disease, longer disease duration, higher disability levels, and lower brain volume. Nearly half the seizure events occurred in trials involving fingolimod or other sphingosine-1-phosphate receptor modulators—an observation that needs further investigation (*J Neurol Neurosurg Psychiatry* doi:10.1136/jnnp-2023-332996).

Risk factors for young onset dementia

An investigation among 360 000 participants of the UK Biobank study explored sociodemographic, genetic, lifestyle, environmental, psychiatric, and blood marker risk factors for young onset dementia. In a multivariable Cox proportional hazards regression model, 15 factors reached statistical significance. However, only three—orthostatic hypotension and a history of depression or alcohol use disorder—were associated with hazard ratios greater than 2 (*JAMA Neurol* doi:10.1001/jamaneurol.2023.4929).

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