# education

**FROM THE JOURNALS** Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

## Is becoming richer good for your heart?

This huge retrospective analysis of 3123 US counties, encompassing more than 100 million individuals from 2010 to 2017, found that every 10 point increase in economic prosperity was associated with a modest 0.4% lowering of cardiovascular mortality in adults aged 40-64 years. The authors note that post-recession economic stagnation and poor social cohesion in the US have been associated with a rise in "deaths of despair" (such as drug poisoning, suicide, alcoholic liver disease). Economic stress may also have upregulated inflammatory processes and increased cardiovascular mortality. However, numerous confounders complicate the picture; not least that healthy middle-aged people may have voted with their feet and abandoned economically stagnant areas, leaving those most predisposed to cardiovascular disease behind.

*JAMA* doi:10.1001/jama.2020.26141

## What causes cerebral palsy?

Birth asphyxia accounts for less than 10% of cases of cerebral palsy, so what explains the other 90% of this common neurodevelopmental disorder that affects up to three in every 1000 people? This cross sectional study used exome sequencing of two cohorts and found pathogenic genetic variants in 32.7% of paediatric patients and 10.5% of adult patients with cerebral palsy. The lower yield with adult patients reflected the need for narrower testing as there was much less availability of data about the parents of subjects with cerebral palsy, which was needed for comparison.

The molecular diagnostic yield in this study was in line with results for other neurodevelopmental disorders which are known to co-exist with cerebral palsy such as epilepsy and autism. Using a combined cohort without details of the type and severity of cerebral palsy was a significant limitation of the study. And its observational nature means that there's no proof that the genetic variants cause cerebral palsy. Further study to translate the results of genetic studies into clinical practice is the next vital step.

*JAMA* doi:10.1001/jama.2020.26148

## Global surgical cancer care: levelling up

About 80% of people with cancer require some sort of surgery. How do postoperative outcomes differ across high income countries and low to middle income countries (HIC and LMICs)? Unsurprisingly, this international prospective cohort study found that patients in LMICs presented with more advanced disease than in HICs. LMICs also had higher 30 day postoperative mortality for gastric and colorectal cancer patients, but there was no difference after breast cancer surgery. Complication rates were similar globally, but more likely to cause death in LMICs and played a significant part in the disproportionate numbers of postoperative deaths in cancer patients in poorer countries.

Both patient-related factors (such as poor nutrition) and health system factors (such as lack of critical care) play a role. The authors urge better perioperative interventions to reduce avoidable mortality from common surgical complications in global surgical cancer care.

*Lancet* doi:10.1016/S0140-6736(21)00001-5

## Predisposition to breast cancer: it's bigger than BRCA

Knowing that you carry pathogenic variants in genes that predispose you to a particular cancer (such as BRCA1 and 2 and breast cancer) is useful because you can choose risk-reducing surgery or drugs and enhanced screening. Existing knowledge of gene variants is based on high risk populations, but few studies have searched multigene panels across a wider population of women.

This US case-control study found evidence of 12 pathogenic variants in 5% of women with breast cancer (versus 1.63% in controls) and confirmed the increased risk associated with BRCA1 and 2. The study also found that a further 16 candidate gene variants weren't associated with an increased risk. At the moment, only women with a known family or personal history of breast and ovarian cancer are offered genetic testing. Studies such as this one pave the way to offering risk estimates for all individuals to guide tailored screening, cancer testing, prevention, and management.

*N Engl J Med* doi:10.1056/NEJMoa2005936

## Moderna trials ongoing

A phase III randomised US trial among individuals at high risk of covid-19 found that two doses of the mRNA-1273 (Moderna) vaccine given 28 days apart were effective in preventing covid-19 from two weeks after the second dose compared with placebo. The vaccine showed 94.1% efficacy against covid-19. All 30 people (of >30 000 participants) who became seriously unwell with covid-19 (including one who died) were in the placebo group. Moderna is the third covid vaccine licensed in the UK. Important questions remain about longer term safety, duration of immunity (and a way of measuring it), and transmissibility.

*N Engl J Med* doi:10.1056/NEJMoa2035389

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CPD READING
0.5 HOURS

# Non-steroidal anti-inflammatory drugs (NSAIDs) for musculoskeletal pain

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, University of Birmingham and Birmingham City Hospital, and Patricia McGettigan, Queen Mary's University, London.

**A 65 year old patient has been troubled with intermittent low back pain for years, for which you prescribed ibuprofen 400 mg up to three times daily as needed. For the past four months, persistent knee pain, not associated with stiffness, has limited his mobility. He is overweight, physically inactive, and has recently been diagnosed with hypertension. Paracetamol has had little benefit. He asks if taking ibuprofen regularly might ease his knee pain.**

## What are non-steroidal anti-inflammatory drugs (NSAIDs)?

NSAIDs are commonly used for pain management. They reduce inflammation and pain by reducing the activity of cyclo-oxygenase (or COX) enzymes and inhibiting prostaglandin synthesis.[1]

- Older, non-selective NSAIDs such as ibuprofen, diclofenac, and naproxen inhibit both COX-1 and COX-2 enzymes
- Newer, selective NSAIDs (COX-2 inhibitors, coxibs) such as celecoxib and etoricoxib selectively inhibit COX-2, which plays a greater role in prostaglandin mediated pain and inflammation.

The National Institute for Health and Care Excellence (NICE) guidelines recommend NSAIDs as first line analgesics for low back pain and sciatica[2] and osteoarthritis.[3] They are also used for musculoskeletal pain from acute injury. In England there were about 11.5 million prescriptions for oral NSAIDs in 2018.[4]

### WHAT YOU NEED TO KNOW

- Oral non-steroidal anti-inflammatory drugs (NSAIDs) can reduce musculoskeletal pain but increase the risk of gastrointestinal (perforation, ulcers, bleeding), cardiovascular (myocardial infarction, heart failure, hypertension), and renal adverse events
- Topical NSAIDs are also effective for osteoarthritis, with fewer adverse events than oral NSAIDs
- Opioids do not provide greater pain relief than NSAIDs for musculoskeletal pain

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## How well do NSAIDs work for musculoskeletal pain?

### Oral NSAIDs

*Spinal pain*

NSAIDs are slightly more effective than placebo at reducing pain intensity and disability in people with acute and chronic low back pain,[6 7] as per Cochrane systematic reviews. The differences are small and not likely to be clinically relevant; about 7 points on a 0–100 pain scale. There is no difference in effects of selective and non-selective NSAIDs.

Overall, five people (95% confidence interval 4–6) with spinal pain (that is, low back or neck pain with or without radicular pain) need to be treated with NSAIDs, rather than placebo, for one additional person to achieve clinically important pain relief (>10 points on a 0–100 scale) over two weeks.[8]

*Osteoarthritis*

NSAIDs marginally improve osteoarthritis pain compared with placebo over 12 weeks, based on a network meta-analysis (58 451 participants).[9] More notable benefits (>10 points on a 0–100 scale) are seen with high daily doses of diclofenac (150 mg), naproxen (1000 mg), ibuprofen (2400 mg) and etoricoxib (60 mg).[9]

*Other arthritic and musculoskeletal conditions*

NSAIDs are effective in reducing pain from axial spondyloarthritis,[11] rotator cuff tendinopathy (shoulder pain),[12] and acute ankle sprain,[14] as per systematic reviews. There is scant and conflicting evidence for lateral elbow pain.[13] Recent draft NICE guidance advises against the use of NSAIDs for some types of chronic pain, such as fibromyalgia and chronic pelvic pain.[16]


### Topical NSAIDs

*Osteoarthritis*

Topical NSAIDs are superior to placebo in relieving pain from osteoarthritis, as per a network meta-analysis[10] and a Cochrane review.[17] Diclofenac patches were most effective for pain, and piroxicam for functional improvement. Only diclofenac patch and ibuprofen gel/cream provide clinically important pain relief (>1.2 points on a 0–10 scale).[10] Pain relief is similar to oral NSAIDs in knee osteoarthritis with fewer side effects, as per two randomised controlled trials.[18 19] A randomised controlled trial (775 participants) found no additional benefit of combining topical and oral NSAIDs over either formulation alone for knee osteoarthritis.[20] Topical NSAIDs do not increase the risk of gastrointestinal adverse events or cardiovascular events compared with placebo.[21] European guidelines advise topical NSAIDs as first line treatment for hand osteoarthritis.[22] The Cochrane review found no evidence for their use in other chronic musculoskeletal pain.[17]

*Acute injuries*

Topical NSAIDs provide good levels of pain relief for musculoskeletal pain from acute injuries such as a muscle pull, as per high quality evidence from a Cochrane review (8386 participants). Gel formulations of diclofenac, ibuprofen, and ketoprofen and diclofenac patches are the most effective.[15] Topical NSAIDs may improve lateral elbow pain (or tennis elbow), but the evidence is of low quality.[13]

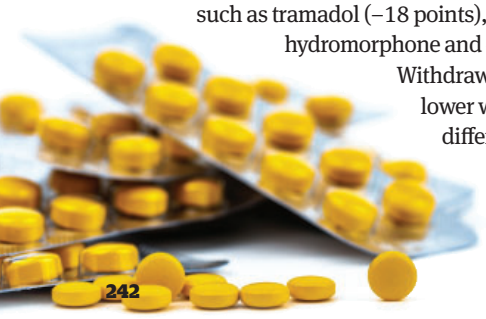
## How do NSAIDs compare with other drugs?

Paracetamol[23] and opioids[24 25] are ineffective for low back pain and may provide modest short term pain relief in osteoarthritis, as per systematic reviews.

For acute low back pain, there is no difference between NSAIDs and paracetamol on pain intensity (mean difference −0.7, 95% CI −2.5 to 1.1), as per a Cochrane review.[6] Small trials show comparable pain relief between NSAIDs and paracetamol-codeine, tramadol, or meptazinol.[6] Data on function or quality of life are limited.

A Cochrane review on chronic low back pain found no difference between NSAIDs and paracetamol and pregabalin in pain intensity, based on data from small trials.[7] A single trial reported greater global improvement with celecoxib compared with tramadol (risk ratio 1.3, 95% CI 1.2 to 1.4).[7] There is insufficient evidence for sciatica or neck pain.

For knee or hip osteoarthritis, NSAIDs are slightly more effective than paracetamol (standardised mean difference −0.3, 95% CI −0.4 to −0.2) as per a systematic review.[26] A trial (892 participants) found that combining ibuprofen with paracetamol reduces knee pain in the short term more than paracetamol but not ibuprofen alone.[27] A systematic review found comparable reduction in pain from knee osteoarthritis with NSAIDs (−18 points), weak opioids such as tramadol (−18 points), and strong opioids such as hydromorphone and oxycodone (−19 points).[28] Withdrawal rates due to toxicity were lower with NSAIDs. There was no difference between duloxetine, an antidepressant, and oral NSAIDs in osteoarthritis in a systematic review.[29]



## What are the harms?

### Gastrointestinal events

Taking any NSAID increases the risk of upper gastrointestinal adverse events (perforations, ulcers, bleeding) by two to four times compared with non-use, as per a systematic review.[30] Coxibs and diclofenac yield the lowest increase in risk. Dyspepsia (indigestion) affects 8-12% of people taking high dose non-selective NSAIDs.[31] The risk is 12% lower with coxibs and 66% lower with a combination of a non-selective NSAID plus a proton pump inhibitor.[32]

The increase in gastrointestinal risk can be up to sevenfold greater with use of high versus low/medium daily doses of NSAIDs.[30 33] The risk seems to be higher in the first week, reduces thereafter with continuing use, and drops one week after stopping use.[33] Taking two or more NSAIDs concurrently substantially increases gastrointestinal risk.[33]

In older adults, combining NSAIDs with aspirin or anticoagulants increases the risk of gastrointestinal bleeding by 13 times compared with non-use.[34]

### Cardiovascular events

Coxibs and diclofenac increase the risk of myocardial infarction by about 70% compared with placebo,[30] while ibuprofen 2400 mg daily doubles the risk.[30] Naproxen seems to be safer, but observational data show it increases the odds of myocardial infarction by 53%.[35] A trial (24 081 participants) found that celecoxib was equivalent to ibuprofen and diclofenac for cardiovascular risk, but the trial had methodological concerns such as high drop-out rate and low average dose of celecoxib taken.[36] Observational studies find NSAIDs increase the risk of haemorrhagic stroke by a third, mostly related to diclofenac or meloxicam use.[37]

NSAIDs double the risk of heart failure compared with placebo,[30 38] the risk being greater in people with renal impairment, particularly if they are taking diuretics.[39] Patients with established cardiovascular disease have a higher risk of hospitalisation for heart failure while taking NSAIDs than those without; odds ratio 10.5 (95% CI 2.5 to 44.9) versus 1.6 (95% CI 0.7 to 3.7).[40]

No safe NSAID treatment window exists in people with cardiovascular disease. Risk starts to increase within a week of starting NSAID treatment[35] and increases further with longer use. Stopping NSAID use drops the risk level similar to that of non-users after three months.[41] Diclofenac was associated with the highest risk of death and recurrent myocardial infarction immediately after the start of treatment (hazard ratio 3.3, 95% CI 2.6 to 3.9, at days 1-7 of treatment) and throughout the treatment course in a Danish nationwide cohort study.[42] The increased cardiovascular risk seems to be dose dependent for celecoxib, ibuprofen, and naproxen, whereas both low and high doses of diclofenac increase risk by similar amounts.[43]

**Tips for safer prescribing of NSAIDs**

- Use with caution—that is, for the shortest time and lowest effective dose possible
- Review existing medications, such as concurrent use of anticoagulants or antiplatelet medicines, before prescribing NSAIDs
- For knee or hand osteoarthritis, topical preparations are preferred to oral NSAIDs as they are associated with similar benefits and less risk of harms
- Ibuprofen (≤1200 mg daily) and naproxen have the lowest cardiovascular risk but do increase risk of gastrointestinal adverse events[58]
- Avoid high dose ibuprofen (2400 mg daily), diclofenac, and coxibs in people with cardiovascular conditions[58]
- Moderate doses of celecoxib may be non-inferior to naproxen and ibuprofen in terms of cardiovascular safety
- Avoid NSAIDs in people with chronic kidney disease. Regularly monitor renal function in people at risk of renal failure, including obtaining a baseline serum creatinine level when starting NSAID therapy
- NICE guidelines advise co-prescription of a proton pump inhibitor with non-selective NSAIDs in people with musculoskeletal pain aged over 45 years[3] and in those with a history of dyspepsia or past ulcer or taking antithrombotic medicines[58]
- For people who have had an NSAID-related upper gastrointestinal bleed, but who must take NSAIDs, co-prescription of a proton pump inhibitor, misoprostol, or double-dose histamine blockers has been shown to prevent future events[59]
- Avoid NSAIDs in pregnancy, particularly in the first and third trimester

### Renovascular events and hypertension

NSAIDs can impair renal function. Risk ratios range from 1.3 to 2.2 among individual NSAIDs compared with non-use.[44] Coxibs have a similar risk of renal failure. The risk seems to be dose dependent, regardless of the type of NSAID used—relative risk of renal failure in NSAID users (compared with non-users) is 2.5 with low or medium daily doses and 3.4 with high daily doses.[45]

NSAID use can increase mean blood pressure by 5.0 mm Hg (95% CI 1.2 to 8.7).[47] Ibuprofen, compared with celecoxib or naproxen, is associated with increased systolic blood pressure and a higher incidence of new onset hypertension.[48]

**Assess your patient's risk profile before prescribing NSAIDs**

### Pregnancy

In the first trimester NSAIDs can increase the risk of miscarriage.[49] In the third trimester, NSAIDs pose fetal risks, such as preterm birth[50] and premature closure of the ductus arteriosus.[51] NSAID use in the second trimester is reasonably safe, but there have been reports of ductus arteriosus constriction and oligohydramnios (deficient volume of amniotic fluid).[52] Fetal monitoring from 20 weeks of pregnancy onwards is recommended in women with long term NSAID use.

### Respiratory events

The prevalence of NSAID-exacerbated respiratory disease is about 9% in adults with chronic asthma.[53] Coxibs are less likely to be a problem for asthmatic patients.[54] NSAID use is associated with a complicated course of respiratory tract infections, as per a recent review of case-control studies.[55]

Despite recent concerns, there is currently no evidence that the acute use of NSAIDs increases the risk of developing covid-19 or of more severe covid-19.[56] However, there is only limited data for those taking NSAIDs long term.

## How are NSAIDs given and monitored?

Given the potential harms of drugs, it is important to discuss the benefits and risks with your patient, and their expectations for symptomatic relief. Consider non-pharmacological therapies for pain relief as well.

Assess your patient's risk profile before prescribing NSAIDs—such as age, history of gastrointestinal or cardiovascular events, hypertension, asthma, renal insufficiency, or bleeding disorders. Lower doses, and intermittent use may be safer, particularly for gastrointestinal safety. NSAIDs often have a ceiling dose, above which additional benefit is unlikely but risk of harm is more likely—for example, the analgesic ceiling dose of ibuprofen is 400 mg/dose,[57] with a maximum dose of 2400 mg/day. See box for tips on safer prescribing.

Drug interactions are important. NSAIDs can block the antiplatelet effect of low dose aspirin used for prevention of cardiovascular disease, so combined use is discouraged. Coxibs such as celecoxib do not seem to do this as aspirin affects platelets via COX-1,[60] but they can nevertheless increase cardiovascular risk.[61 62] The antihypertensive effect of diuretics may be negated with NSAID use because of blockage of prostaglandins responsible for natriuresis.

## How cost effective are they?

NSAIDs that are available over the counter (such as ibuprofen and naproxen) or on prescription (such as celecoxib) are relatively cheap. Modelling studies find that co-prescribing a proton pump inhibitor with any NSAID is cost effective for osteoarthritis pain relief.[63 64]

Competing interests: See bmj.com.

Cite this as: *BMJ* 2021;372:n104

Find the full version with references at http://dx.doi.org/10.1136/bmj.n104

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

Two patients from a community pharmacy in Sydney suggested it was important to clarify whether taking two oral NSAIDs or combining oral with topical NSAIDs result in additional benefits. They also suggested recommendations for identifying adverse events associated with NSAIDs and examples of health conditions and medications in which it may be best to check with a doctor or a pharmacist before taking NSAIDs. We revised the manuscript accordingly. We thank the patients for their comments.

**EDUCATION INTO PRACTICE**

- In which situations would you consider prescribing oral NSAIDs for musculoskeletal pain relief?
- What are the implications of prescribing NSAIDs for musculoskeletal pain in patients taking aspirin?
- How would you discuss the risks and benefits with your patient when prescribing NSAIDs for chronic musculoskeletal pain?

PRACTICE POINTER

# Blood test monitoring of immunomodulatory therapy in inflammatory disease

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**Immunomodulation is the cornerstone of treatment in many immune mediated inflammatory disorders, including inflammatory bowel disease, autoimmune rheumatic disease, and inflammatory skin diseases. Most require pre-treatment screening blood tests and regular blood test monitoring thereafter to detect potential toxicity. This article seeks to provide a simplified overview of blood test monitoring requirements, and is aimed at general practitioners who, increasingly, are taking responsibility for monitoring and prescribing these medications.**

CPD READING
0.5 HOURS

## What conditions are commonly monitored in general practice?

General practitioners care for a wide range of patients who are treated with immunomodulators. Commonly prescribed immunomodulators are listed in the box. The conditions treated include psoriasis (UK prevalence 2.2-2.8%[2]), rheumatoid arthritis (UK prevalence 1%[3]), and inflammatory bowel disease (worldwide prevalence 0.3%[4]). In the UK, prescribing responsibilities are transferred from specialist care to primary care using Effective Shared Care Agreements, written local agreements between specialist services and GPs. A large proportion of GPs are either directly involved in caring for patients on immunomodulators or come into contact with them on a regular basis and should therefore be aware of the drug toxicities and monitoring recommendations.

## Why is monitoring important?

Immunomodulators can cause significant adverse events, including hepatotoxicity, leucopenia, and neutropenia. The prevalence of mild and/or transient blood test abnormalities is relatively common. For example, in a large cohort study of 10 863 patients with rheumatoid arthritis or psoriatic arthritis taking disease-modifying anti-rheumatic drugs, liver enzymes above the reference range occurred in 14-22% of cases, depending on the drug combination; while severe reactions (>2× upper limit of normal) occurred in 1-2% of cases.[5]

In a meta-analysis of 66 studies comprising 8302 patients with inflammatory bowel disease on 6-mercaptopurine/azathioprine, the cumulative incidence of myelotoxicity was 7%. The cumulative incidence of severe myelotoxicity was 1.1%.[6] Mortality rates among patients with inflammatory bowel disease who developed myelotoxicity were low at 0.94%.[6] While mild blood test abnormalities are frequent, they are generally transient and even cases with severe blood test abnormalities resolve promptly with discontinuation or dose reduction.[7] Serial abnormal tests are more likely to be associated with pathological liver/bone marrow disease, but risk of progression to serious disease is difficult to assess given that drug exposure is stopped or reduced in most cases.[7] Furthermore, some uncertainty exists around the degree of risk for liver toxicity attributable to methotrexate treatment, independent of that of other risk factors and pre-existing liver pathology.[7]

However, guidelines from the British Society for Rheumatology for methotrexate provide evidence showing, for example, that abnormal liver enzymes are predictive of histological findings on liver biopsy.[1] Monitoring needs to balance detection of abnormalities that may lead to harm against those commonly seen abnormalities that are mild or transient and potentially lead to over-investigation.

### WHAT YOU NEED TO KNOW

- Patients taking immunomodulatory therapy require regular blood test monitoring to identify adverse drug reactions such as hepatotoxicity and bone marrow suppression
- Monitoring levels vary considerably, with under-monitoring and over-monitoring being common
- Multiple guidelines exist, with some variation in recommended practice, although recommendations tend to be based on expert consensus

**Immunomodulators commonly prescribed in inflammatory disease**

**Initiated in secondary care with ongoing monitoring, and prescribing commonly transferred to general practice**

- Sulfasalazine
- Methotrexate
- Thiopurines (including azathioprine, 6-mercaptopurine)
- Leflunomide
- Hydroxychloroquine (no routine laboratory monitoring is required)[1]

**Generally monitored in secondary care**

- Ciclosporin, mycophenolate mofetil, tacrolimus
- Biological/monoclonal antibody agents, including tumour necrosis factor-alpha inhibitors, T-cell activation inhibitors, interleukin inhibitors, Janus-associated tyrosine kinase inhibitors, and B-lymphocyte associated monoclonal antibodies

thebmj Visual summary

# DMARDs - the long haul

Long term monitoring for adverse events

Long term monitoring is required for people taking immunomodulatory agents for inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, or psoriasis. This graphic shows the main adverse effects occuring during long term treatment

**Frequency of harms**

Proportion of patients experiencing harm, as defined by the British National Formulary

| Drugs | Myelosuppression | Hepatotoxicity | Renal impairment |
|---|---|---|---|
| AZA, 6-MP: Azathioprine or 6-mercaptopurine | 1-10% Genotype and dose dependent | 0.1-1% 1-10% with high dose 6-MP | Not stated |
| LEF: Leflunomide | 1-10% | Estimated at 1-10% (usually occurs within first 6 months) | 0.01-1% |
| MTX: Methotrexate | 1-10% | 0.1-1% | 0.01-1% 1-5% at high dose |
| SSZ: Sulfasalazine | Estimated at 1-10% (usually occurs within first 6 months) | 0.1-1% | Not stated |

## Long term monitoring

Once established on stable dose - typically from 3 months after starting treatment

Based on professional guidelines, all tests below are typically carried out at these intervals, according to shared care agreements with specialists and patients, but local guidance varies

- AZA, 6-MP, MTX: Every 12 weeks
- LEF: Every 8 weeks
- SSZ: Every 12 weeks for 12 months

**Minor impact** — Monitor and refer if trend continues

**Major impact** — Contact specialist and consider treatment interruption

### Advice for specific drugs

**SSZ**

For patients taking sulfasalazine, haematological abnormalities usually occur within first 6 months after initiating treatment

**AZA, 6-MP**

Neutropenia is dose dependent and more common with azathioprine than 6-mercaptopurine

**SSZ**

Eosinophilia is a particular risk for patients taking sulphasalazine

**AZA, 6-MP, MTX**

Thrombocytopenia is more common in patients taking one of these three drugs

### Full blood count

**White cell count**
- Downward trend
- Repeat in 2 weeks
- <3.5 x $10^9$/L

**Neutrophils**
- Downward trend
- Repeat in 2-4 weeks
- <1.6 x $10^9$/L

**Eosinophils**
- >0.5 x $10^9$/L
- Interrupt if unexpected

**Platelets**
- <140 x $10^9$/L

**Mean corpuscular volume**
- >105 fL
- Assess risk of concurrent folate/B12/thyroid deficiency. Contact specialist and consider interruption in treatment if also present with other risk factors

### Liver function

**Transaminases (ALT/AST)**
- Upward trend
- Repeat in 2-4 weeks. Refer if upward trend continues or levels persistently raised
- >2x ULN*

**Albumin**
- Downward trend
- Repeat in 2-4 weeks
- <30g/L
- Interrupt if unexpected

**Procollagen III N-terminal peptide †**
- >10 µg/L — On one occasion
- >8 µg/L — On two occasions
- >4.2 µg/L — On three occasions within 12 months

**MTX**

Only applicable for patients with psoriasis taking methotrexate

### Renal function

**6-MP**

Hepatotoxicity is more common at high doses of 6-mercaptopurine

**LEF**

Hepatotoxicity usually occurs within first 6 months after initiating treatment with leflunomide

**Estimated glomerular filtration rate**
- <60 mL/min

**Creatinine**
- >30% rise
- Within 12 months

**AZA, 6-MP, MTX**

Renal impairment is particularly important at high doses of these three drugs. Methotrexate can be nephrotoxic

* ULN = upper limit of normal

† Action limits may be assay specific; use local values where available

## How is immunomodulatory therapy initiated in secondary care?

Several baseline screening tests should be undertaken before starting treatment, to assess the risks of serious side effects associated with the particular drug.[1-15] These tests (eg, for pregnancy and occult infection) are generally arranged by specialists. Patients may be directed to their GP to ensure that relevant vaccinations are up to date. Some agents, such as leflunomide and methotrexate, are contraindicated in pregnancy.

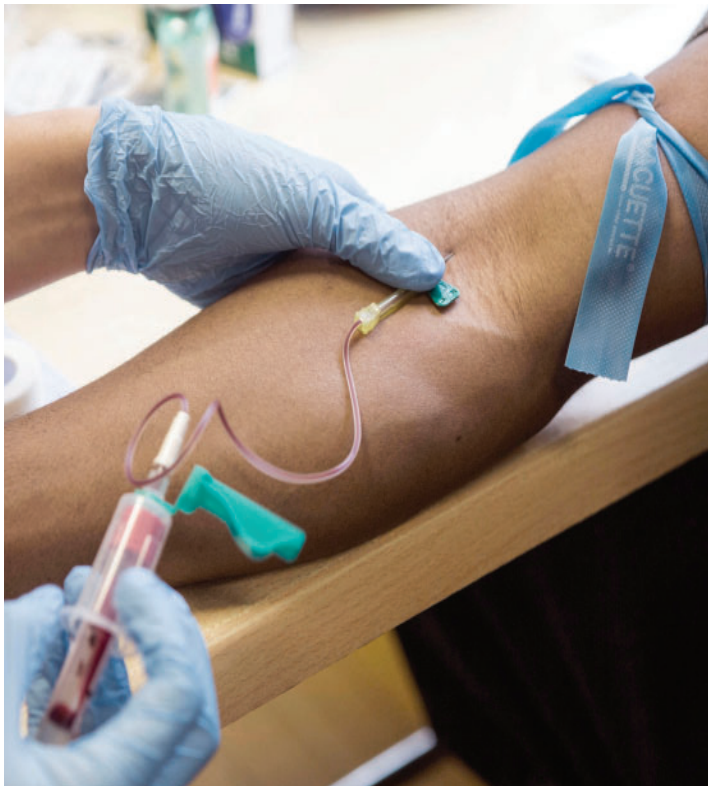
Monitoring for adverse effects immediately after starting treatment, or after a dose change, is generally the responsibility of specialists. These blood tests largely reflect those used for longer term monitoring, but with increased frequency (every 1-2 weeks) until stable dosing is achieved (usually within 1-3 months[13]). Further details can be found in specialist guidance.[1-15]

Regular, long term monitoring (ie, for the duration of treatment with the drug while on a stable dose) is often performed in general practice, although in some cases this may remain the responsibility of specialists. Effective and explicit handover of care from specialists to general practitioners is critical and needs to be understood by all parties, including the patient. In the UK, this should be done via an Effective Shared Care Agreement, which should clearly detail which tests are required, who is responsible for testing, how often, and what action is needed in the event of abnormalities. Furthermore, at an individual patient level, communication from specialist outpatient clinics should include a statement regarding the ongoing monitoring requirements.

## What do guidelines say about monitoring requirements for long term treatment?

Guidance on which blood tests to perform and the frequency of testing is provided by the relevant professional bodies, the National Institute for Health and Care Excellence (NICE) and the British National Formulary (BNF)[1-15] and is summarised in the infographic. These guidelines are generally in agreement in terms of which tests to undertake and the frequency of monitoring: 8-12 weekly for full blood counts and liver function tests to identify any bone marrow or hepatic toxicity, and renal function tests to assess capacity for drug clearance (eg, for renally excreted drugs such as 6-mercaptopurine/azathioprine, which can exacerbate risk of toxicity) and/or nephrotoxicity itself (eg, for drugs such as methotrexate). The exception is the American College of Gastroenterology guidelines[15] which do not recommend an explicit frequency for blood testing, stating only that tests should be done "regularly."

In specific cases, additional tests are recommended. For example, in patients with psoriasis on methotrexate, measurement of procollagen III N-terminal peptide is also advised as an indicator of hepatic fibrosis, although this is usually performed in secondary care.[9] Monitoring requirements are tailored to individual risks, and the recommendations described here and in the infographic are provided only as a guide. Some patients, such as those with relevant comorbidities (eg, malignancy) or on multi-agent therapy (eg, combination therapy as is commonly used in rheumatoid arthritis), may be at higher risk of adverse events and therefore warrant closer monitoring.[1]



## What do guidelines recommend for managing abnormal results?

Variations exist between guidelines on drugs and conditions in the UK[1-13] and elsewhere,[14 15] particularly in the action limits (ie, blood test values outside which clinical action is warranted) used, although the principles remain the same (supplementary file, bmj.com).

### 6-mercaptopurine/azathioprine

For 6-mercaptopurine/azathioprine, the British Society for Rheumatology guidelines suggest monitoring a wider range of parameters, including eosinophils, platelets, mean corpuscular volume, and albumin,[1] which are not mentioned in other guidelines. Slight variations in action limits are also evident for neutrophils, transaminases, and assessment of renal function. While in each case guidelines suggest contacting respective specialists, the wording varies in intensity. For instance, the British Society for Rheumatology guidelines state for abnormal transaminases: "Contact rheumatology team urgently and consider interruption in treatment,"[1] while the British Society of Gastroenterology uses the phrase "Stop and check thiopurine metabolites" (a test requested by specialists).[10] The British Association of Dermatologists recommendations imply a more pragmatic approach to abnormal results based on more "careful evaluation and increased frequency of repeat testing," although it does acknowledge that "dose reduction or drug withdrawal may be needed."

### IMPACT OF COVID-19

In the context of covid-19, some variations exist on guidance for blood test monitoring in established immunomodulatory therapy:

- The British Society of Gastroenterology advises reducing any therapy-associated monitoring blood tests to minimum safe frequency, and suggests that many routine tests can be deferred until the situation has improved, depending on local capacity[23]
- The British Association of Dermatologists advises that patients who have been on the same medication for a substantial period of time with adequate disease control and blood monitoring that has remained satisfactory may be able safely to increase the time interval for blood monitoring on a case-by-case basis[24]
- The British Society for Rheumatology advises that clinicians may need to be flexible about blood testing and that it is usually safe to reduce blood testing frequency to three-monthly or even less in stable patients. It states that cases need to be reviewed on an individual basis, weighing up the risks of continuing without blood testing, compared with the benefit of staying on DMARDS[25]

Guidance for monitoring during initiation remains unchanged.

NICE recommends that patients follow comprehensive social distancing and hand hygiene measures for 14 days before having planned care; this includes diagnostic tests.[26]

For individuals with symptoms associated with covid-19, the British Society for Rheumatology guidance also suggests:[25]

- considering stopping medication and seeking specialist advice on when to restart
- undertaking additional blood tests after self-isolation and within two weeks of restarting medication
- if these tests are within the normal range, reverting to a flexible monitoring schedule on a case-by-case basis (see above); if abnormal, seek specialist advice

### Methotrexate

For methotrexate, the British Society for Rheumatology guidelines are the same as for 6-mercaptopurine/azathioprine.[1] By contrast, the British Association of Dermatologists does not include eosinophils or albumin in its recommendations for monitoring methotrexate, and in cases of abnormal results, suggests discussion with haematology or gastroenterology in cases of suspected myelo or hepatotoxicity, respectively.[9] The British Society of Gastroenterology guidelines for methotrexate require monitoring for a more limited range of parameters (white cell count and transaminases only) and suggest stopping treatment if these are outside action limits.[10]

### Leflunomide and sulfasalazine

Recommendations on handling abnormal results for patients on leflunomide and sulfasalazine are only provided in the British Society for Rheumatology guidelines and mirror those used for patients taking 6-mercaptopurine/azathioprine and methotrexate.[10]

In all cases, results of laboratory tests should be interpreted in the context of the individual patient, the severity, the speed of change of any abnormalities, and the expected action of the therapeutic agent. For example, a sudden change in liver function test results in an ostensibly asymptomatic patient who has otherwise tolerated a drug well may reflect other causes of liver damage. In this context, awareness of local pathways for managing patients with abnormal test results is important.

## Practical challenges

Growing evidence suggests that the number of patients who are under- and over-tested when compared with guidance is considerable and highly variable across a range of conditions.[16-18] Reasons for this are complex and multifactorial, but include patient, practitioner, and system factors (table 1, bmj.com).[16 17] Included in this is the frequent need for interaction between primary and secondary care, and the availability of specialist advice. The implications of under- and over-testing are significant. For instance, under-testing risks adverse events such as liver damage or bone marrow suppression, while over-testing is costly to the NHS, increases the workload of overstretched primary care services, and risks false positives and overdiagnosis. In addition, frequent testing is inconvenient for patients (eg, time off work, discomfort, costs),[17 18] potentially having a negative effect on the acceptability of their treatment plan. Testing strategies therefore need to balance safety, cost, deliverability, and the burden of monitoring for patients.

Improvements in monitoring will need to address the evidence underpinning the frequency of testing and ensure that healthcare infrastructure is in place, such as by use of electronic reminder systems.[19 20] Critically, approaches to reduce under- and over-testing will need to engage patients, such as by making sample collection more convenient and enabling patients to be more involved in managing their condition by providing access to test results and/or educational advice on the importance of testing.[17 21] Given their existing involvement in blood testing for specialists and general practitioners, clinical laboratories may be uniquely placed to oversee this monitoring service.

Competing interests: None declared.

Cite this as: *BMJ* 2021;372:n159

Find the full version with references at http://dx.doi.org/10.1136/bmj.n159

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

We held a focus group with eight patients who are receiving immunomodulatory treatment and asked them about the impact of their treatment on their daily lives. Their responses informed the "What the patients say" box and the focus throughout the article on the impact of monitoring on patients.

### EDUCATION IN TO PRACTICE

- What impact does immunomodulatory treatment and monitoring have on your patients' quality of life?
- What systems do you have in place to ensure adequate monitoring?
- How well does your patients' blood test monitoring conform to guidelines? Consider auditing attendance for blood tests, frequency of abnormalities, and patient recall for abnormalities

## SPOT DIAGNOSIS **A wrist injury**

A man in his 20s presented with deformity and severe pain in his left shoulder and wrist after a mid-air collision with another rider's bike. The patient's torso had collided with the rider's bike, causing him to land on his left upper chest and arm. After Advanced Trauma Life Support (ATLS) assessment the patient was found to be stable and resuscitation was not needed. Two isolated injuries were identified: a closed displaced fracture of the left clavicle and a deformed left wrist with no distal neurovascular compromise. Orthogonal radiography (anteroposterior and lateral views) of the left wrist was performed (figs 1 and 2).

The patient was left hand dominant.

**What is the diagnosis?**

Submitted by Kashif Ahmad and Girish Vashista

Patient consent obtained.

Cite this as: *BMJ* 2021;372:n101

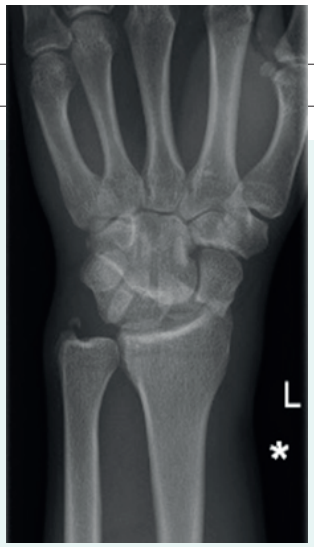



**Fig 1** | Anteroposterior radiograph of left wrist

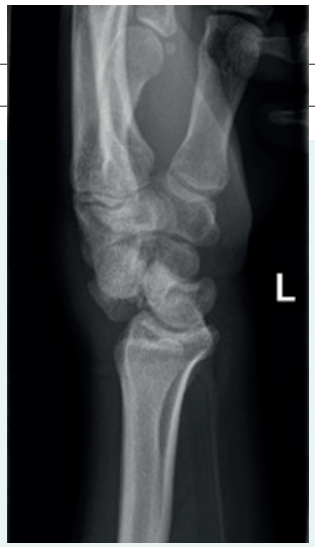



**Fig 2** | Lateral radiograph of left wrist

## answers

### SPOT DIAGNOSIS **A wrist injury**

**What is the diagnosis?**

Trans-scaphoid perilunate fracture dislocation.

Perilunate dislocations are typically caused by axial loading of the carpus from high energy trauma (eg, road traffic incidents, industrial injuries, falls from height), resulting in hyperextension, ulnar deviation, and intercarpal supination.

These severe injuries involve dissociation of one or more carpal bones that articulate with the lunate—in this case, the capitate is dislocated dorsally from the lunate, which remains articulated with the distal radius (figs 3 and 4). The "piece of pie" sign on the anteroposterior radiograph is caused by rotation of the lunate. A complete dissociation of the lunate is termed a lunate dislocation.

Orthogonal radiographs can help with early recognition and avoid complications such as chronic carpal instability, reduced function, median nerve dysfunction, and avascular necrosis.

**LEARNING POINTS**

- Perilunate and lunate fracture dislocations are often missed orthopaedic emergencies
- Follow ATLS protocols for initial assessment and resuscitation
- Suspect this injury with high energy traumas when axial loading of the carpus has occurred
- Assess neurovascular status, request orthogonal radiographs, and promptly refer to orthopaedics

**PATIENT OUTCOME**

The patient was urgently referred to orthopaedics, according to ATLS protocol. He underwent a closed reduction of the left wrist and splinting with below elbow casting.[4-6] Definitive fixation was scheduled within six weeks allowing the patient to make a full recovery. This is required to reduce the risk of complications.[6] The clavicle fracture was managed conservatively.

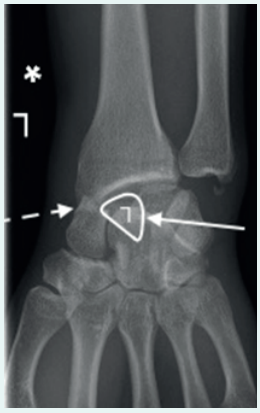



**Fig 3** | Anteroposterior radiograph of left wrist showing "piece of pie" sign (white arrow), highlighting a lunate (L) pathology. A transscaphoid fracture is evident (dashed white line)

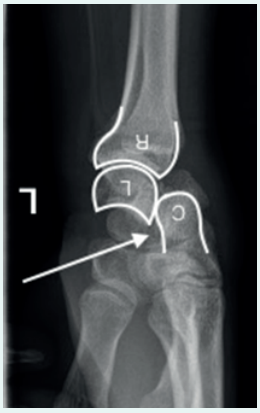



**Fig 4** | Lateral radiograph of left wrist showing the capitate (C) dislocated dorsally (arrow) and not within the articular surface of the lunate (L). R= distal radius

CPD READING
0.5 HOURS

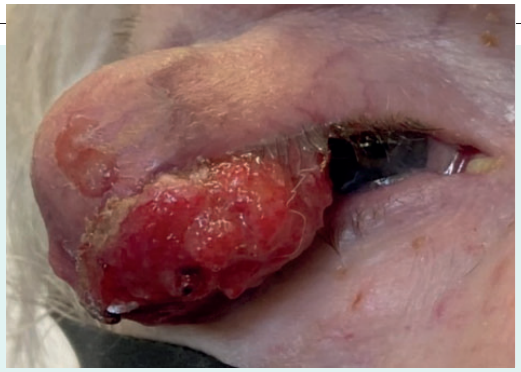
You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

## MINERVA

### Rapidly growing eyelid mass



This is a sebaceous cell carcinoma on the eyelid of a man in his 50s (fig 1). The patient had presented to his doctor a year earlier with a small nodule on the eyelid and was treated for a chalazion with oral antibiotics and given guidance on lid hygiene. Despite a substantial increase in the lesion's size and because the patient was shielding during the coronavirus disease 2019 pandemic, he did not seek further advice.

The lesion was non-painful and occasionally bled on contact. No tender lymphadenopathy or symptoms suggestive of malignancy were elicited. Histology after incisional biopsy showed sebaceous cell carcinoma. Distal spread was not evident on imaging and conjunctival map biopsy. Treatment was curative by excisional biopsy.

Differential diagnoses for this lesion include Merkel cell carcinoma, lymphoma, chalazion, and granulation tissue. Safety netting review is indicated if the lesion were to bleed, continue to grow, or be present after three months. If lesions are present on the eyelid, full examination should include eyelid eversion.

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Patient consent obtained.
Cite this as: *BMJ* 2021;372:n194

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

### Bats and infection

Roughly 6400 species of mammal have been recorded and, amazingly, 1423 of them are bats. Except for the polar regions, extreme desert climates, and a few oceanic islands, bats are found all over the world. They are the only mammals that can fly using muscle power and they are also unique in their ability to harbour viruses without showing signs of disease. Understanding how they balance immune tolerance with host responses to infection may be the key to preventing virus transmission from bats to humans (https://www.nature.com/articles/s41586-020-03128-0).

### Neonatal antibiotics

Follow-up of Finnish babies born at term showed that gains in height and weight during their first six years were lower in boys who had been exposed to antibiotics neonatally. No such effect was seen in girls. In contrast, antibiotic use after the neonatal period was associated with increased body mass index in both sexes. The investigators suggest that antibiotics perturb the gut microbiome and that this influences growth. However, this doesn't explain why only boys are affected (*Nat Commun* doi:10.1038/s41467-020-20495-4).

### Nutrition and asthma

The effects of nutrition on health may be influenced by common genetic variants. In a UK longitudinal study, higher intake of long-chain omega-3 fatty acids in childhood was associated with a substantially lower risk of incident asthma—but only in those children who carried the minor G allele of the fatty acid desaturase gene. The finding was replicated in a second cohort, which raises the prospect of a personalised approach to asthma prevention (*Eur Respir J* doi:10.1183/13993003.03633-2020).

### Stumped by the hump

The average birthweight of babies born at term in Norway began to increase in 1991. A decade later it had risen by around 50 g. Birthweight then declined gradually to its previous level. A similar pattern occurred in Sweden but not in Finland (*Epidemiology* doi:10.1097/EDE.0000000000001211). The cause is a mystery. The change didn't correspond to trends in neonatal mortality or other birthweight associated pregnancy outcomes. Nor could it be explained by trends in known predictors of birthweight such as maternal smoking.

### Alcohol use after bariatric surgery

A Danish study of more than 13 000 people who underwent a gastric bypass procedure for obesity finds that they're vulnerable to developing unhealthy alcohol habits. Five years after surgery, risk of an alcohol use disorder was sevenfold higher than in a control group who didn't receive surgical intervention (*Int J Epidemiol* doi:10.1093/ije/dyaa147). Similar findings are reported from a study of US veterans which estimated that, for every 20 to 30 patients undergoing sleeve gastrectomy or Roux-en-Y bypass, one will develop unhealthy alcohol use (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2020.28117).

### Mental health in early life

Poor mental health in children increases the risk of several adverse outcomes in adulthood, including psychological distress, low educational attainment, unemployment, unstable relationships, and criminal offending. A longitudinal study finds parallel disadvantages in levels of biomarkers (*JAMA Psych* doi:10.1001/jamapsychiatry.2020.2893). Among 9000 participants, affective symptoms and conduct problems in childhood and adolescence were associated with less favourable levels of fibrinogen, C reactive protein, and high density lipoprotein in middle age.

Cite this as: *BMJ* 2021;372:n322