education

FROM THE JOURNALS Edited highlights of weekly research reviews

Denosumab and risk of hypocalcaemia

Many people with osteoporosis are unable to tolerate oral bisphosphonates—many others would prefer a six monthly denosumab injection to a once weekly pill that comes with orders to stay upright and not eat or drink for 30 minutes after taking it. However, denosumab carries a risk of hypocalcaemia, explored in a cohort study of women in the US with chronic kidney disease.

The risk of needing emergency treatment for hypocalcaemia increased with stage of chronic kidney disease: 3% of dialysis-dependent patients and 0.57% of non-dialysis-dependent patients with chronic kidney disease stages 4 and 5 had a hospital admission or emergency department visit for hypocalcaemia within 12 weeks of starting denosumab, compared with 0.00% and 0.03% respectively in those starting oral bisphosphonates.

Ann Intern Med doi:10.7326/M24-00

Tirzepatide for heart failure

GLP-1 studies seem so 2023: why study a glucagon-like peptide-1 (GLP-1) agonist when you can study a GLP-1 and glucose-dependent insulinotropic polypeptide agonist such as tirzepatide? The latest study recruited 731 patients with heart failure and an ejection fraction of at least 50% and a body mass index of 30 or more. Participants were randomised to receive either tirzepatide (up to 15 mg a week) or placebo and were followed up for 52 weeks. Of those in the tirzepatide group, 9.9% reached the composite primary outcome of death from cardiovascular causes or a worsening heart failure event, compared with 15.3% in the placebo group (hazard ratio 0.62 (95% CI 0.41 to 0.95)).

This difference was driven by fewer heart failure events—there were actually three more cardiovascular deaths in the tirzepatide group, although this difference wasn't statistically significant. Improvements in quality of life were also greater in the tirzepatide arm of the trial.

N Engl J Med doi:10.1056/NEJMoa2410027

The mechanics of tirzepatide

A secondary analysis of the same study explored the possible mechanisms for these clinical benefits. Chronic systemic inflammation and enlarged blood volume are hallmarks of obesity-related heart failure with preserved ejection fraction, both of which seem to be modified by tirzepatide. Blood volume was reduced from 12 weeks onwards compared with the placebo group, while systolic blood pressure was reduced from four weeks of treatment.

Inflammation, as measured by high sensitivity C reactive protein, was reduced by 24 weeks, and those taking tirzepatide even saw a small improvement in estimated glomerular filtration rate at 52 weeks and a 25% reduction in albumin-creatinine ratio.

Nat Med doi:10.1038/s41591-024-03374-z

Rapid correction of hyponatraemia

Traditional clinical wisdom includes the need to slowly reverse severe hyponatraemia to avoid osmotic demyelination syndrome. A systematic review and meta-analysis of studies involving over 10 000 patients has found no statistically significant increase in the risk of osmotic demyelination syndrome with rapid correction of severe hyponatraemia (≥8-10 mmol/L per 24 hours) compared with slow correction (<8 or 6-10 mmol/L per 24 hours) or very slow correction (<4-6 mmol/L per 24 hours). Furthermore, the researchers found moderate certainty evidence that rapid correction was associated with fewer in-hospital deaths (32 and 221 fewer per 1000 treated patients compared with slow and very slow correction respectively).

JAMA Intern Med doi:10.1001/jamainternmed.2024.5981

Ablation for chronic subdural haematoma

With our ageing population—increasing numbers of whom take antiplatelets and anticoagulants—chronic subdural haematoma is estimated to become the most common cranial neurosurgical disease by 2030. For those requiring surgery, the rate of recurrence leading to repeat surgery is around 15%.

Three randomised control trials of middle meningeal artery ablation in addition to surgery have just been published, aiming to find out whether artery ablation can reduce the risk of recurrence and progression in people with symptomatic non-acute subdural haematoma. Unfortunately, the answer is still unclear: it "appears to have added benefit over standard treatment" concludes an editorial, but which group of patients stand to benefit the most, and by how much?

N Engl J Med doi:10.1056/NEJMoa2313472, doi:10.1056/NEJMoa2401201, doi:10.1056/NEJMoa2409845, doi:10.1056/NEJMe2410915

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

Cite this as: *BMJ* 2024;387:q2632

PRACTICE POINTER

Haematuria in children

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CPD READING

0.5 HOURS

A 12 year old boy presented with a history of recurrent frank haematuria. He reported three or four episodes in the past three months, with each episode quickly fading after a couple of days. On detailed questioning, he revealed that, during each episode, he experienced transient mild dysuria, urinary frequency, urgency, and central abdominal discomfort. Abdominal examination revealed no tenderness, his foreskin was retractable, and no meatal inflammation or excoriation was visible. In clinic his urine looked clear yellow with no visible blood. Urine dipstick revealed 3+of blood.

What is haematuria?

Visible haematuria (macroscopic) is visible bloody discoloration of urine. With easy availability of urine dipstick tests, the incidental discovery of persistent (defined as more than 6 months) non-visible haematuria (microscopic haematuria or NVH) may also occur. Visible haematuria is rare, and its incidence is unknown, whereas non-visible haematuria has been found in up to 5% of school children on mass screening in Asian schools,[1 2] with up to 0.5% persisting three to six months later.

Unlike in adults, underlying malignancy as a cause of haematuria in children is extremely rare (<0.1%).[3-5] Although the underlying cause cannot be determined by whether the haematuria is visible or non-visible, isolated non-visible haematuria is most commonly idiopathic, whereas visible haematuria may stem from the kidney (such as IgA nephropathy or autoimmune disease) or the urinary tract (such as posterior urethritis, urinary tract stones, balanitis, or urinary tract infection[4 6]). It would, however, be unusual for haematuria to be the only feature of clinical conditions such as urinary tract infection or glomerulonephritis.[1]

WHAT YOU NEED TO KNOW

- Visible haematuria in children can be caused by many individually rare conditions; a small number of investigations can help to identify those which require urgent action
- Isolated non-visible haematuria is common and usually transient; the yield from investigations is very low
- Ongoing symptomatic visible haematuria should be referred urgently for hospital investigation. Non-visible haematuria with proteinuria should also be referred

Observational studies of patients presenting to tertiary care settings with visible haematuria identified clinically significant findings such as dysuria, colicky abdominal pain, and signs of urinary tract infection in 62% of cases.[1 2] Whether non-visible haematuria should be investigated is being debated because of the potential risk of end stage kidney failure, mainly as a result of glomerulopathies presenting decades later. One cohort study, following young adults after compulsory military service medicals in Israel, found that, among those with persistent (on three sequential tests over six months) isolated non-visible haematuria without proteinuria and normal creatinine, 0.7% eventually developed end stage kidney failure over 20 years of follow-up, compared with 0.05% of those without haematuria.[7]

There are no accepted evidence-based guidelines on how to investigate and manage haematuria in children, resulting in an abundance of investigations that rarely change management. Existing guidelines are mainly from expert tertiary paediatric opinion with no economic evaluation or incidence data for primary care. Here we present a pragmatic approach derived from available literature, guidelines from the National Institute for Health and Care Excellence (NICE),[8 9] and expert views from a general practitioner, general paediatrician, paediatric nephrologist, and paediatric urologist.

What should I look for on history and examination?

The table lists the key clinical features and relevant investigations for visible haematuria. Notable points to consider for patients with visible and non-visible haematuria are:

- Do a general paediatric examination, measure weight, height, body mass index (BMI), and blood pressure.[10]
- Examine patients for peripheral oedema suggestive of protein loss or fluid retention.
- Examine the back of legs for non-blanching purpuric rash suggestive of IgA vasculitis, (formerly called Henoch-Schönlein purpura).
- Examine genitalia for signs of vulvovaginitis in girls and bleeding or white scarring of the foreskin suggestive of balanitis xerotica obliterans in boys. Both can stain blood into the urine or underwear.
- Post-infectious and IgA nephropathy are the most common causes of inflammatory haematuria—take a careful infection history of preceding weeks. Explore other symptoms and signs of autoimmune nephritis as in the table.
- Be suspicious of reports of recurrent visible haematuria, especially if accompanied by other medically unexplained symptoms or unexplained

Key clinical features and suggested investigations for visible haematuria

Clinical features	Suggested investigations	Next steps
Haematuria of kidney origin		
• Systemic features of immunological diseases: - Lethargy - Facial butterfly (eg, systemic lupus erythematosus) - Purpuric rash on back of legs (eg, IgA vasculitis, formerly known as Henoch-Schönlein purpura) - Joint swelling - Cough - Oedema (can be subtle as fluctuating swelling around the eyes in the morning) • Clear pattern of viral upper respiratory infection trigger: - If concurrent, likely to be IgA nephropathy - If several weeks prior, more likely to reflect post-infective (streptococcal) glomerular nephritis • Urine visibly cloudy, tea or cola colour • High blood pressure (as per age-sex-height centile norms)[10] • Proteinuria on dipstick (≥+) • Absence of urinary symptoms (dysuria, urgency, frequency)	• Check GFR and electrolytes: - Creatinine ranges are designed for the average sized age-matched child - GFR is best estimated using a height based equation, the most validated being "Bedside Schwartz" (eGFR = 36.2 × (height (cm))/(creatinine (µmol/L))[11] • Spot early morning urinary ACR: - In glomerulonephritis severity of proteinuria correlates with disease activity - Early morning samples reduce false positives from orthostatic proteinuria - Spot urine protein correlates well with 24 hour urine collection, which is impractical in children • Immunological investigations (eg, autoimmune titres): - Requires specialist care as interpretation and true positives are highly dependent on pre-test probability	• Refer to paediatrician if: - eGFR <90% - Raised ACR • Urgently refer to paediatrician if urine ACR >220 mg/mmol (nephrotic range)
Haematuria of urinary tract origin		
• Clear recent history of trauma • Urinary symptoms or history of recurrent urinary tract infections • Urine visibly bright red—terminal haematuria suggestive of urethral origin • In boys examine foreskin for bleeding or scarring (white scarring indicates balanitis xerotica obliterans) • Ballooning and non-retractility of foreskin is not pathological unless recurrent signs of inflammation. Non-retractile foreskin is present in 8% of 7 year olds.[12] Vulvitis/vaginitis in girls may also present with blood in the urine • Look for bruising in perineum due to bicycle saddle or other injuries	• Renal tract imaging: - Kidney, ureters, and bladder ultrasound scan (USS) provide good anatomical information - USS detects 80% of kidney but only 25-38% of ureteric stones[13 14] - Consider CT if ureteric calculi suspected and USS is negative - Minimising radiation exposure is important in children, but modern CT radiation doses are low and can detect 90% of stones[15 16]	• Refer all stones and suspected stones to specialist care • Unexplained bruising in perineum or genitalia should raise safeguarding concerns, and an appropriate referral should be made

GFR = glomerular filtration rate. eGFR = estimated glomerular filtration rate. ACR = albumin to creatinine ratio. CT = computed tomography.

genital trauma and take safeguarding advice as appropriate. If factitious or induced illness is suspected as a cause of reported haematuria, advice must be sought from local social services or a paediatrician.

- Ask patients about sensorineural deafness and first degree family history of chronic kidney disease as several rare familial haematuria syndromes exist, notably Alport syndrome, with several inheritance patterns. Male children with X-linked Alport syndrome have non-visible haematuria, with proteinuria in childhood progressing to end-stage kidney failure in their 20s. Early detection and treatment with angiotensin-converting enzyme (ACE) inhibitors can slow disease progression. About 15% of female carriers (all have non-visible haematuria) progress to end-stage kidney failure by the age of 60 years.[17] Genomic haematuria panels are available for these high risk groups and are undertaken by genetic or tertiary care services.
- Ask about travel or migration history. Children who have spent time in sub-Saharan Africa or South East Asia may be infected with *Schistosoma haematobium*, with haematuria (visible or non-visible) often the only symptom.
- Perform a focused abdominal examination for a kidney mass. An abdominal mass is palpable in 80% children with a Wilms's tumour. This most commonly presents in children aged 2-3 years and up to the age of 8 years.[18]

What investigations can be requested in primary care?

Initial investigations depend on whether the likely origin is from the kidney (nephritis) or urinary tract (table).

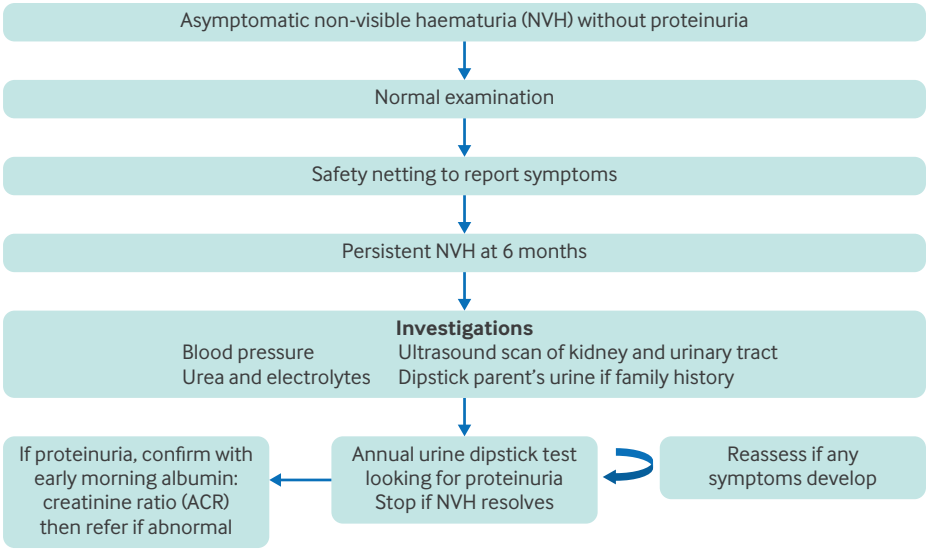
- Confirm haematuria with urine dipstick testing.
- In well infants, discoloration of nappy material may mimic blood, so confirm this by collecting a clean catch sample.
- Check early morning urine albumin to creatinine ratio (ACR) if dipstick testing shows proteinuria; do baseline blood tests (urea, creatinine, electrolytes) and calculate glomerular filtration rate (GFR) (table).
- In practice, renal ultrasound is commonly used in the assessment of visible haematuria, but not all studies or guidelines support its usefulness in this context.[13]
- Genetic testing is available only in secondary or tertiary care for specific indications; refer if child has high tone sensorineural hearing loss or if there is a first degree relative with haematuria or unexplained chronic kidney disease.

What are the differential diagnoses?

Table 2 in the full article on bmj.com presents differential diagnoses for visible and non-visible haematuria. Causes of non-visible haematuria are similar to those for visible haematuria but with much lower yield from investigations. In two retrospective cohort studies of US children's hospitals with 700 children investigated,[1 2] fewer than 1% with non-visible haematuria had actionable findings.[21]

EDUCATION INTO PRACTICE

- What causes do you think about when assessing children with haematuria?
- Do you routinely investigate children with haematuria?
- When do you refer children with haematuria?



Suggested flowchart for management of asymptomatic, incidental non-visible haematuria

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Parents of children with non-visible haematuria were asked in clinic about their diagnostic journey. There was a spectrum of reactions, from being unfazed to continuing concern at the diagnostic uncertainty despite normal blood and imaging tests. All expressed the difficulty of hearing different information from different healthcare professionals. This feedback encouraged us to emphasise the low yield of investigations and the need for clear communication with patients and parents, empowering them by offering choices about the extent of investigations.

How should I manage a paediatric patient with haematuria?

Visible haematuria

Refer all patients with visible haematuria to a general paediatrician. Most children with normal initial investigations will not have further episodes of visible haematuria. Other indications for referral include:

- Persistent proteinuria, defined as ACR >3 mg/mmol in a morning urine sample
- Recurrent visible haematuria without a cause
- Any abnormal results from investigations
- Patients with suspected infection with *Schistosoma haematobium* based on travel or migration history.

Symptomatic patients (high blood pressure, significant proteinuria, passing blood clots, persistent significant discomfort not improving with treatment for urinary tract infections) should be discussed with a secondary care paediatrician for a more urgent review.

Non-visible haematuria

If there is non-visible haematuria and clinical features of urinary tract infection, send a urine culture and treat as a urinary tract infection as per the NICE guideline on urinary tract infection in children.[8] A clinically well child with persistent, isolated non-visible haematuria and with normal blood pressure and blood and urine tests can be referred to an outpatient clinic with appropriate safety-netting and primary care monitoring

Despite very low yield from investigations, no consensus guideline has been produced for non-visible haematuria. Non-visible haematuria is most commonly intermittent in otherwise healthy and asymptomatic children. Most cases are idiopathic and settle within six months.

The figure presents a suggested flowchart for management of asymptomatic incidental non-visible haematuria based on published practices from several review articles.[19 20 22 23]

In the UK paediatric nephrology and urology are organised in regional networks via local paediatricians as first access point. Specialist imaging, cystoscopy, or kidney biopsies may be required, as well as a multidisciplinary assessment of the child to reach a diagnosis. In retrospective cohort studies, paediatric kidney biopsy in cases of non-visible haematuria showed either early glomerulonephritis or basement membrane abnormalities, but results did not change management.[24]

Informing patients and parents, shared decision making

The causes of haematuria in children are generally benign and reversible, and patients and parents can often be reassured accordingly. In visible haematuria, initial investigations in primary care (if practical) such as blood pressure, urine and blood tests, and ultrasound scan will probably point to the underlying cause, and a referral is then made to a paediatrician for follow-up. In cases of non-visible haematuria that is intermittent and short lasting (<6 months), although the underlying cause often remains elusive, patients and parents can be reassured that it is unlikely to be harmful. If intermittent non-visible haematuria persists beyond six months or keeps recurring then a referral to a paediatrician should be made, and urine, renal function tests, and blood pressure be monitored long term to detect early signs of renal impairment. Patients and parents should be provided with safety-netting advice such as to seek medical assessment should haematuria worsen, change from non-visible haematuria to visible haematuria, or associated symptoms such as dysuria or passing of blood clots develop.

Competing interests: None declared.

Cite this as: *BMJ* 2024;387:e072501

Find the full version with references at doi: 10.1136/bmj-2022-072501

GUIDELINES

Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management—summary of updated NICE guidance

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This is a summary of selected recommendations from NICE guideline NG240: Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management.

Bacterial meningitis and meningococcal disease are uncommon but life-threatening conditions. Early recognition is important but difficult because of the non-specific ways in which individuals present. The National Institute for Health and Care Excellence (NICE) initially published guidance on the conditions in 2010 and, after a surveillance review in 2018, updated it following changes in guideline development methodology and to reflect recent developments in vaccination.[1] The 2024 guidance also extends the population of the original guideline from children only to including recommendations for adults.[1]

The term "bacterial meningitis" includes meningococcal meningitis without meningococcal sepsis and meningitis caused by other bacteria, while the term "meningococcal disease" includes meningococcal sepsis with or without meningococcal meningitis. Evidence for the two conditions was reviewed separately but considered in parallel. Whether separate recommendations were needed for each condition was decided based on the evidence and Guideline Committee's experience. In this article, we summarise selected recommendations related to early recognition of these conditions, timing of investigations, initiating antibiotic therapy, and follow-up.

WHAT YOU NEED TO KNOW

- Identification of red flag combinations of symptoms and signs should raise the index of suspicion of bacterial meningitis or meningococcal disease
- A senior clinical decision maker should perform an initial assessment and ensure that antibiotics start within 1 hour of the person arriving at hospital
- Review people who have had bacterial meningitis or meningococcal disease within 4-6 weeks after discharge from hospital

CPD READING

0.5 HOURS

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Committee's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Recognition

In these new recommendations, most of the symptoms and signs identified were at least moderately (≥50%) or highly (≥90%) sensitive or specific for a diagnosis of bacterial meningitis or meningococcal disease (infographic). However, the evidence appraised was mostly based on individual symptoms and signs, as limited data were available for the diagnostic accuracy of combinations, and from adult populations. The presence of these individual symptoms or signs alone may not be sufficient to make a diagnosis because of the substantial overlap with other conditions that present similarly.

Therefore, the Guideline Committee considered the evidence along with their clinical knowledge and experience to identify combinations of symptoms and signs (red flag combinations) that should raise the index of suspicion or prompt an assessor to strongly suspect bacterial meningitis or meningococcal disease. Recommendations were classified as "strongly suspect" if there were the red flag combinations. However, they should not be used in isolation, and the guideline

GRADE WORKING GROUP GRADES OF EVIDENCE

High certainty—we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

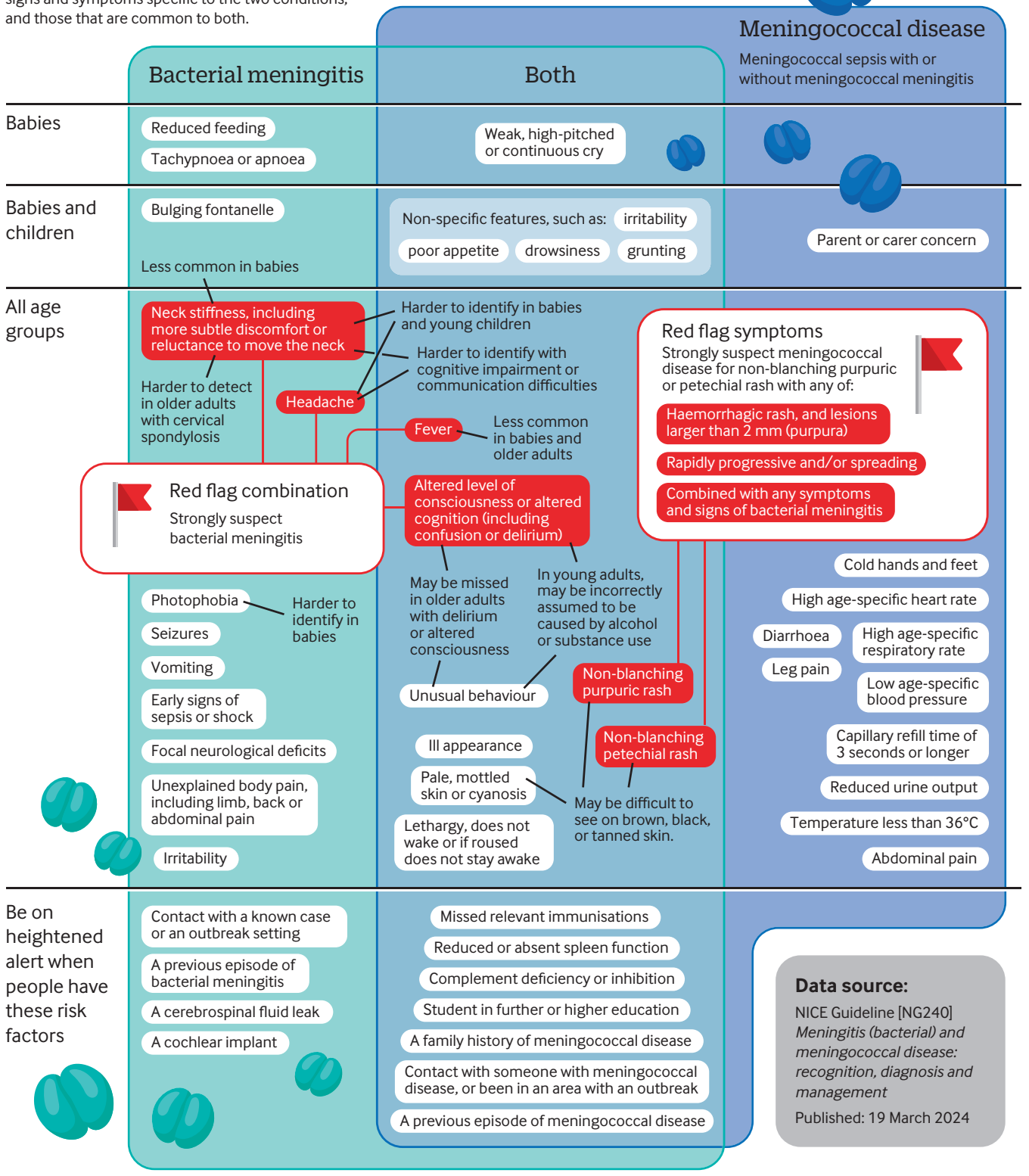
Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

thebmj Visual summary

Identifying bacterial meningitis and meningococcal disease

Bacterial meningitis and meningococcal disease are uncommon life-threatening conditions. Early recognition is important but difficult due to the non-specific ways in which individuals present. This graphic summarises signs and symptoms specific to the two conditions, and those that are common to both.



Data source:

NICE Guideline [NG240] *Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management*

Published: 19 March 2024

contains further information about when to suspect bacterial meningitis and meningococcal disease in the absence of these red flag symptoms and signs.

Evidence on risk factors that increase the likelihood of an individual having bacterial meningitis or meningococcal disease was also evaluated. Recommendations were classified as "be on heightened alert to the possibility of" if a risk ratio of >1.25 (moderate association) or >2.00 (strong association) was found between a risk factor and bacterial meningitis or meningococcal disease, or based on the Guideline Committee's experience. Being on heightened alert may prompt strong suspicions for bacterial meningitis or meningococcal disease in the absence of red flag combinations.

- Strongly suspect bacterial meningitis in people with all the symptoms in the red flag combination:
  - Fever
  - Headache
  - Neck stiffness
  - Altered level of consciousness or cognition (including confusion or delirium).
- Be on heightened alert to the possibility of bacterial meningitis (including meningococcal meningitis) in people with any of these risk factors:
  - Missed relevant immunisations, such as meningococcal, *Haemophilus influenzae* type b (Hib), or pneumococcal vaccines
  - Reduced or absent spleen function
  - Congenital complement deficiency or acquired inhibition
  - A student in further or higher education, particularly if they are in large shared accommodation (such as halls of residence)
  - A family history of meningococcal disease
  - Have been in contact with someone with Hib disease or meningococcal disease, or have been in an area with an outbreak of meningococcal disease
  - A previous episode of bacterial meningitis or meningococcal disease
  - A cerebrospinal fluid leak
  - A cochlear implant.
- Strongly suspect meningococcal disease in people with any of these red flag symptoms:
  - Haemorrhagic, non-blanching rash with lesions larger than 2 mm (purpura)
  - Rapidly progressive and/or spreading non-blanching petechial or purpuric rash
  - Any symptoms and signs of bacterial meningitis (see infographic), when combined with a non-blanching petechial or purpuric rash.
- Be on heightened alert to the possibility of meningococcal disease in people with any of these risk factors:
  - Missed meningococcal vaccinations
  - Reduced or absent spleen function
  - Complement deficiency or inhibition
  - A student in further or higher education, particularly if they are in large shared accommodation (such as halls of residence)
  - A family history of meningococcal disease
  - Have been in contact with someone with meningococcal disease, or have been in an area with an outbreak
  - A previous episode of meningococcal disease.
- If you send a person home after clinical assessment for bacterial meningitis and meningococcal disease:
  - Give safety netting advice (see recommendation 1.3.2 of full guideline)
  - Ask them to return for further assessment if they develop new symptoms, if a rash changes from blanching to non-blanching, or if existing symptoms get worse.

Antibiotic therapy pre-hospital

These recommendations were updated, now including or amending suggestions of recommended antibiotic therapy pre-hospital. Following evidence review, administration of pre-hospital antibiotic therapy was not associated with improved clinical outcomes in patients with suspected bacterial meningitis and meningococcal disease.[5 6] However, in the real world setting, it remains difficult to distinguish bacterial meningitis from other conditions that do not require antibiotic therapy, patients who have meningococcal disease deteriorate rapidly, and there can be substantial delay in transferring patients to hospital. Therefore, pre-hospital antibiotic therapy should be given where meningococcal disease is strongly suspected unless it will delay transfer to hospital, or where transfer to hospital is likely to be significantly delayed for people with strongly suspected bacterial meningitis.

Ceftriaxone is the preferred option because it is a broad spectrum antibiotic, but it is less commonly available outside of hospital than benzylpenicillin. Administering the antibiotic intramuscularly, rather than intravenously, is more practical.

- If there is likely to be a clinically significant delay in transfer to hospital for people with strongly suspected bacterial meningitis, give intravenous or intramuscular ceftriaxone or benzylpenicillin outside of hospital.
- For people with strongly suspected meningococcal disease, give intravenous or intramuscular ceftriaxone or benzylpenicillin as soon as possible outside of hospital, unless this will delay transfer to hospital.
- Do not give antibiotics outside of hospital if the person has severe antibiotic allergy to either ceftriaxone or benzylpenicillin.

Timing of investigations and antibiotic therapy in-hospital

Initiation of antibiotic therapy for suspected bacterial meningitis or meningococcal disease before investigations may hinder diagnosis or lead to unnecessary antibiotic use if patients have a non-bacterial illness. Previous NICE guidance recommended giving antibiotics without delay and what investigations to perform, but did not comment on timeframes or sequencing.

Following evidence review, early (0 to 3 hours) compared with later (≥2 to >3 hours) in-hospital antibiotic administration for bacterial meningitis is associated with lower rates of mortality in adults,[7 8] but there is limited evidence to inform a specific timeframe. For suspected meningococcal disease, there is no evidence comparing different timings of in-hospital antibiotic administration.

The hour after arrival in hospital is widely regarded as the "golden hour" for people with life-threatening conditions and was considered enough time to stabilise a patient, take blood samples, and administer antibiotic therapy. When bacterial meningitis is suspected, it may not always be possible to perform a lumbar puncture, but doing so before starting antibiotic therapy should be the goal when this can be done within one hour.

- A senior clinical decision maker should perform an initial assessment and ensure that:
  - Antibiotics start within one hour of the person with suspected bacterial meningitis arriving at hospital, and in line with the section on antibiotics for bacterial meningitis in hospital [in the full guideline]
  - Blood tests and lumbar puncture are performed before starting antibiotics (if it is safe to do so and will not cause a clinically significant delay to starting antibiotics), and in line with the sections on blood tests and lumbar puncture [in the full guideline].
- A senior clinical decision maker should perform an initial assessment and ensure that:
  - Antibiotics start within one hour of the person with suspected meningococcal disease arriving at hospital, and in line with the section on antibiotics for meningococcal disease in hospital [in the full guideline]
  - Blood tests are performed before starting antibiotics, and in line with the section on blood tests [in the full guideline].

Hospital discharge and post-discharge care

A wide range of long term complications are associated with bacterial meningitis and meningococcal disease, some of which may not be evident for several months or years.[9 10] Do not discharge people with bacterial meningitis and meningococcal disease from hospital until relevant assessments have taken place and an appropriate follow-up plan has been arranged.

The updated recommendations comment on timing of follow-up visits, how long people should be followed up for, and which assessments should be undertaken. Patients prefer written information, such as a detailed discharge summary, and think that it is helpful and informative.[11] A review at four to six weeks after discharge is newly recommended for all adults, in line with the existing recommendation for babies, children, and young people, to discuss any known complications and ensure any delayed complications are not missed. The Guideline Committee did not specify who should undertake this review because there could be variation in practice locally but acknowledged that such assessments are usually performed in secondary care.

- For people who are taking antiepileptic drugs, refer for a medicines review three months after hospital discharge with a clinician with an interest in epilepsy, an epilepsy specialist nurse, or a neurologist.
- Document the follow-up plan for managing complications in the discharge summary.
- For adults who have had bacterial meningitis or meningococcal disease, arrange for a review with a hospital doctor at four to six weeks after discharge from hospital. As part of this review, cover:
  - The results of their audiological assessment (if available at this time) and whether cochlear implants are needed
  - Damage to bones and joints
  - Skin complications (including scarring from necrosis)
  - Psychosocial problems
  - Neurological problems
  - Care needs.
- For babies under 12 months old who have had meningitis or meningococcal disease, arrange a review with a paediatrician for one year after discharge. At this review, assess for possible late-onset neurodevelopmental, orthopaedic, sensory, and psychosocial complications.
- For babies, children, and young people, community child development services should follow up and assess the risk of long term neurodevelopmental complications for at least two years after discharge.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

LG is a lay member of the Guideline Committee. Committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

GUIDELINES INTO PRACTICE

- Think about the last time you suspected someone to have bacterial meningitis and meningococcal disease. What symptoms and signs did you consider, and how did you provide timely management in your setting?
- When discharging patients with confirmed bacterial meningitis and meningococcal disease, what follow-up do you arrange routinely?

Implementation

Real-world data demonstrate that the "golden hour" of commencing antibiotic therapy within one hour of arrival to hospital is often missed. In one retrospective case record study, median door-to-antibiotic time was 3.8 hours (interquartile range 1.4-6.1).[12] Existing secondary care pathways should be reviewed to ensure that there is timely assessment by a senior decision maker and that investigations and antibiotic therapy are not delayed.

Multiple recommendations related to follow-up after discharge may affect primary and secondary care resources to ensure complications of bacterial meningitis and meningococcal disease are detected and managed appropriately. Psychosocial and family support recommendations may be expensive to implement at an individual level; however, the overall population covered by the recommendations is relatively small. Therefore, implementation of the follow-up care is not anticipated to have a significant resource impact.

Competing interests: See bmj.com.

Cite this as: *BMJ* 2024;387:q2452

Find the full version with references at http://dx.doi.org/10.1136/bmj.q2452

CASE REVIEW

Multiple pruritic eruptions and hyperpigmentation

A woman in her 40s presented with a three year history of pruritic eruptions on the dorsum of her hands. She had previously been treated for fungal infection, eczema, and lichen planus using antifungal ointment, and topical and oral corticosteroids, but showed no improvement. She also reported a history of anhidrosis. She was known to have polycythaemia vera and had been taking hydroxyurea for many years. On examination, symmetrical keratotic, flat, and polygonal violaceous plaques with telangiectasia were observed on the dorsum and palms of her hands. Dark brown longitudinal pigmentation was seen in the nails. Facial examination showed hyperpigmentation and telangiectasia. Additionally, the patient presented with ichthyosis-like lesions (light brown, dry, polygonal scaly lesions) on both legs, accompanied by apparent hyperpigmentation (figure).

Laboratory evaluation showed unremarkable results for electrolytes, creatine kinase, antinuclear antibodies, erythrocyte sedimentation rate, C reactive protein. Test results for hepatitis, HIV, and syphilis were also negative. Histopathological analysis of a hand dorsum lesion showed epidermal hyperkeratosis and vacuolar degeneration of basal cells, with mild lymphocytic infiltration, angiogenesis, presence of melanophages and melanin granules, and decrease of sweat glands in the dermis.

1 What are the differential diagnoses?

2 What is the most likely diagnosis?

3 How would you manage this condition?

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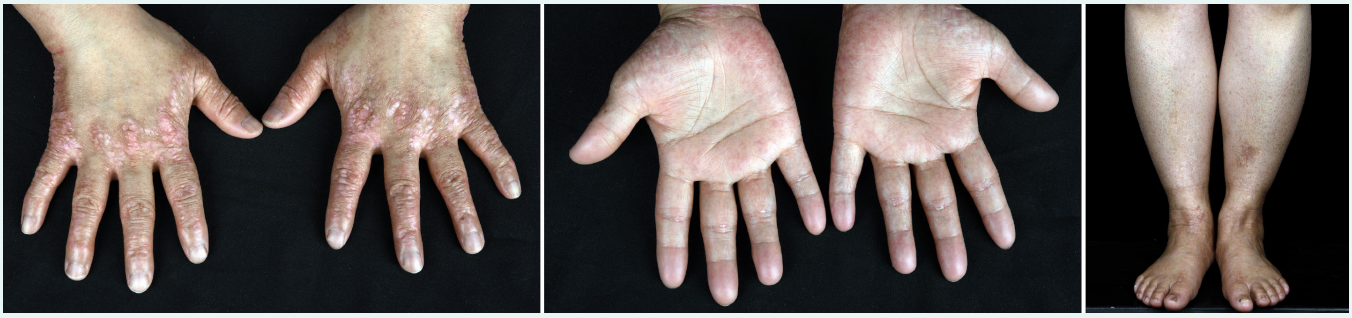
Patient consent obtained.

Cite this as: *BMJ* 2024;387:e079262



Symmetrical polygonal violaceous plaques with telangiectasia on the dorsum and palms of patient's hands (left, middle). Dark brown longitudinal pigmentation in the nails (left). Acquired ichthyosis-like lesions on both legs (right)

answers

CASE REVIEW **Multiple pruritic eruptions and hyperpigmentation**

1 What are the differential diagnoses?

Differential diagnoses include chronic actinic dermatitis, lichen planus, dermatomyositis, and hydroxyurea dermopathy.

2 What is the most likely diagnosis?

Hydroxyurea dermopathy. Hydroxyurea is a cytostatic agent used for the treatment of haematological disorders such as chronic myelogenous leukaemia, polycythaemia vera, and essential thrombocythaemia. An estimated 13% of patients have mucocutaneous changes during long term treatment. Cutaneous adverse effects from long term treatment with hydroxyurea include acquired ichthyosis, acral erythema, hyperpigmentation, alopecia, photosensitivity, palmoplantar keratoderma and, less commonly, lichenoid eruptions, melanonychia, leg ulcers, actinic keratoses, and squamous cell carcinoma. These lesions are referred to as hydroxyurea dermopathy.

3 How would you manage this condition?

Hydroxyurea dermopathy is characterised by spontaneous regression on discontinuation of hydroxyurea. In most patients, clinical manifestations improve within one to 12 months after stopping hydroxyurea without recurrence. A comprehensive evaluation of the severity of cutaneous symptoms and haematological disorders is needed to determine the appropriateness of stopping treatment with hydroxyurea. If cessation is not feasible, consider substituting hydroxyurea with alternatives such as busulfan. If substitution is not possible, symptomatic management is the only option. For instance, topical corticosteroids can be applied if skin rash is accompanied by pruritus. In cases of dryness, desquamation, or fissures, moisturising creams are beneficial.

LEARNING POINTS

- Hydroxyurea dermopathy can present as acral erythema, hyperpigmentation, lichenoid eruptions, melanonychia, actinic keratoses, and other typical features of various skin conditions, although they rarely occur simultaneously.
- Hydroxyurea dermopathy is characterised by spontaneous regression on stopping treatment with hydroxyurea.
- Diagnosis of hydroxyurea dermatopathy is often overlooked in haematological patients and misdiagnosed in dermatological patients.

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LEARNING MODULE

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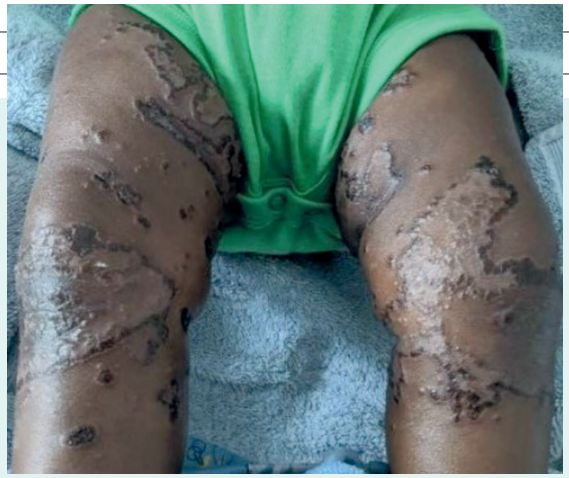
Desquamating pruritic rash in a toddler

This toddler presented with a three month history of widespread well demarcated desquamating and pruritic rash involving the neck, trunk, legs, and nappy area but sparing the perioral region. He was born at full term and was otherwise well with no concerns about growth or development. Hair texture and growth were normal. He had intermittent diarrhoea, which his parents attributed to antibiotics prescribed to treat the rash, although with no improvement. He was almost exclusively breastfed and was receiving iron and vitamin D supplementation because he was an extremely picky eater.

A nutritional profile showed plasma zinc 4.7 umol/L (range 11-24 umol/L). Full blood count showed haemoglobin of 106 g/L (range 105-135 g/L) with hypochromia and microcytosis. Genetic testing excluded hereditary causes of zinc deficiency. The rash resolved after four weeks of treatment with 0.6 mg/kg oral zinc sulphate twice daily. Zinc deficiency is among the most common micronutrient deficiencies and might unusually give rise to a widespread rash rather than the classic perioral and nappy rash seen in acrodermatitis enteropathica.



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Parental consent obtained.
Cite this as: *BMJ* 2024;387:e079522

Genetic determinism

Most human traits and diseases have a polygenic pattern of inheritance. Take human height as an example. Twin studies have established that it is largely genetically determined, but genome-wide association studies have identified more than 12 000 genetic variants contributing to the phenotype (*Nature* https://www.nature.com/articles/d41586-022-03029-4). A historian of science argues that we should remember the dark history of the belief that inheritance dictates destiny and move away from the notion that specific genes are responsible for particular traits and diseases (*London Rev Books* https://www.lrb.co.uk/the-paper/v46/n21/lorraine-daston/degrees-of-wrinkledness).

Secondary hypertension in young adults

An underlying cause was identified in almost a third of 2000 young adults being investigated for hypertension in centres in France (*Hypertension* doi:10.1161/HYPERTENSIONAHA.124.22753). The commonest diagnoses, in descending order of frequency, were primary aldosteronism, renal disease, pheochromocytoma, and functional paraganglioma. Secondary hypertension was commoner in people aged 30 to 40 than in those 18 to 30. Predictors of an underlying cause of hypertension were female sex, hypokalaemia, no familial history of hypertension, and a body mass index below 25 kg/m².

Predicting sudden cardiac death

Which patients recovering from a myocardial infarction are most likely to benefit from an implantable cardioverter defibrillator? An analysis of data from 140 000 post-myocardial infarction patients fails to give an answer (*Eur Heart J* doi:10.1093/eurheartj/ehae326). Despite information on demographics, medical history, clinical characteristics, biomarkers, electrocardiography, echocardiography, and cardiac magnetic resonance imaging, it was impossible to predict with any accuracy which patients would experience a sudden cardiac death.

Why does central venous access fail?

Central venous access devices allow intravenous therapy, haemodynamic monitoring, and blood sampling, but many fail or cause complications before treatment is completed. A secondary analysis of data from a trial comparing different types of central line devices reports that the most frequent problems are bloodstream infection, occlusion, accidental dislodgement, catheter fracture, and thrombosis (*J Hosp Med* doi:10.1002/jhm.13414). The practical message is that we should pay more attention to preventing infection and improving how the device is secured.

Tracking of blood pressure from childhood to adulthood

On the subject of hypertension, a longitudinal study from Finland, which examined participants nine times from childhood to mid adult life, reports that those with elevated blood pressure as children or adolescents were twice as likely to have raised blood pressure or hypertension as adults. Even so, a substantial proportion returned to normal levels of blood pressure as they got older (*JAMA Pediatr* doi:10.1001/jamapediatrics.2024.4368).

Animal capital

More than 1.5 million living animal species have been described and several million more are probably awaiting discovery. Although 65 000 of these species are vertebrates, most humans are aware of only a few dozen. Rather than concentrating conservation efforts on a few species—often photogenic apex predators—it might be better to promote understanding of the benefits of biodiversity (*npj Sustain Agric* doi:10.1038/s44264-024-00030-4).

Cutaneous stigmata of infective endocarditis

Osler's nodes (tender, purple swellings on fingertips) and Janeway lesions (irregular, non-tender, purpuric macules on the palms and soles) are classic cutaneous findings in infective endocarditis. They are thought to be caused by septic microemboli from the valvular vegetation. An illustrated case report reminds us that, although present in only a few percent of cases, when they are observed transoesophageal echocardiography is urgently required (*JAMA Dermatol* doi:10.1001/jamadermatol.2024.0481).

Cite this as: *BMJ* 2024;387:q2592