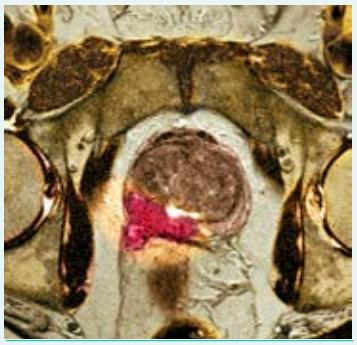
education

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman



MRI guided biopsy for suspected prostate cancer

"Magnetic resonance imaging (MRI) with or without targeted biopsy, was non-inferior to standard biopsy, and the 95% confidence interval indicated the superiority of this strategy over standard biopsy. Fewer men in the MRI targeted biopsy group than in the standard biopsy group received a diagnosis of clinically insignificant cancer." Here some seriously awesome investigators have to twist their minds in order to use the mandatory "non-inferiority" word. The UK-based PRECISION trial will change practice in the diagnosis of prostate cancer and mean that fewer men will receive unnecessary treatment.

To say more about it would involve some really detailed explanation of the population enrolled, the diagnostic strategies which were compared, and the outcome measures used. Suffice to say that when the lessons of this trial are adopted in practice, MRI will reduce transrectal biopsies and at the same time identify the high Gleason score cancers that really need treatment. Better diagnosis will reduce overdiagnosis and overtreatment.

N Engl J Med doi:10.1056/NEJMoa1801993

Stage III colorectal cancer: three or six months of chemo?

"The IDEA collaboration was a prospectively conducted study involving 12 834 patients with stage III colon cancer who were enrolled in six individual trials and randomly assigned to receive either 3 months or 6 months of adjuvant therapy with oxaliplatin and a fluoropyrimidine. Robust data were generated regarding benefits and risks according to the duration of therapy in these patients. As expected, a shorter duration of adjuvant therapy was associated with a significantly lower incidence and severity of adverse events, especially neurotoxicity, but also symptomatic side effects such as the hand-foot syndrome, mucositis, nausea, fatigue, and diarrhea."

This summary perfectly encapsulates the message of the six trials bundled into this report, and as a patient I would have no hesitation in opting for the shorter course. But readers skimming through the abstract would take away quite a different message: "Among patients with stage III colon cancer receiving adjuvant therapy with FOLFOX or CAPOX, noninferiority of 3 months of therapy, as compared with 6 months, was not confirmed in the overall population. However, in patients treated with CAPOX, 3 months of therapy was as effective as 6 months, particularly in the lower-risk subgroup."

Once again non-inferiority rears its stupid head, and if you look at the fine print you will see that it is accompanied by its even stupider twin, disease-free survival. I long for the day when valuable datasets like this are accompanied by interactive decision tools for patients and clinicians, rather than reduced to bogus binary statistical categories.

N Engl J Med doi:10.1056/NEJMoa1713709

Oral ibuprofen best for patent ductus arteriosus closure

The debate about using drugs to close a patent ductus arteriosus in premature babies is mostly about whether to do it and when. Then there is the question of what drug to use. A systematic review and network meta-analysis gives a plain answer: high-dose oral ibuprofen. It has a much better success rate than intravenous ibuprofen or indometacin. In all groups including placebo there was no difference in mortality, necrotising enterocolitis, or intraventricular haemorrhage.

JAMA doi:10.1001/jama.2018.1896

Siponimod and secondary progressive multiple sclerosis

Siponimod is a new word that rhymes with God, but I doubt whether it will be used much by hymn writers. And sadly I'm not sure it will be widely used by people with secondary progressive multiple sclerosis (SPMS), though you might think otherwise reading the conclusion of the abstract: "Siponimod reduced the risk of disability progression with a safety profile similar to that of other S1P modulators and is likely to be a useful treatment for SPMS. Funding: Novartis Pharma AG."

The primary end point was one I haven't come across before: time to the occurrence of a prespecified number of confirmed disability progression events. Adverse events were spectacularly common in both active and placebo groups, but lymphopenia, increased liver transaminase concentration, bradycardia and bradyarrhythmia at treatment initiation, macular oedema, hypertension, varicella zoster reactivation, and convulsions occurred more frequently with siponimod than with placebo.

Lancet doi:10.1016/S0140-6736(18)30475-6

Lancet doi:10.1016/S0140-6736(18)30426-4

GUIDELINES

Lyme disease: summary of NICE guidance

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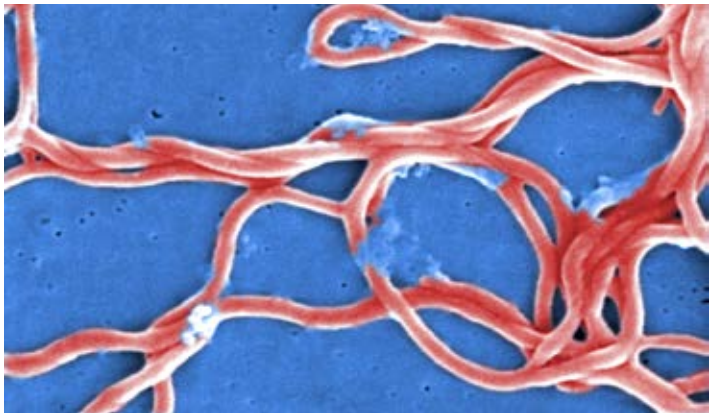
Further information about the guidance, a list of members of the guideline committee, and the supporting evidence statements are in the full version on bmj.com.

Lyme disease is caused by a specific group of *Borrelia burgdorferi* bacteria, which can be transmitted to humans through a bite from an infected tick. This can result in a number of clinical problems ranging from skin rash to serious involvement of organ systems, including arthritis, and neurological problems. People with skin and non-specific symptoms most commonly present to their general practitioner and are often treated in primary care, whereas people with symptoms affecting organ systems are commonly referred to specialists.

The guideline focuses on diagnosis and management of Lyme disease according to clinical presentation and symptoms rather than using the differing classifications of Lyme disease, which are poorly defined and contested. There is a lack of good quality evidence on the epidemiology, prevalence, diagnosis, and management of Lyme disease.



HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Committee members involved in this guideline update included four lay members who contributed to the formulation of the recommendations summarised here.

WHAT YOU NEED TO KNOW

- Lyme disease can occur anywhere in the UK
- Erythema migrans is diagnostic of Lyme disease
- Use a combination of clinical presentation and laboratory testing to guide diagnosis and treatment in people without erythema migrans
- Symptoms of Lyme disease may take months or years to resolve even after treatment
- Consider a second course of antibiotics for people with ongoing symptoms as treatment may have failed

CPD READING
0.5 HOURS

RECOMMENDATIONS

Awareness

The incidence of Lyme disease is unknown. Most estimates are based on laboratory confirmed cases and therefore do not include those diagnosed on clinical presentation alone or those that go undiagnosed. The indicative rash, erythema migrans, is not always present, noticed, or recognised, and other symptoms overlap with many other common conditions. The following recommendations were developed to raise awareness of factors affecting Lyme disease risk and when to suspect Lyme disease.

- Be aware that:
  - The bacteria that cause Lyme disease are transmitted by the bite of an infected tick
  - Ticks are mainly found in grassy and wooded areas, including urban gardens and parks
  - Tick bites may not always be noticed
  - Infected ticks are found throughout the UK and Ireland; although some areas seem to have a higher prevalence of infected ticks, prevalence data are incomplete
  - Particularly high risk areas are the south of England and Scottish Highlands, but infection can occur in many areas
  - Lyme disease may be more prevalent in parts of central, eastern, and northern Europe (including Scandinavia) and parts of Asia, the US, and Canada.
- Be aware that most tick bites do not transmit Lyme disease.
- Give people advice about:
  - Where ticks are commonly found (such as grassy and wooded areas, including urban gardens and parks)
  - The importance of prompt, correct tick removal and how to do this (see box, p 37)
  - Covering exposed skin and using insect repellents that protect against ticks
  - How to check themselves and their children for ticks on the skin
  - Sources of information on Lyme disease, such as Public Health England, and organisations providing information and support, such as patient charities.

Lyme disease: Antibiotic choices

thebmj Visual summary

This graphic summarises guidance on choice of antibiotic for the treatment of Lyme disease, produced by the UK's National Institute for Health and Care Excellence (NICE). It recommends offering one initial course of antibiotics, and considering a second course of an alternative antibiotic for people with ongoing symptoms. If a person's symptoms continue following two completed courses of antibiotics, its advice is to consider discussion with a national reference laboratory or referral to a specialist appropriate for the person's symptoms

KEY

First, second, or third choice — 1st Doxycycline — Oral or intravenous administration

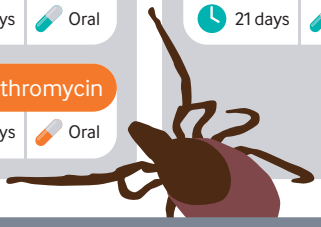
Duration of regimen — 21 days — Oral

Erythema migrans and/or non-focal symptoms

- 1st Doxycycline — 21 days — Oral
- 2nd Amoxicillin — 21 days — Oral
- 3rd Azithromycin — 17 days — Oral

Lyme disease affecting the cranial nerves or peripheral nervous system

- 1st Doxycycline — 21 days — Oral
- 2nd Amoxicillin — 21 days — Oral



Lyme disease affecting the central nervous system

- 1st Ceftriaxone — Enhanced dose — 21 days — IV
- 2nd Doxycycline — Enhanced dose — 21 days — Oral

Lyme carditis

- 1st Doxycycline — 21 days — Oral
- 2nd Ceftriaxone — First choice for haemodynamically unstable patients — 21 days — IV

Lyme disease arthritis or acrodermatitis chronica atrophicans

- 1st Doxycycline — 28 days — Oral
- 2nd Amoxicillin — 28 days — Oral
- 3rd Ceftriaxone — 28 days — IV

Dosing recommendations

Doxycycline

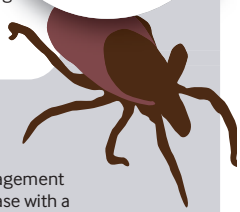
Age 12+ / Children 45 kg +	100 mg 2x per day — or — 200 mg daily	Enhanced dose: 200 mg 2x per day — or — 400 mg daily
Children 9–12 years under 45 kg	**Day 1:** 5 mg per kg 2 divided doses	**Subsequent days:** 2.5 mg per kg — or — up to 5 mg/kg in severe cases

Doxycycline and azithromycin have no marketing authorisation in the UK for children under 12. However, use in children aged 9 years and above is accepted specialist practice. Informed consent should be obtained, and full responsibility taken by the prescriber

Azithromycin

Age 12+ / Children 50 kg +	500 mg daily
Children under 50 kg	10 mg per kg daily

Do not use azithromycin to treat people with cardiac abnormalities because of its effect on QT interval



Ceftriaxone

Age 12+ / Children 50 kg +	2 g daily — Enhanced dose: 2 g 2x per day — or — 4 g daily
Children under 50 kg	80 mg per kg daily

Amoxicillin

Age 12+ / Children 33 kg +	1 g 3x per day
Children under 33 kg	30 mg per kg 3x per day

Discuss management of Lyme disease with a specialist in children and young people , unless they have isolated erythema migrans with no other symptoms

For Lyme disease suspected during pregnancy, use appropriate antibiotics for stage of pregnancy

DIAGNOSIS

Figure 1 details the guidance for use of tests in diagnosis of Lyme disease.

- Diagnose Lyme disease in people with erythema migrans (fig 2), a red rash that:
  - Increases in size and may sometimes have a central clearing
  - Is not usually itchy, hot, or painful
  - Usually becomes visible from one to four weeks (but can appear from 3 days to 3 months) after a tick bite and lasts for several weeks
  - Is usually at the site of a tick bite.
- Be aware that a rash that is not erythema migrans can develop as a reaction to a tick bite. This rash:
  - Usually develops and recedes within 48 hours from the time of the tick bite
  - Is more likely than erythema migrans to be hot, itchy, or painful
  - May be caused by an inflammatory reaction or infection with a common skin pathogen.
- Consider the possibility of Lyme disease in people presenting with several of the following symptoms, because Lyme disease is a possible but uncommon cause of: fever and sweats; swollen glands; malaise; fatigue; neck pain or stiffness, migratory joint or muscle aches and pain; cognitive impairment; headache; paraesthesia.
- Consider the possibility of Lyme disease in people presenting with symptoms and signs relating to one or more organ systems (focal symptoms) because Lyme disease is a possible but uncommon cause of: neurological symptoms; inflammatory arthritis; cardiac problems such as heart block or pericarditis; eye symptoms such as uveitis or keratitis; skin rashes such as acrodermatitis chronica atrophicans or lymphocytoma.
- If a person presents with symptoms that suggest the possibility of Lyme disease, explore how long the person has had symptoms and their history of possible tick exposure. Do not rule out the possibility of Lyme disease in people with symptoms but no clear history of tick exposure.
- Use a combination of clinical presentation and laboratory testing to guide diagnosis and treatment in people without erythema migrans (see fig 1). Do not rule out diagnosis if tests are negative but there is high clinical suspicion of Lyme disease.

The most common laboratory tests used when Lyme disease is suspected are serological tests that detect antibodies to the bacteria causing Lyme disease. This is based on a two tier approach, where a sensitive initial test is performed first, followed by a more specific confirmatory test in case of a positive or equivocal initial test result. When combined with clinical assessment, the tests can be helpful in supporting diagnosis.

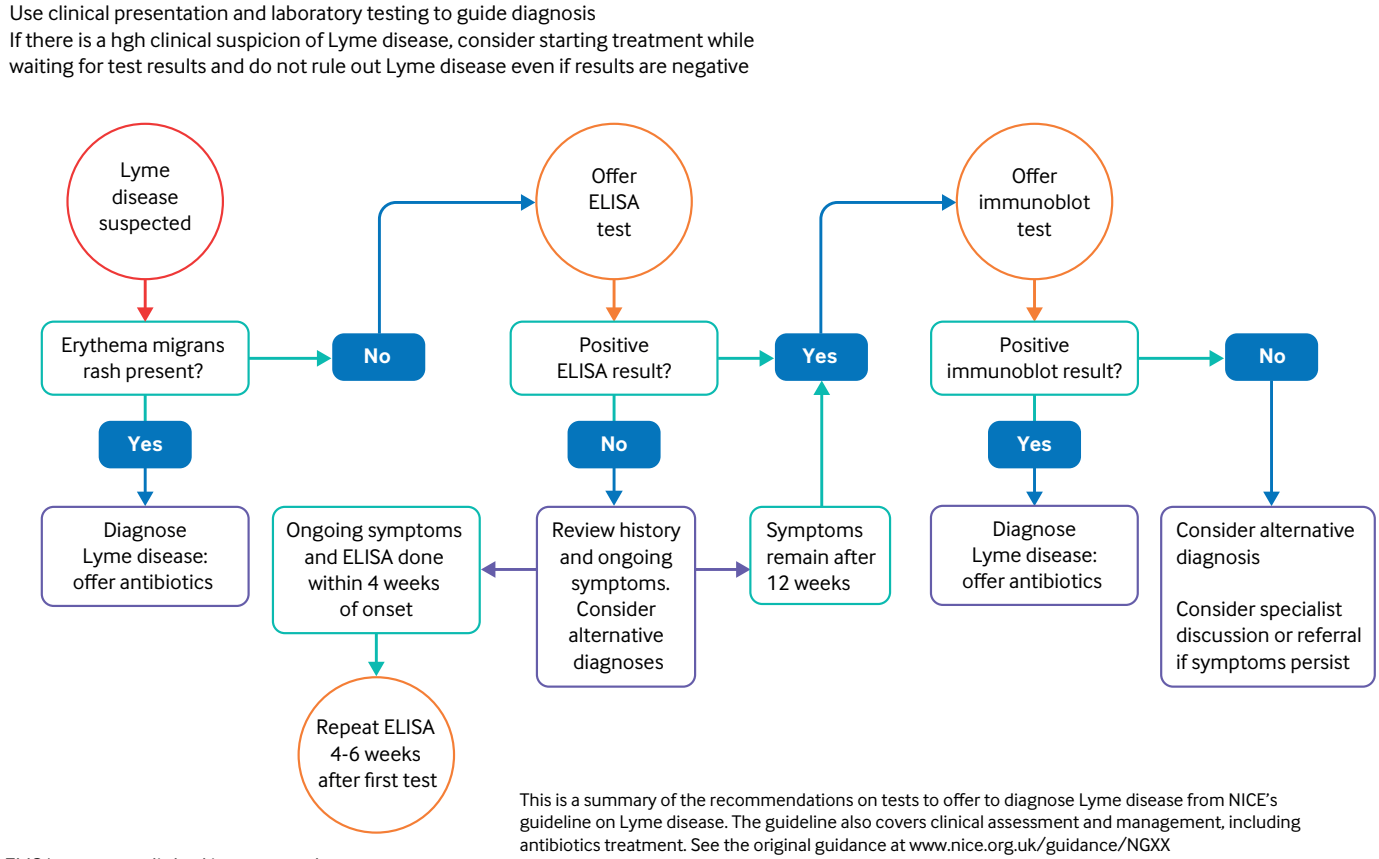


Fig 1 | Algorithm for laboratory investigations and diagnosis of Lyme disease

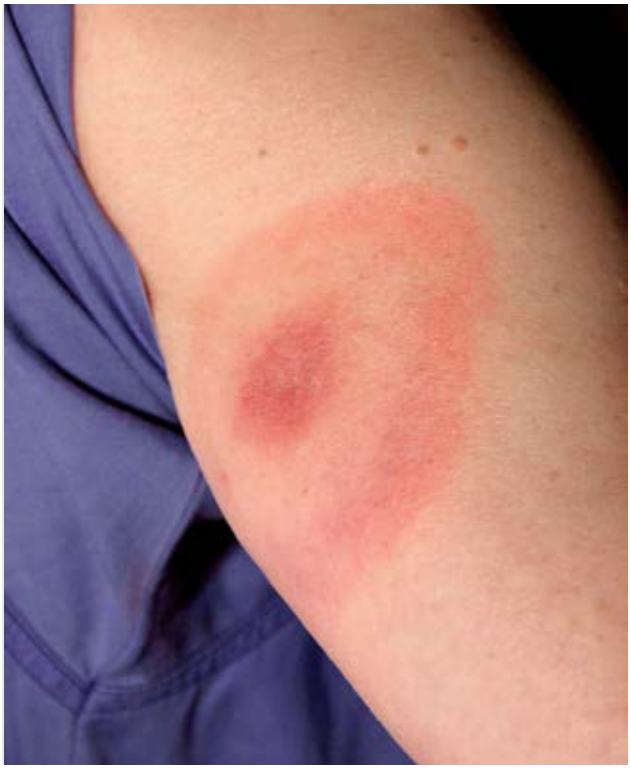
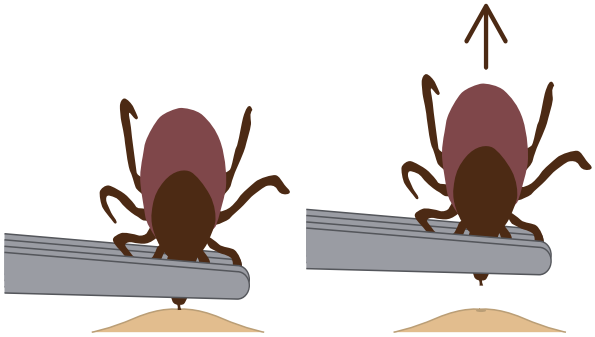


Fig 2 | Classic erythema migrans of Lyme disease

GUIDELINES INTO PRACTICE

- Which groups of patients do you tend to test or treat for Lyme disease? Does this guideline provide ideas on how to alter your practice?
- Which groups of patients would you discuss with a specialist for suspected Lyme disease? Does this guideline provide ideas on how to alter your practice?
- How might you share learning from this guideline with colleagues?



CORRECT REMOVAL OF TICKS

- If you have been bitten, remove the tick as soon as possible
- Use a pair of fine-tipped tweezers or a tick removal tool
- Grasp the tick as close to the skin as possible
- Pull upwards slowly and firmly, as tick mouthparts left in the skin can cause a local infection
- Once the tick is removed, apply antiseptic to the bite area or wash with soap and water and keep an eye on it for several weeks for any changes

MANAGEMENT

Doses and duration of antibiotic treatment have been chosen at the higher ranges of formulary doses and lengths of treatment to avoid the possibility of under-treatment. There was a lack of evidence to support extended courses of antibiotics for people with persisting symptoms.

- Treat people with Lyme disease according to the infographic
- Discuss diagnosis and management of all children and young people with Lyme disease and symptoms in addition to erythema migrans with a specialist
- If an adult with Lyme disease has focal symptoms, consider a discussion with or referral to an appropriate specialist without delaying treatment
- If symptoms that may be related to Lyme disease persist, do not continue to improve, or worsen after antibiotic treatment, review the person's history and symptoms to explore:
  - Possible alternative causes of the symptoms
  - If reinfection may have occurred
  - If treatment may have failed
  - Details of previous treatment, including whether the course of antibiotics was completed
  - If symptoms may be related to organ damage caused by Lyme disease, such as nerve palsy.
- Consider a second course of antibiotics for people with ongoing symptoms if treatment may have failed. Use an alternative antibiotic to the initial course.
- If a person has ongoing symptoms after two completed courses of antibiotics for Lyme disease:
  - Do not routinely offer further antibiotics and
  - Consider discussion with the English or Scottish national reference laboratory or discussion or referral to a specialist appropriate for the person's symptoms.

Explain the diagnosis and uncertainties

The uncertainty that exists as a result of lack of good evidence is difficult for people with Lyme disease and can lead to fear and frustration.

- Tell people that tests for Lyme disease have limitations. Explain that both false positive and false negative results can occur and what this means.
- Explain that most tests for Lyme disease assess the presence of antibodies and that the accuracy of tests may be reduced if:
  - Testing is carried out too early (before antibodies have developed)
  - The person has reduced immunity (such as a person receiving immunosuppressant treatment) that might affect the development of antibodies.
- Explain to people with ongoing symptoms after antibiotic treatment for Lyme disease that:
  - Continuing symptoms may not mean they still have an active infection
  - Symptoms of Lyme disease may take months or years to resolve even after treatment
  - Some symptoms may be a consequence of permanent damage from infection
  - There is no test for active infection and an alternative diagnosis may explain their symptoms.

Competing interests: See bmj.com.

Cite this as: *BMJ* 2018;361:k1261

Find the full version with references at http://dx.doi.org/10.1136/bmj.k1261

SPOT DIAGNOSIS

An incidental finding on a knee radiograph

A 24 year old man attended the emergency department with pain in the lateral left knee after intercepting a pass when playing football. Plain anteroposterior and lateral radiographs of the knee were obtained, which ruled out the presence of a fracture or lipohaemarthrosis, but instead showed several distinctive lesions (fig 1). The patient was referred for a magnetic resonance imaging (MRI) scan of the knee because of ongoing pain and loss of function. The MRI showed a complex tear of the posterior horn of the lateral meniscus, which required surgical intervention. What is the incidental finding seen on the knee radiograph?

Submitted by James Russell and Joanna Farrant

Patient consent obtained.

Cite this as: *BMJ* 2018;360:k596

bmj.com

Find the full version with accompanying video

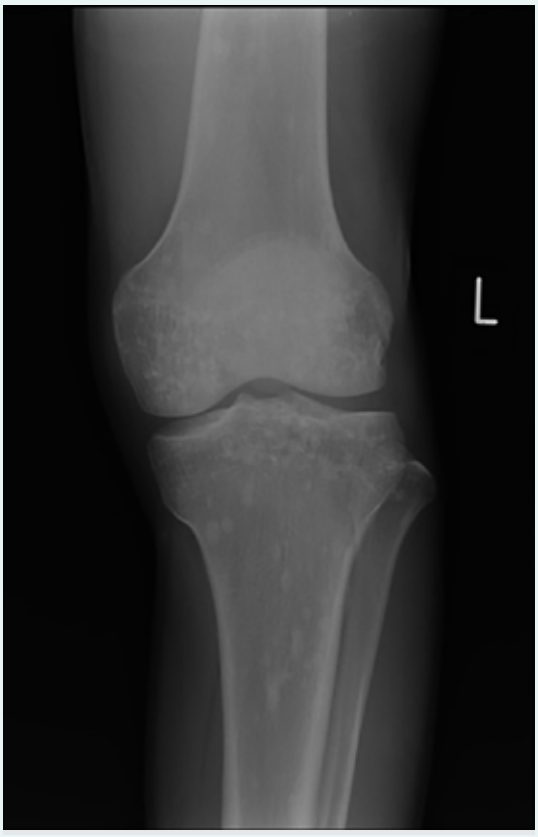


Fig 1 | Anteroposterior radiograph of the left knee

If you would like to write a Case Review for Endgames, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

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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.

answers

There are multiple well defined sclerotic foci within the bones (fig 2), in keeping with a diagnosis of osteopoikilosis ("spotted bone disease"). This is an autosomal dominant condition characterised by multiple bone islands, which typically cluster symmetrically around joints.

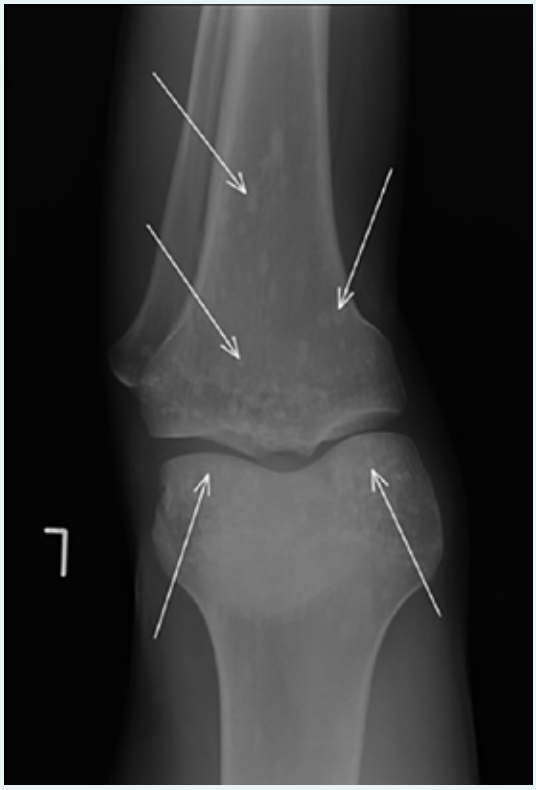
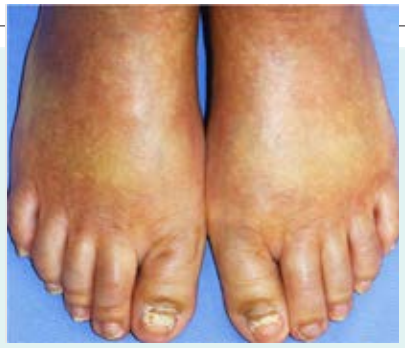


Fig 2 | Anteroposterior radiograph of the left knee, with white arrows pointing out multiple well defined sclerotic foci distributed symmetrically around the joint

Drug-induced localised scleroderma

A 70 year old woman presented with skin hardening on her feet. Symptoms had started one month after completing docetaxel, trastuzumab, and pertuzumab chemotherapy for breast cancer. Examination revealed symmetrical, glossy, yellow-brown sclerotic skin on the toes, dorsal feet, and lower legs (figure). Blood tests, including antinuclear antibodies, urine analysis, and chest computed tomography, were unremarkable. Histopathological examination confirmed scleroderma. Docetaxel-induced localised scleroderma was diagnosed. Docetaxel chemotherapy was suspended, and oral prednisolone (20 mg/day) was initiated.

Scleroderma can manifest as an adverse reaction to several drugs, including docetaxel, bisoprolol, bleomycin, pepleomycin, D-penicillamine, bromocriptine, pentazocine, and balicatib. In addition to withdrawal of the culprit drug, corticosteroids and ultraviolet phototherapies can be effective, if instituted early. Systemic therapies, including cyclophosphamide and methotrexate, have been used with some success in a small case series. There is no definitive treatment at the advanced stage, so early diagnosis is key.



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Patient consent obtained.

Cite this as: *BMJ* 2018;360:k1326

Scarlet fever

After decades of falling incidence, scarlet fever is on the rise. Current rates in England are the highest for 50 years and all parts of the country are affected. Outbreaks are common in nurseries and schools and the median age of cases is four years (*Lancet Infect Dis*). Analysis of *Streptococcus pyogenes* isolates shows a diversity of emm types, so the increase in incidence can't be explained by the emergence of a new virulent strain with enhanced capacity to cause scarlet fever.

Migrant health

It's usually thought that the health of migrants is poor in comparison with the health of people in the host country. A study from Scotland which linked census information to mortality data challenges this idea (*PLoS Med*). Mortality among people from ethnic minority groups born outside the UK, in particular people born in Pakistan, Bangladesh, the Caribbean, or China, was strikingly lower than that of the white Scottish population. This finding is something of a paradox, since migrants are more likely to live in adverse socioeconomic circumstances, and have suboptimal access to healthcare.

Paracetamol in pregnancy

The NHS website says that paracetamol is usually safe in pregnancy and that there's no clear evidence of harmful effects on an unborn baby. Wisely, it hedges its bets with advice to take the lowest effective dose for the shortest possible time. Analysis of data from two Scandinavian cohorts shows what a difficult area this is (*Int J Epidemiol*). Although there was a small increase in risk of cerebral palsy in children exposed in utero to paracetamol, it was impossible to be sure whether this was an effect of paracetamol or of the illness that made the drug necessary.

Zika virus and microcephaly

The final report of the case-control study carried out in Recife, north east Brazil in response to the epidemic of microcephaly confirms the initial finding of a strong association with Zika virus infection (*Lancet Infec Dis*). Almost as important, it exonerates two other possible causes. One was the insecticide, pyriproxyfen, which was used in reservoirs of drinking water to control *Aedes aegypti*; the other was vaccine administration during pregnancy. However, this might not be the end of the story, as only 35% of cases of microcephaly had congenital Zika virus detected.

Diagnosing heart failure

Guidelines from the National Institute for Health and Care Excellence for diagnosing heart failure call for a detailed history and clinical examination and, if evidence of heart failure is found, measurement of natriuretic peptides and referral for echocardiography and specialist assessment. This is a long way from what is actually happening in England, according to an analysis of linked records. Out of more than 35 000 patients eventually diagnosed with heart failure, only one in five had it recorded in a primary care consultation, despite the fact that most of them had been seen by a general practitioner in the previous year. Even when heart failure had been recognised, the recommended pathway was rarely followed (*Heart*).

Speed cameras

People who complain about speed cameras probably need to think again. A modelling study from New York city, where there are 140 such cameras, finds that they save both money and lives (*Injury Prevent*). Indeed, the investigators conclude that speed cameras are among the most cost effective public health interventions, and reckon that it would be a good idea to install more. They draw a parallel with vaccination programmes which, as coverage increases, improve herd immunity to a level where epidemics can't be sustained. More cameras would reduce the risk of injury for everyone.

Cite this as: *BMJ* 2018;361:k1487