PROBLEM SOLVING IN CLINICAL PRACTICE

USE YOUR EARS

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ep9

Arch Dis Child Educ Pract Ed 2004;**89**:ep9–ep14. doi: 10.1136/adc.2003.044479

A 6 year old, previously healthy boy called Oliver attended his general practitioner because of right shoulder pain that had developed over the course of one day. The GP does not know the family as they are new to the practice having moved from the USA a few years before. Oliver was a full term normal delivery, is fully immunised, and has no previous medical concerns. On examination Oliver looks generally well. He is not palpably febrile although the GP forgot to formally check his temperature. Oliver is reluctant to use his right arm but his other joints are normal. There is no rash.

The GP wonders whether Oliver has transient synovitis secondary to a viral infection, but he has seen this most frequently affecting the hip joint rather than the shoulder. He decides that the most likely diagnosis is a trivial injury or an awkward sleeping posture. He explains this to Oliver's mother and outlines the differential diagnosis. The GP decides not to treat with a non-steroidal anti-inflammatory drug (NSAID) as he is concerned that it may mask any pain due to inflammatory joint disease. He arranges to review Oliver if there is no improvement over the next few days.

The following day Oliver becomes generally unwell with fever, nausea and vomiting. He also develops redness near the joint. His mother contacts the GP as advised and is seen a few hours later at the end of surgery. Oliver's temperature is 38℃ and he is even more reluctant to move his arm. There is an area of erythema measuring 1 × 2 cm in the right axilla.

The GP considers septic arthritis in his differential diagnosis but decides that the joint pain is not severe enough and that the most likely diagnosis is cellulitis. He prescribes oral flucloxacillin (125 mg four times a day) and asks Oliver to return for reassessment the following day.

The next morning Oliver's temperature is 38.5℃ and the range of movement of his right shoulder is very limited. The area of erythema has spread and is now 2 × 3 cm. The GP now becomes more concerned that Oliver may have septic arthritis, perhaps secondary to the cellulitis. He refers him to the local hospital for assessment.

Oliver presents to the paediatric assessment unit where a GP trainee coming to the end of a six month paediatric attachment assesses him. Oliver's parents confirm that there have been no similar episodes in the past, there has been no trauma, and no one else in the family has joint problems. In addition, there have been no local sites of trauma that would act as a portal of entry for infection.

On examination Oliver's temperature is 38℃, his pulse rate is 120/min and his respiration normal. He is holding his right arm flexed at the elbow, at an angle to his body as though to protect it from any movement. There is an erythematous slightly raised patch of skin inferior to the right axilla with irregular borders that is warm and tender and measures 2 × 3 cm. A few shotty axillary lymph nodes are palpable on the affected side. Right shoulder joint movements, both active and passive, are limited by pain. All other joints are normal on examination. The remainder of the examination is also normal.

The senior house officer considers a differential diagnosis of cellulitis or erysipelas, with pain limiting the movement of the adjacent joint. He thinks it is more likely to be cellulitis as the edges of the rash are not clearly demarcated, and there appears to be subcutaneous tissue involvement because the rash is slightly raised and tender to the touch. He decides that Oliver needs hospital admission for further investigation and intravenous antibiotics.

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COMMENT

- Cellulitis is an infection of the skin with some extension into the subcutaneous tissues. An extremity is the most common location, but it can involve any part of the body. The margins are usually indistinct

Differential diagnosis of monoarticular arthritis

- Septic arthritis (emergency treatment required)
- Transient synovitis
- Acute rheumatic fever
- Juvenile idiopathic arthritis
- Systemic lupus erythematosis
- Henoch Scholein purpura
- Serum sickness
- Leukaemia

- Erysipelas represents a distinct form of superficial cellulitis that is associated with marked swelling of the skin and does not involve subcutaneous tissues. The margins of involved and normal tissues are sharply demarcated, particularly at a bony prominence

During the insertion of the cannula the house officer draws blood for culture, full blood count, liver function tests, erythrocyte sedimentation rate (ESR) and C-reactive protein; he also arranges an *x* ray of Oliver's right shoulder. He considers that the most likely infective organisms are *Staphylococcus aureus* or *Streptococcus pyogenes*, and prescribes intravenous flucloxacillin and benzylpenicillin (according to local guidelines for skin infections). He highlights the admission during the evening ward round, as he has lingering concerns that Oliver may have septic arthritis and would like the registrar to assess him.

Oliver is seen in the early evening by the registrar. He elicits tenderness to palpation of the erythematous skin and limited movement of the right shoulder joint.

The registrar considers the causes of monoarticular arthritis. His main concern is to investigate for a possible septic arthritis, as if present it would need to be aspirated. He requests an ultrasound scan of the shoulder joint and an orthopaedic opinion. The registrar asks the orthopaedic registrar to review the child before the first dose of antibiotics, as he is aware of the importance of joint aspiration and culture of the organism before antibiotics to optimise the chance of identifying the infective organism and obtaining antibiotic sensitivities.

COMMENT

- Fever, joint pain and redness are often caused by bacterial infections, which may cause rapid joint destruction. Septic arthritis is almost always monoarticular in children and predominantly involves large joints. The most common organisms in this age group are *Staphylococcus aureus* and *Streptococcus pyogenes*. *Haemophilus influenza* must be borne in mind even if the child has been immunised in view of recent reports of vaccine failures (Oliver presented prior to the recent HIB booster campaign).

The orthopaedic registrar reviews Oliver and the results of the initial investigations (Table 1). The raised white cell and neutrophil count, and increased ESR and C-reactive protein indicate that a bacterial infection is most likely, although they would also be consistent with an autoimmune disease. In view of the normal ultrasound scan, and the clinical features of a skin infection, he considers that Oliver does not have a septic arthritis, and that the most likely diagnosis is cellulitis. He agrees with the current treatment of intravenous flucloxacillin and benzylpenicillin.

Table 1 Results of the initial investigations

Right shoulder *x* ray	Normal
Ultrasound scan of the shoulder joint	Normal
White cell count	19.4×10^9/l
Neutrophil count	17.05×10^9/l
C-reactive protein	127 mg/l
Erythrocyte sedimentation rate	78 mm in the first hour

Investigations

- Plain radiographs may show subtle signs of joint effusion such as widening of the joint space, soft tissue swelling, obliteration of normal fat planes, or osteomyelitis
- Bone scans are rarely indicated in the diagnostic evaluation of septic arthritis but may be helpful if multifocal disease is suspected in neonates. It also assists with the detection of an associated osteomyelitis
- Ultrasound scans allow selection of children who need aspiration and drainage[1]; the definitive diagnosis being made by examination of synovial fluid obtained through arthrocentesis. False negative ultrasound scans can be a problem if performed within the first 24 hours of symptoms[2]
- ESR is raised in 90% of cases of septic arthritis but lacks specificity
- White blood cell count is raised in 30–60% of cases but also lacks specificity[3]

The paediatric registrar is reassured by the ultrasound scan and the orthopaedic opinion, but remains puzzled by the case. He decides to discuss the situation with the on–call consultant paediatrician.

The consultant paediatrician agrees that the case is not straightforward. He is concerned that the severity of the pain and tenderness is out of proportion with the degree of erythema and considers the possibility of early necrotising fasciitis. He checks that the child has no history of recent chickenpox, which is associated with a notable increase in the incidence of necrotising fasciitis. He also checks that the child has not received any NSAIDs, which he remembers may increase the incidence of necrotising fasciitis. He knows that necrotising fasciitis is caused by group A streptococcus, and considers adding clindamycin to the current regimen.

COMMENT

- Varicella is the most commonly identified risk factor in children with invasive group A streptococcal (GAS) infection. Case reports have described an association between use of NSAIDs and invasive GAS infections in children with varicella but a causal relation has not been established.[4]
- Clindamycin is a lincosamide antibiotic that can be used for the treatment of anaerobic, streptococcal, and staphylococcal infections, and is believed to improve the outcome of invasive GAS infection in children.[5] The reason for considering its use in this case is because it appears to suppress the synthesis of bacterial toxins and it achieves high intracellular levels in phagocytic cells. It also has a longer post-antibiotic effect than β lactam antibiotics such as penicillin. Moreover, when the inoculum of bacteria is high the division rate decreases, so antibiotics such as the β lactams (penicillin and flucloxacillin), which act on the cell wall of actively dividing cells, are less effective. Adding an antibiotic such as clindamycin, which is not affected by inoculum size or stage of growth, is thus beneficial. The major disadvantage of clindamycin is its propensity to cause antibiotic associated diarrhoea.[3]

The consultant paediatrician asks if the child looks generally well. He checks that he is normotensive and that his resting pulse rate has returned to normal when his temperature is under control. He instructs the registrar to review the case regularly. If there is any haemodynamic deterioration he asks to be informed so he can consider the addition of clindamycin, the possible use of intravenous immunoglobulin (IVIG), and the need for intensive care.

COMMENT

- IVIG may be an effective adjunctive therapy for streptococcal toxic shock syndrome (STSS), possibly because of its ability to neutralise bacterial exotoxins. A single dose of IVIG resulted in a decrease in IL-6 and TNF-alpha in most patients tested for cytokine production.[6] IVIG might be effective by specific neutralisation of streptococcal toxins and non-specific inhibition of monocyte/T cell activation but its evidence-based role in STSS remains to be determined.[4]

The consultant sees Oliver the next morning on the ward round. Oliver continues to have spikes of fever and the area of erythema has increased to a diameter of 10 cm. The movement of his right shoulder remains limited (unchanged). He is haemodynamically stable.

The consultant is reassured that Oliver is haemodynamically stable. After the night time telephone call he had been concerned about STSS. However, he knows that in this condition shock is present at admission or within 8 hours in nearly all patients. He reflects on the fact that Oliver has been on antibiotics for 12 hours, but considers that it is too soon to expect much improvement. His working diagnosis continues to be cellulitis.

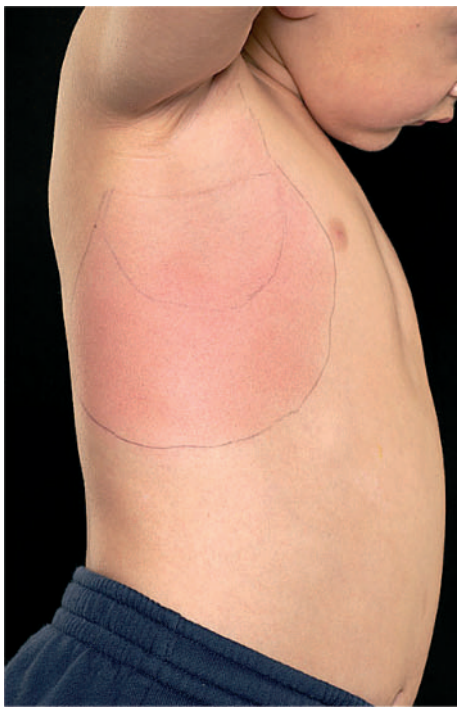

Figure 1 Rash in the right axilla and lateral chest wall. (Source: Media Resource Centre, Cardiff and Vale NHS Trust/University of Wales College of Medicine. Reproduced with permission of the child's parents.)

The next morning (second day of admission) Oliver continues to have spikes of fever, but the movement of his shoulder has improved slightly and he looks generally a little better. However the rash has continued to spread, it is deeply erythematous and has a diameter of 17 cm (fig 1) .Cervical and axillary lymphadenopathy is noted.

The consultant is alarmed that although the subcutaneous tissue is less tender, the rash has spread despite 36 hours of intravenous broad spectrum antibiotics. He considers the differential diagnosis of fever associated with a rash and arthralgia in children with the junior staff, considering the differential in several main categories; infectious and post-infectious, rheumatic diseases, vasculitides and neoplastic diseases (Table 2). They discuss the factors for and against each of these diagnoses to guide further investigations.

In view of this differential diagnosis the consultant requests an autoimmune screen including antinuclear antibody (ANA) and viral serology including parvovirus B19 (IgG and IgM), and antistreptolysin O titre. He considers ordering viral hepatitis serology, but as the liver function test results are normal he decides to defer this investigation. He also orders a repeat C-reactive protein, ESR and white cell count to help monitor the progress of the disease. He asks his paediatric colleague with an interest in infectious diseases to see Oliver.

The paediatrician with an interest in infectious diseases reviews the history with Oliver's parents. The first thing he notices is that the family has an America accent. They moved to Britain from America four years ago. Oliver's immunisations are up to date including MMR. The family visited his grandmother in Massachusetts four weeks ago. During this visit he played in grassland. The family could not recall a tick bite or removing an engorged tick. They reported no other foreign travel. Since their return from the USA they have visited a farm in Wales. Oliver did not drink from any streams, nor did he drink unpasteurised milk. The family has no animals.

On examination he notes that although the rash is spreading, there is an area of central clearing. The arthralgia of the right shoulder remains, and he notes some cervical and axillary lymphadenopathy. The investigations repeated earlier that day show that the C-reactive protein has increased to 227 mg/l, and the ESR to 98 mm in the first hour despite 48 hours' treatment with antibiotics.

The infectious diseases specialist decides that in view of the travel history, the central clearing of the rash, and the associated arthralgia, Lyme disease is the most likely diagnosis. He also considers metastatic cellulitis due to *Haemophilus influenzae*, particularly in view of recent vaccine failures, but the negative blood cultures are against this.

He advises that Lyme serology testing is performed, including IgM and IgG. Bearing in mind the frequency of false positive serology in Lyme disease, he also suggests that the Western blot (immunoblot) technique of detecting antigen is used. He considers that if the diagnosis is Lyme disease then it is the early localised form of the condition and that the most appropriate treatment would be amoxycillin (amoxycillin is the treatment of choice for young children and doxycycline for children older than 8 years). However, as he cannot be certain that Oliver does not have metastatic *H influenza*, he chooses to prescribe ceftriaxone.

Table 2 Differential diagnosis of the rash and musculoskeletal symptoms considered at morning ward round

Differential diagnosis	Factors supporting this diagnosis	Factors not supporting this diagnosis
Rheumatic diseases		
Pauciarticular juvenile idiopathic arthritis (JIA)	Lymphadenopathy is sometimes present in JIA	The diagnosis of JIA is based on the physical finding of arthritis (or synovitis) in at least one joint that persists for at least 6 weeks, with other causes being excluded. Typically knees ankles and wrists are affected Rash is ''salmon pink'' There is often hepatosplenomegaly in JIA
	Elevated ESR	
Systemic lupus erythematosis	Fever	Arthralgia that is not episodic No malar rash
Vasculitis		
Kawasaki disease	Fever, rash (although not polymorphic) and lymphadenopathy	No stomatitis
		No conjunctivitis Fever duration <5 days
Serum sickness	Acute onset Fever	No recent medications Rash not urticarial
Henoch-Schlonlein purpura		Rash not purpuric High fever unusual
Bacterial infection		
Septic arthritis	Elevated ESR, C-reactive protein	Ultrasound normal, blood culture negative (but only positive in 30% of cases)
Osteomyelitis	Elevated ESR in 90%	Ultrasound not showing elevation of the periosteum (may be seen in experienced hands within the first week)
	Elevated CRP in 98%	?need for bone scan to exclude this diagnosis but no bony tenderness noted
	(Normal *x* ray compatible as *x* ray remains normal until >50% bone has been demineralised)	
Viral infection		
Rubella		MMR vaccine up to date Rash not typical
Parvovirus B19		Arthralgia usually symmetric, involving hands, wrists, knees, and feet; arthralgia not symmetrical in this case Erythema infectiosum (fifth disease) characterised by a erythematous malar rash (slapped cheek) and a reticulated lace like rash on the extremities Rash not typical Fever did not resolve when rash appeared
Hepatitis viruses	Never had a blood transfusion	May get arthritis with hepatitis B
Post-infectious		
Rheumatic fever	May have some minor criteria—fever, arthralgia, and raised acute-phase reactants. Perhaps the rash is erythema marginatum?	No carditis
		No chorea No subcutaneous nodules No polyarthritis
Reactive arthritis		No history of sore throat, no hepatosplenomegaly, no diarrhoea, no compatible rash
Neoplastic		
Acute leukaemia		No haematological abnormalities

Oliver improves on ceftriaxone. Lyme disease IgG and IgM are positive. A few days later the diagnosis is confirmed by a positive Western blot test.

The infectious diseases specialist explains the diagnosis to the family, informing them that Oliver has the early localised form of the disease. He advises that in addition to the 5 days of intravenous ceftriaxone that he has so far received, he should be treated with 4 weeks of oral amoxycillin. He provides the parents with the Centers for Disease Control and Prevention Travellers Health Information on Lyme disease[7] and advises about clothing and insect repellant to avoid future bites. He also advises about the examination of the skin for engorged ticks to avoid future infection.

COMMENT

- The duration of antibiotic therapy for the early localised form of Lyme disease in children is 14–21 days, and for those with arthritis 28 days. The antibiotic of choice in children older than 8 years is oral doxycycline (100 mg twice daily), and for children younger than 8 years oral amoxycillin (25–50 mg/kg/day twice daily). The treatment for persistent or recurrent arthritis, carditis and neurological symptoms is ceftriaxone or penicillin.

Oliver was treated with amoxycillin for 28 days because he had significant arthralgia. On reflection, since he had already received 5 days of intravenous ceftriaxone before the diagnosis being established, a 23 day course of amoxycillin would have sufficed.

Oliver's arthralgia completely resolved by the time the ceftriaxone was stopped. He has made a complete recovery.

LYME DISEASE

Lyme disease is a multisystem inflammatory disease caused by spirochetes, known collectively as *Borrelia burgdorferi*, which are spread by the bite of infected *Ixodes scapularis* ticks. Lyme disease was first described in studies of an outbreak of ''juvenile rheumatoid arthritis'' in Connecticut, USA which led to the identification of Lyme arthritis.

Figure 2 The spirochete *Borrelia burgdorferi* (Source: Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

There are three closely related borrelial species that cause Lyme disease, all included within the general term *B burgdorferi* sensu stricto. *B burgdorferi* sensu stricto itself is the sole cause of Lyme disease in the United States. *B afzelii* and *B garinii* cause Lyme disease in Europe and Asia. It has been suggested that the clinical differences between European and American disease (more arthritis and more multiple erythema migrans lesions in the United States) may be due to differences in the causal organism.

B burgdorferi is a microaerophilic, fastidious organism. It is about 30 µm in length and 0.2 µm in width and stains well with acridine orange and silver stain (fig 2). However, histological or immunological staining are very low yield diagnostic tests, because of the paucity of organisms in tissues. There is also a low yield when attempting to culture the organism. Thus, the diagnosis of Lyme disease is generally based on clinical features and confirmed by serologic testing.

Ixodes tick eggs are deposited in the spring and the tiny larvae emerge several seeks later. These immature ticks (fig 3) feed once during the summer, usually for two days, on the blood of small mammals such as field mice. *B burgdorferi* is

Figure 3 *Ixodes scapularis* (deer) tick. Adult female, adult male, nymph, and larva on a centimetre scale (Source: Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

Figure 4 The white tailed deer.

acquired from mice that remain spirochetaemic but healthy. The following spring the larvae evolve into nymphs, which also feed once (for 3–4 days) during the summer, either on field mice or larger mammals such as dogs, deer or man. It is the nymphal stage that is most likely to bite and gorge on man. These nymphs will then moult into adults in the autumn. Adult ticks attach themselves to a host, usually the white tailed deer (fig 4), where they then mate.

Adult ticks are more easily seen and felt than nymphs, and people wear more clothing in autumn and winter than in the summer. These two factors explain why adult ticks are an uncommon vector and why the incidence of early Lyme disease is less during these seasons. A recent study suggests that in an area in which 15% of adult ixodid ticks carry *B burgdorferi*, only about 1% of people bitten develop Lyme disease. Moreover, only about 30% of patients with Lyme disease recall the tick bite.

What to do if bitten

Many people who seek medical attention for a tick bite have been bitten by a tick that would not transmit Lyme disease. Questions to ask are:

- What was the size of the tick? In the summer only nymphal *I scapularis* ticks are looking for a blood meal, as adults do not appear until autumn. The nymphal ticks are round and very small, the size of a poppy seed; adult ticks are larger and much easier to see
- Was the tick attached? The tick can not spread Lyme disease unless it was attached to the skin
- How long was the tick attached? It takes >36 hours for the nymph tick to feed and to transmit Lyme disease

The risk of infection with *B burgdorferi* after a recognised deer tick bite, even in highly endemic areas, is sufficiently low that prophylactic antimicrobial treatment is not routinely indicated for most people. However, if an engorged tick is removed then it may have spread Lyme disease and there are then three options:

- Observe and wait for features of early Lyme disease
- Treat as though for Lyme disease
- Perform serological testing and treat if there is evidence of infection

Clinical features

The clinical manifestations of Lyme disease can generally be divided into three phases: early localised, early disseminated, and late or chronic disease.

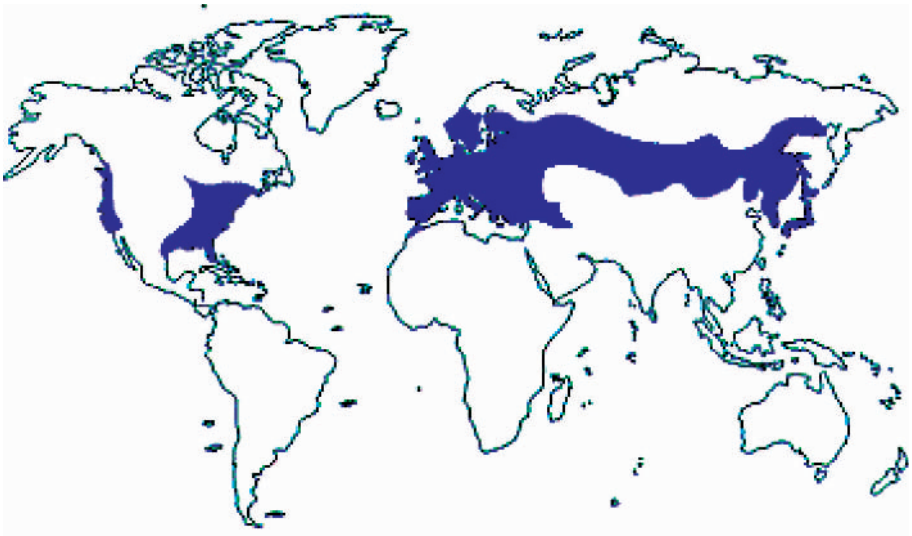

Figure 5 Geographical distribution of *Ixodes scapularis*. (Reproduced with permission from www.afraidtoask.com)

Early localised disease

Early localised disease includes erythema migrans (EM) and associated findings. EM occurs in up to 90% of patients, usually within one month of being bitten by a tick. EM is not present, or not detected, or not recalled, in the remaining patients. It is often found in or near the axilla, the inguinal region, behind the knees, or at the belt line as ticks take their meals in these warm, moist regions of the body. It typically expands during the course of a few days, often with central clearing. The lesion may be uniformly red or have a more complex ''bull's eye'' appearance due to central clearing. Ten per cent of patients with EM have multiple lesions. Multiple lesions are due to the spirochetaemia rather than multiple tick bites. Early localised disease may also be associated with non-specific complaints resembling a viral syndrome. Symptoms include fatigue, malaise, headache, myalgia, arthralgia, and regional or generalised lymphadenopathy.

Early disseminated disease

Early disseminated disease occurs days to months after a tick bite and may be the first manifestation of *B burgdorferi* infection, without preceding EM. Carditis develops in approximately 8% of patients with untreated Lyme disease. The cardiac manifestations include any degree (or combination of degrees) of heart block or mild myopericarditis. In the vast majority of cases, the cardiac disease begins to resolve during or even before antibiotic therapy. Neurological features occur in about 10% of untreated patients and can include lymphocytic meningitis, cranial nerve palsies (especially the VII nerve which may be bilateral) and radiculoneuritis.

Late or chronic disease

Late or chronic disease occurs months to years after the onset of infection and may not be preceded by other features of Lyme disease. Musculoskeletal symptoms are most common, but neurological manifestations, skin disease, and non-specific symptoms can also occur. Musculoskeletal problems are seen in 80% of previously untreated patients. These include arthralgia (20%), intermittent episodes of arthritis (50%), and chronic, usually monoarticular disease, that most often affects a knee (10%). Many patients with arthritis have prior arthralgia. Antibiotic treatment is typically effective for the arthritis even if given orally. Tertiary neuroborreliosis is an important feature of late Lyme disease. The clinical features of tertiary neuroborreliosis include encephalopathy, neurocognitive dysfunction, and peripheral neuropathy.

Clinical message

- Always take a travel history
- Rash, fever and arthritis have a broad differential diagnosis
- The consequences of missing Lyme disease can be significant in terms of long term morbidity

Lyme disease risk areas

The areas in which Lyme disease is found are those in which ixodid ticks abound (fig 5). In the United States, 90% of cases occur in just nine states: Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Minnesota, Wisconsin, and California. In Britain, Lyme disease is found mainly in south east England.

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