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Leishmaniasis

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There are an estimated 1.5–2 million new cases and 70,000 deaths per year worldwide from leishmania visceral and skin diseases.[1] Leishmania parasites are transmitted to humans by the bite of the phlebotomus sandfly. It is uncommon in the UK and most physicians are unfamiliar with the clinical presentation and management; there were only 58 reported cases of leishmaniasis in England, Wales and Northern Ireland in 2005.[2] This article reviews the two main clinical types of leishmaniasis, with a focus on presentation in the UK.

Visceral leishmaniasis

The greatest disease burden of visceral leishmaniasis (VL) worldwide is in India and Sudan (Fig 1), but many patients in the UK have contracted their infections from the Mediterranean basin, sometimes after relatively short exposure on holiday. The incubation period from infected sandfly bite to disease presentation is typically several months but can be longer.

Clinical features

Patients with VL present with chronic fever, splenomegaly and pancytopenia (Box 1). Weight loss is common and patients may present with the sequelae of pancytopenia (bleeding, severe anaemia and intercurrent infections). Clinical examination may also reveal hepatomegaly and lymphadenopathy. Other abnormalities include hypoalbuminaemia and polyclonal hypergammaglobulinaemia (which may cause false-positive results with autoantibody tests).

Diagnosis

Diagnosis of VL can be made by direct visualisation of parasites via microscopy or culture. The best tissue to examine is a bone marrow biopsy, although splenic aspirates are used at specialised institutions because they provide additional information about the load of infection. These should be performed only by those with experience because of the risk of bleeding. Specialised parasitology laboratories can also perform polymerase chain reaction (PCR) tests on these samples to detect leishmania DNA. Two serology tests to look for antileishmania antibodies are available:

- The direct agglutination test: a semiquantitative agglutination test using killed leishmania parasites and increasing dilutions of patients' blood or serum (sensitivity 92.7–96.4%).
- The RK39 dipstick: a qualitative test using recombinant leishmania

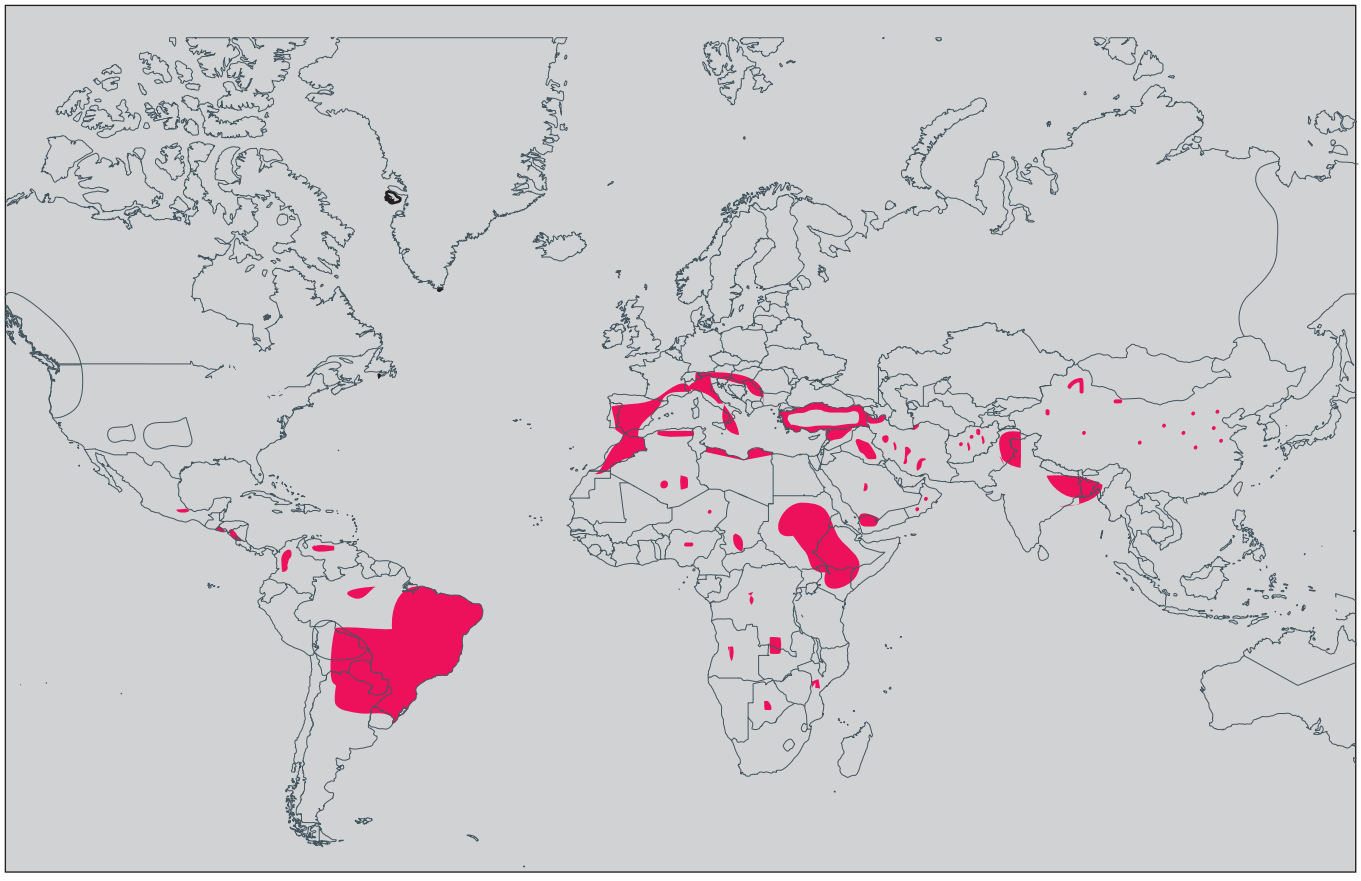

Fig 1. Geographical distribution of visceral leishmaniasis. Reproduced with permission from the World Health Organization.[1]

antigen with patients' blood (sensitivity 87.7–97.1%).[3]

Experience is needed to interpret these tests. They remain positive despite adequate VL treatment, thus cannot be used to assess cure post-treatment or following relapse. In endemic areas the specificity can be low, as exposed populations without clinical disease may have an antibody response (up to 32% of the population in some areas). Nearly half of patients with HIV will have false negative serology.[4]

Treatment

The first-line drug for treating VL in the UK is liposomal amphotericin B. The current treatment regimen which gives a 95% cure rate is 20 mg/kg in five doses over 10 days (ie 4 mg/kg/day on days 1, 2, 3, 5 and 10).[5] Trials from India have reported a 90% cure rate after a single dose of liposomal amphotericin B.[6] Side effects include renal impairment, hypokalaemia, infusion reactions and anaemia.

Other treatments such as sodium stibogluconate (SSG) are still widely used in other parts of the world because they are cheap and easy to use.[7] Combination treatments have been proposed to avoid parasite resistance to therapy which has been reported in patients from India.[8]

Drug treatments for VL, including those used in the UK when patients are intolerant of, or poorly responsive, to liposomal amphotericin B, are summarised in Table 1.[9]

Visceral leishmaniasis in immunosuppressed patients

The presentation and management of VL is different in immunosuppressed patients. Worldwide, HIV is the main immunosuppressive influence seen in conjunction with VL, but other immunosuppressive states seen in patients with VL in the UK are advanced age, immunosuppressive therapy and treatment with tumour necrosis factor antibody therapies.

The main clinical features of VL may be absent or atypical, and there may be evidence of leishmania parasites in unusual body sites (eg skin, gut, genitourinary tract). Establishing the diagnosis of VL therefore may be more difficult.[10] Abnormal tissue from any body site should be examined for evidence of leishmania parasites if the patient has been in an endemic area and is immunosuppressed.

Patients who remain immunosuppressed may respond poorly to the standard treatment protocols, so an attempt to improve their immune status is a key strategy in their management. If this is not possible, long-term prophylactic treatment may be considered after the initial treatment course as there is a high risk of recurrence after apparently successful treatment. When patients fail first-line treatment courses, second-line therapy needs to be considered from the options listed in Table 1. There is little evidence to guide the choice of prophylactic and second-line treatment courses and management of these patients should be discussed with an expert.

Box 1. Visceral leishmaniasis (VL) case history.

A 61-year-old man presented to his local hospital with fever, malaise, anorexia and weight loss. He was diagnosed with adult onset Stills disease because he had a very high ferritin level and a mild pancytopaenia with a reactive bone marrow. He was commenced on prednisolone and azothioprine which gave him some symptomatic relief but he represented eight months later with worsening symptoms. He had developed splenomegaly and lymphadenopathy, and the pancytopaenia had worsened (Hb- 7.9 g/dl, total white cell count -0.6×10^9/l, platelet count -106×10^9/l). Leishmania amastigotes were seen on a second bone marrow sample. He had visited Egypt, Turkey and Spain on short holidays in the last two years. He had recently been diagnosed with type 2 diabetes but was HIV-negative. His leishmania serologies (DAT test and RK39) were positive. He was treated with a standard course of liposomal amphoterecin B, but before the last dose developed acute renal impairment with a rise in creatinine to 730 umol/l. A renal biopsy showed a florid tubulointerstitual nephritis with lymphocytes and eosinophils, thought to be secondary to liposomal amphoterecin B. This was treated with a short course of prednisolone and his renal impairment resolved quickly and there was no relapse of VL. He remains well.

Cutaneous leishmaniasis

Several species of *Leishmania* protozoa can cause localised cutaneous leishmaniasis (CL). A simple geographical classification (Fig 2) divides species into 'old world' species, from Africa, the Middle East and Central Asia (OWCL), and 'new world' species, from South and Central America (NWCL).

Of the patients seen from 1998–2009 at the Hospital for Tropical Diseases, London, 40% (90) had OWCL and 60% (133) had NWCL. Of the OWCL patients, 71% were tourists to the Mediterranean, 36% migrants or visiting friends and relatives, and 17% were military personnel. Of the NWCL, 44% were backpackers and 39% soldiers (Wall EC unpublished data).

Presentation and diagnosis

CL typically presents with a nodule(s) at the sandfly bite(s) site that enlarges and ulcerates over several weeks. The incubation period can be months to years (usually <2 years) after the initial bite. The lesions are usually in exposed body areas such as the face and

Key points

- Suspect visceral leishmaniasis in patients with chronic fever, pancytopaenia and splenomegaly
- Suspect cutaneous leishmaniasis in patients with chronic ulcers in exposed areas of the body
- Elicit a travel history, including enquiries about travel to the Mediterranean basin
- Immunosuppression alters disease presentation and management
- Leishmaniasis is uncommon in the UK; expert help exists though

KEY WORDS: mucocutaneous leishmaniasis, new world cutaneous leishmaniasis (NWCL), old world cutaneous leishmaniasis (OWCL), visceral leishmaniasis

Table 1. Drug treatment for visceral leishmaniasis.

Drug	Cost*	Length of treatment (days)	Route of administration	Efficacy (%)**	Side effects	Where used
Liposomal amphotericin B	£££	10	iv	95	Renal impairment Hypokalaemia Anaemia	Europe
Amphotericin B	££	30	iv	95	As above, but more frequent infusion reactions	India
Sodium stibogluconate	££	28	im iv	95	GI upset Myalgia Cardiac conduction problems Transaminitis Raised amylase	Africa Brazil
Miltefosine	UK: £££ India: £	28	Oral	94	GI upset Reproductive toxicities	India
Paromomycin	£	21	im	94.6	Transaminitis Injection site pain Ototoxicity	India

* Approximate cost of whole course of treatment for adult patient.
** Relates to initial cure rate at end of treatment course in HIV-negative patients.
GI = gastrointestinal; im = intramuscular; iv = intravenous.

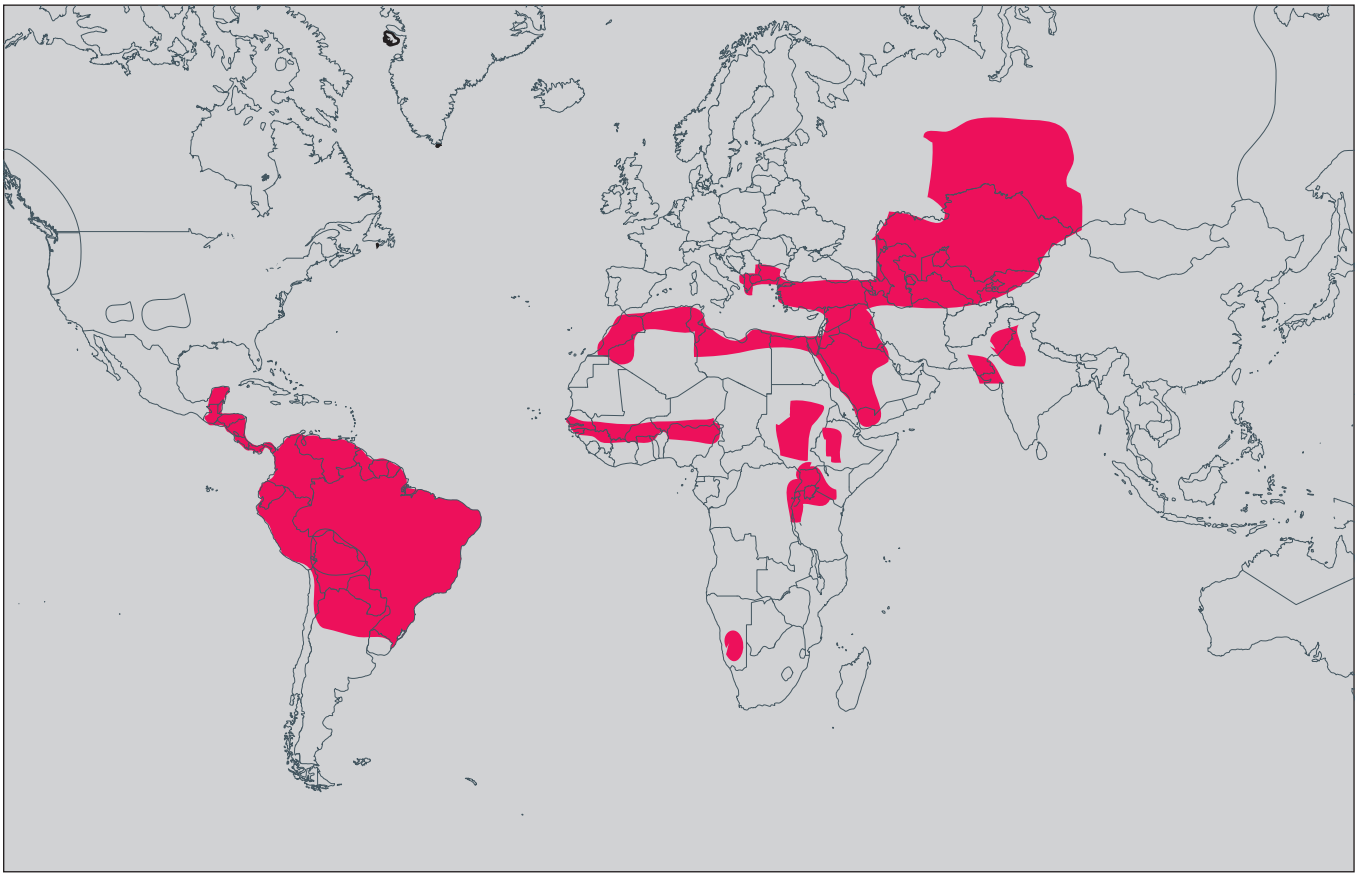

Fig 2. Geographical distribution of cutaneous leishmaniasis. Reproduced with permission from the World Health Organization.[1]

hands (Fig 3). The edge of the lesion is well demarcated and raised, and there may be satellite lesions in the same area. The ulcer base may be crusted, bloody or with pus. Occasionally there is a nodular lymphangitis that can be palpated in the surrounding area.

Spontaneous resolution can occur, so at the time of clinical presentation there may be signs of healing, particularly in the centre of the lesion (up to 50–75% cases have healed within 4–6 months in some OWCL species[11]). The differential diagnosis for these lesions includes infected insect bites, mycobacterial skin infections and malignancy.

Diagnosis

Diagnosis of CL is by direct visualisation of the parasites via microscopy and culture of a biopsy from the ulcer edge. Typical histopathological features are granulomatous inflammation and leishmania amastigotes. Leishmania DNA can be detected by PCR, so confirming infection and identifying the leishmania species. This is important if *viannia* species is suspected and the patient is at risk of mucocutaneous disease.

PCR testing has also shortened the time to diagnosis. At the HTD parasitology laboratory, microscopy is 62–77% sensitive and culture takes on average 11.6 days to a definitive result, whereas PCR results take on average eight days to process (Wall EC; unpublished data). Lesions difficult to biopsy (eg facial, ear, finger) can be scraped or aspirated, although the diagnostic yield is lower.

Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis (MCL) is caused by the *Leishmania viannia* subgroup of species found in South America. So-called 'espundia', occurs in 1–10% of cases of NWCL in endemic areas.[12]

Presentation

Patients present with nasal stuffiness and bleeding, ulceration and perforation of the nasal septum from mucosal inflammation and destruction (Box 2). This can occur at the same time as the NWCL skin ulcer or many months after it has healed. Left untreated, this can progress to widespread destruction of the palate, lips and cheeks.

Treatment for cutaneous and mucocutaneous leishmaniasis

The first-line treatment for both CL and MCL is sodium stibogluconate (SSG) although several factors need to be considered in choosing the best route of administration and length of treatment (Fig 4). The side effects of intravenous (iv) SSG include myalgia, nausea, raised transaminases and amylase, and cardiac conduction abnormalities.[13]

The risk of these side effects is justified in NWCL because of the risk of subsequent destructive mucocutaneous spread if left untreated. Intralesional infiltration of SSG avoids these toxicities, but needs an experienced physician to administer it and can be transiently painful during the injections. Most OWCL can be treated with intralesional SSG, although very large or numerous OWCL lesions that will need repeated and extensive weekly intralesional SSG

Box 2. Mucocutaneous leishmaniasis (MCL) case history.

A 60-year-old man presented with a six-month history of a leg ulcer which started as an 'infected scratch' and slowly enlarged to 3 cm diameter. The patient was a cameraman and specialised in filming in jungles around the world (Papua New Guinea, Benin and Peru). Examination revealed a raised erythematous thickened edge to the ulcer. There was lymphadenopathy in the groin of the same leg. He also had nasal discomfort for three months, with a bloody, sticky nasal discharge. Examination of his nose revealed thickened and inflamed nasal septum. Biopsies from the ulcer edge and the nasal septum showed a granulomatous inflammation and leishmania amastigotes. A PCR detected leishmania DNA, viannia complex species. The diagnosis was mucocutaneous leishmaniasis. He was treated with intravenous sodium stibogluconate for 21 days. During the treatment course he was asymptomatic but his ALT rose from normal to a peak of 200 IU/L. He had no ECG changes. At the end of treatment the ulcer was the same size but had flattened, all nasal symptoms had gone and his ALT had normalised. At follow-up four months later the ulcer had healed and there remained an atrophic patch on the nasal septum, but no indictors of active disease.

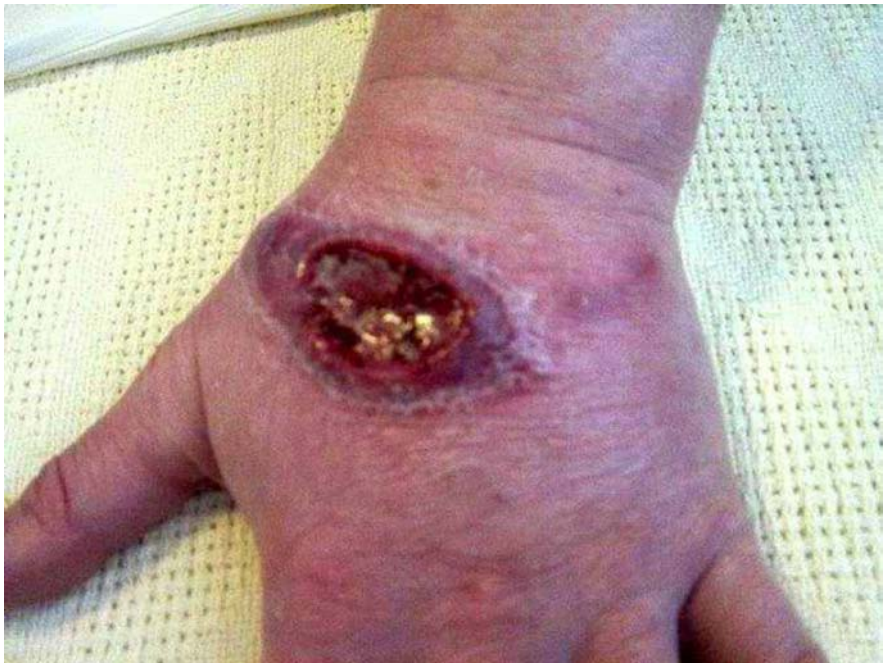

Fig 3. Early Cutaneous leishmaniasis lesion with a raised indurated edges around a central ulcer. Papules can be seen spreading from the lesion. Figure courtesy of Colonel Mark Bailey.

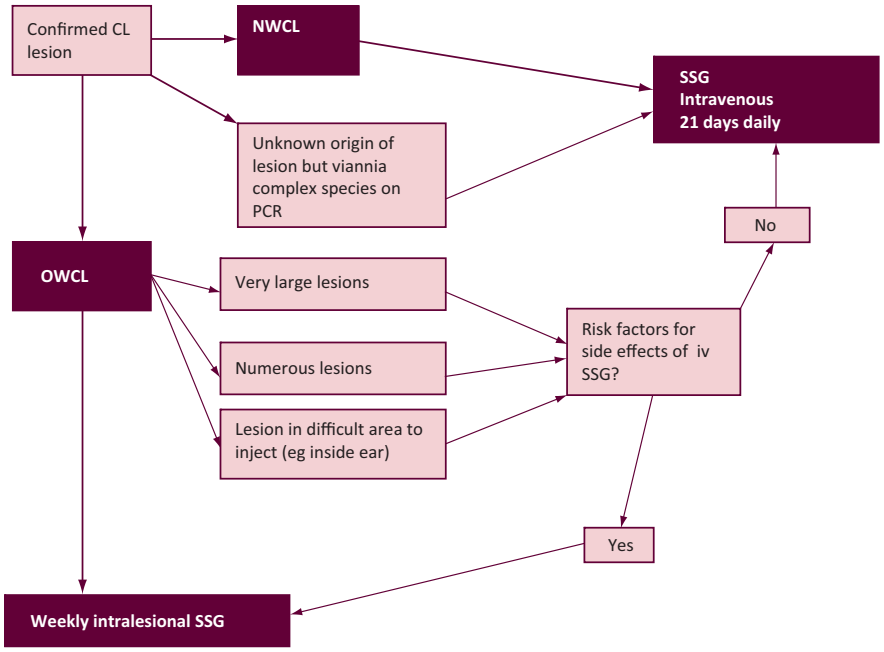

Fig 4. Treatment of cutaneous leishmaniasis (CL). iv = intravenous; NWCL = New World CL; OWCL = Old World CL, PCR = polymerase chain reaction; SSG = sodium stibogluconate.[18,19]

may be treated with iv SSG. Patients with pre-existing cardiac conduction defects or hepatic dysfunction are more likely to develop adverse effects from iv SSG.

Alternative treatments exist, but the evidence for their benefit is mostly limited to small case reports. Physical treatments for OWCL (eg curettage, cryotherapy and thermotherapy) seem to have unfavourable outcomes such as secondary infection, larger scars with depigmentation and risk of dissemination of CL. Topical treatments such as paromomycin seem ineffective. There was hope for oral fluconazole as a treatment for OWCL after a well published trial[14] but several subsequent studies have shown disappointing results. Alternative treatments for NWCL include amphotericin B and miltefosine, but neither has proven cure rates equivalent to SSG.[15–17]

Summary

Leishmaniasis is an uncommon infectious disease in the UK with a variety of clinical presentations. Physicians should remember to consider this diagnosis in patients with an appropriate travel history (including the Mediterranean basin) and seek help with diagnostics from a specialised parasitology laboratory. Treatment regimens may be unfamiliar to the general physician, and thus should also be discussed with an expert.

Leishmaniasis specialist services in the UK

Hospital for Tropical Diseases, London
Specialist physician: Professor DN Lockwood
Specialist parasitologist: Professor PL Chiodini

Liverpool School of Tropical Medicine
Specialist physician: Dr T O'Dempsey
Specialist parasitologist: Dr W Bailey

The Infectious Diseases Unit, Birmingham Heartlands Hospital
Specialist physician: Major MS Bailey

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The management of malaria in adults

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Malaria is one of the most common imported infections in travellers.[1] The number of cases in travellers is trivial set against the global scale of disease, but in this age of frequent international travel it is essential that clinicians are at least aware of when to suspect, and how to diagnose malaria. Detailed specialist advice can always be sought.

Epidemiology

The five species of malaria parasites now known to affect humans differ in their geographic distribution:

- *Plasmodium falciparum:* most common in sub-Saharan Africa and Melanesia (Papua New Guinea and the Solomon Islands).
- *P. vivax:* mainly Central and South America, North Africa, the Middle East and within the Indian subcontinent.
- *P. ovale:* almost exclusively in West Africa.
- *P. malariae:* mainly in Africa.
- *P. knowlesi:* on the island of Borneo and other parts of South-East Asia.[2]

Clinical features

The clinical symptoms and signs of malaria are produced by the asexual forms in the blood which destroy red cells, localise in critical organs, obstruct the microcirculation and release 'toxins', leading to the classical malarial rigor with pronounced fever.[3] The incubation period is variable, but may be as short as seven days and, exceptionally, up to 20 years. Most (>90%) *P. falciparum* infections in travellers occur within six weeks after return from foreign travel. Compliance with antimalarial chemoprophylaxis cannot exclude the diagnosis.

After a prodromal period of fatigue and aching, the abrupt onset ensues of a rigor consisting of a 'cold', 'hot' and 'sweating' phase, and high temperature. In *P. knowlesi* infections the cycle occurs every 24 hours; in *P. falciparum* the periodicity of fever tends to be less predictable, and the fever may be continuous due to the asynchrony of parasite development. Headache, cough, myalgia (flu-like symptoms), diarrhoea and mild jaundice are non-specific symptoms of all malarias. Examination of a patient with mild malaria often

Key points

Malaria must be considered in all patients with fever or history of fever who have visited a malaria endemic country

The challenge in malaria is that of rapid diagnosis and initiation of appropriate antimalarial and supportive treatment

Physicians should be aware of the therapeutic and prognostic implications of life-threatening falciparum versus non-falciparum malaria

Prompt recognition of the severe manifestations of malaria requires an increased level of care or referral to a specialist unit

The water-soluble artemisinin derivative, artesunate, one of the new antimalarial agents, is the current drug of choice in severe falciparum malaria rather than quinine

KEY WORDS: artesunate, malaria, quinine, severe falciparum malaria