

Visceral leishmaniasis – Kala Azar

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Visceral leishmaniasis – Kala Azar

Distribution

At present 90% of all visceral leishmaniasis occurs in India, Bangladesh, Nepal, Ethiopia, Sudan and Brazil. Visceral leishmaniasis may be responsible for 500,000 new cases and > 50,000 deaths per year.

Clinical aspects

After an initial multiplication in the skin, causing a transient small lesion the parasites can further multiply in bone marrow, liver and spleen. This causes visceral leishmaniasis. The incubation period is usually 2 to 6 months. The pathogens are usually *Leishmania donovani* and *L. infantum*. Rarely *Leishmania tropica*. *L. chagasi* is now considered identical to *L. infantum* and was possibly introduced into the New World via infected dogs or rats at the time of the Spanish and Portuguese conquests although there are doubts about this.

Visceral leishmaniasis in Southern Europe was initially considered to be a paediatric disease (hence the name *L. infantum*). However it is clear that all age groups can be infected. The disease is characterised by a persistent inflammatory state with chronic fever, enlarged liver and spleen and a low blood count (pancytopenia = anaemia + leukopenia + thrombocytopenia). This must be distinguished from an aplastic bone marrow. The patient becomes very susceptible to other infections (pneumonia, tuberculosis, dysentery) which can sometimes prove fatal. Symptoms and signs of superimposed bacterial infections may confuse the clinical picture at the time of initial diagnosis. Low blood platelet counts result in a bleeding tendency (nosebleeds, bruising, etc.). Sometimes there are also other symptoms, such as swollen lymph nodes, more common in Sudan than in India. Weight loss and emaciation are frequent and substantial. The skin can turn a dark colour: kala azar (Hindi) means “black fever” and refers to this hyperpigmentation. This was mainly described from Indian cases. The reason of this hyperpigmentation is not clear. The infection can proceed atypically in HIV patients (for example without fever or splenomegaly, or with negative serology). When immunosuppression is induced by chemotherapy, latent kala azar can become clinically apparent.



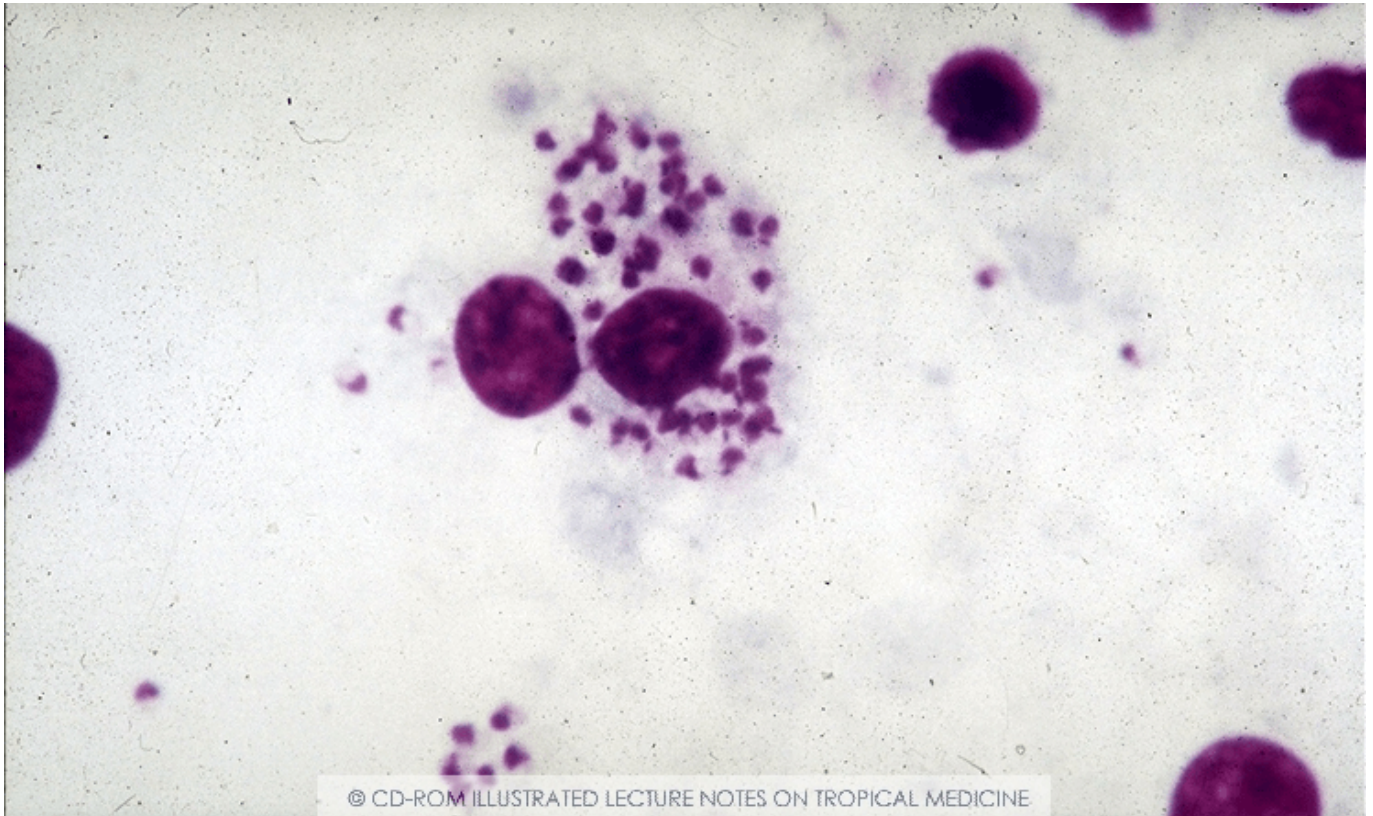
Visceral leishmaniasis (kala azar) with hepatosplenomegaly. Copyright ITM

Post- Kala azar Dermal Leishmaniasis (PKDL)

A skin condition, called post-kala azar dermal leishmaniasis (PKDL), can occur after a patient has suffered from kala azar. PKDL rarely occurs without being preceded by kala azar. PKDL occurs on average 4-8 months after kala azar (range 0-3 years), though there are strong regional variations (In India 2-3 years after the disease, in Sudan typically within six months). This disease occurs mainly in India (up to 20% of kala azar patients) and to a much lesser extent in the Middle East. In Sudan the disease occurs regularly (56% of kala azar patients in one study). It is virtually unknown in the Mediterranean Basin or in South and Central America. It involves discoloured patches and painless nodules on the skin that usually contain few, but sometimes moderate numbers of amastigotes. Most of the lesions occur on the face (98%) and to a lesser extent on the thorax (80%), arms (70%), legs (40%), tongue (40%) and genitals (6%). This disease has a very chronic course (years) and is therefore important for transmission. Parasites do not affect internal organs in PKDL. There is sometimes a concomitant neuritis, which can further contribute to the clinical resemblance to leprosy. In East-Africa, this condition heals spontaneously in up to 80% of patients. Treatment with glucantime can be given for 2 months, or longer (4 months in India, where resistance to antimony is higher). Amphotericin B is an alternative. The therapeutic place of miltefosine for PKDL is not clear at present.

Diagnosis

In endemic areas, fever lasting more than 2 weeks and accompanied by splenomegaly not responding to antimalarial therapy, strongly increases the suspicion of visceral leishmaniasis, but this clinical picture is not sufficient for diagnosis.



Leishmania amastigotes. Copyright ITM

Diagnosis of visceral leishmaniasis is not easy, as none of the tests have 100% sensitivity and 100% specificity. Clinical syndromic diagnosis lacks specificity as malaria, hyperreactive malaria splenomegaly, trypanosomiasis, typhoid fever, disseminated tuberculosis, brucellosis, haematological disorders, splenic abscess or splenomegaly due to portal hypertension all can be accompanied by enlarged spleen, fever, wasting, anaemia and/or lymphadenopathy. Because of the high cost and toxicity of current therapeutic options, empirical treatment is not advised. Therefore confirmatory diagnostic tests must be used. The leishmanin skin test is an indicator of past infection and is not used to diagnose visceral leishmaniasis.

Direct diagnosis

Direct diagnosis is made by demonstrating the presence of amastigotes (in bone marrow, spleen or lymph node aspirate). The parasite is egg-shaped and measures 2-3 x 5 µm. With Giemsa staining, there is a pale blue cytoplasm, a well-defined nucleus and a smaller kinetoplast. Microscopy requires considerable expertise and training. Usually bone marrow is obtained by sternum aspiration. The

technique of spleen aspiration is more sensitive (in some studies very nearly 100%, though in reality slightly lower) than bone marrow aspiration but can be risky (spleen rupture, haemorrhage). The platelet count should be above $40 \times 10^9/\text{litre}$. Active bleeding, severe anaemia, jaundice, moribund state, pregnancy and lack of cooperation are contra-indications. Patients must lie in bed for several hours after the procedure. Vital signs must be checked frequently to allow early recognition of haemorrhage and blood transfusion facilities must be available. To perform the procedure a 21-gauge needle and a 5 ml syringe is required. After penetration of the skin, the plunger is withdrawn, the needle is quickly inserted into the spleen while maintaining suction and withdrawn immediately (i.e. less than 1 second). Lymph node aspiration and/or liver biopsy are sometimes necessary. The parasites can rarely be detected in peripheral blood monocytes.

Serology

Serology is positive in most cases of visceral leishmaniasis. Gel diffusions immunoelectrophoresis, complement fixation test, indirect haemagglutination, Western Blot and countercurrent immunoelectrophoresis have limited diagnostic accuracy and/or feasibility in the field. Indirect fluorescence tests (IFA) are an alternative but require a fluorescent microscope. The direct agglutination test (DAT) is often used as this has a high sensitivity and specificity. Both liquid and freeze-dried antigens can be used, although liquid antigen is associated with poor reproducibility in East Africa (most likely due to decay of liquid antigen during storage and transport). Note that freeze-dried antigen does not require refrigeration. The DAT is simpler than many other tests but requires equipment, such as microplates and micropipettes, training and regular quality control. A suggested cut-off value of 1/3200 is often used but should be evaluated in each setting. An alternative is to consider titres $< 1/1600$ to be negative, borderline between 1/1600 – 1/12800, and positive $> 1/12800$. It can be defended that in a rural endemic area, a patient with more than two weeks fever and splenomegaly with strongly positive DAT values and no response to antimalarials doesn't necessitate formal demonstration of parasites. With borderline serological values tissue aspiration with search for amastigotes will be needed. A possibility in a small regional clinic is to absorb a drop of blood from a patient suspected to have kala azar on a small filter paper and then to punch out a standard size disk from the blood spot. In this way one obtains a well-defined, accurate aliquot of absorbed blood. This can be transported and used for DAT in a well equipped laboratory. Serology remains positive after cure. The fast agglutination screening test (FAST) is a simplified (single serum dilution) and more rapid version of the DAT (2-3 hours versus 18h). Because DAT is not practical in many field conditions alternatives are being studied. ELISA is highly sensitive, but specificity depends upon the antigen used (amastigotes or promastigotes). Recombinant K39 antigen-based dipsticks using immunochromatography (ICT) have been an important step forward and have replaced DAT as first line test K39 is a 39-amino acid repeat that is part of a kinesin-related protein of *L. chagasi*. This

repeat is conserved within the *L. donovani* complex. The ICT tests are easy to perform, rapid and cheap. Twenty µl of serum are added on the dipstick, which is then placed vertically in a test tube. Two drops of chase buffer solution provided with the dipstick are then added. The results are read after 5 to 10 minutes. Even a weak band in the test region is considered positive. A control line has to be visible. It is the most promising tool for the diagnosis of visceral leishmaniasis in peripheral centres. The specific format (brand) of dipstick may play an important role (e.g. Opti-Leish™, DiaMed IT Leish™, DiaMed DUAL IT L/M™ versus Kalazar Detect™).

Formol-gel test.

In kala azar there is a very high production of non-specific immunoglobulins (and a decrease in albumin), especially in advanced disease (i.e. more than 3 months). This can be demonstrated by serum protein electrophoresis, but this impractical in field conditions. The proteins can be precipitated as a gel by formalin. Twenty µl of 40% formaldehyde are added to 200 µl of serum in a glass tube. After twenty minutes, the gelification reaction is visually assessed as positive or negative. The test is simple and cheap. The test can also be positive in patients with hyperreactive malaria splenomegaly.

Katex

A urinary antigen detection test using latex agglutination (KAtex) has been developed to circumvent the limitations of serological tests. It detects a heat-stable low molecular weight carbohydrate antigen. This will become negative upon successful treatment. It can therefore distinguish an active from a past infection. A very high specificity and moderate to high sensitivity were reported. The test requires the boiling of 1 ml of urine for 5 minutes. About 50 µl of the treated urine sample is added onto a reaction zone on a glass slide and a drop of latex is added. The liquids are stirred to a completely homogenous mixture. Any agglutination reaction discerned when compared with a negative control is considered positive. The sensitivity varies with the parasite load.

Culture

Culture can be done from peripheral blood, buffy coat or tissue aspirates. The microculture method improves sensitivity and decreases incubation periods. Cultures are expensive, time-consuming and require expertise. A *Leishmania* parasite can survive for 3 days at a temperature of 4° C, but for only 1 day at room temperature, in Locke transport medium (a buffered glucose-salt solution with antibiotics).

Genome assays

Lack of standardisation and quality control is a major concern of PCR and related assays. A multitude of gene targets, protocols and applications have been described. A PCR assay was developed in order to amplify the kinetoplast minicircle of *Leishmania* species (it can be also be used in vector studies). The kinetoplast minicircle is an ideal target because it is present in 10,000 copies per cell and its sequence is known for most *Leishmania* species. The very high sensitivity of PCR-based assays may actually be a disadvantage by being a marker of infection (transient or permanent) instead of being a marker of disease, as it will pick up also asymptomatic carriers. Detailed genomic analysis of *L. donovani* showed that parasites can have two, three, four or even five sets of chromosomes in one organism. Further study of this ploidy-variation will investigate the possible clinical implications of this unexpected finding.

Montenegro test

Leishmanin is a compound obtained via in vitro culture of promastigotes. A skin test with leishmanin (Montenegro test) is negative during active kala azar, but later becomes positive (after 6 to 12 months). The Montenegro test reflects the suppressed cellular immunity during infection. There is a specific anergy for *Leishmania* parasites during active disease. This test is mainly of epidemiological value. To perform the test 0.1 ml is injected intradermally and the local reaction read after 48 hours (>5 mm induration = positive). A positive test eliminates the existence of active kala azar. Cutaneous leishmaniasis produces a positive Montenegro test.

Treatment of VL

Pentavalent antimonial compounds.

One of the treatment options for visceral leishmaniasis are pentavalent antimony derivatives (antimony, chemical symbol Sb = Stibium). The derivative most frequently used is Glucantime® (meglumine antimonate, 85 mg Sb/ml) and rarely Pentostam® (sodium stibogluconate, 100 mg Sb/ml). The drugs can be administered IM (intramuscularly, painful) or by slow IV (intravenous) injection or infusion (diluted with 5% glucose solution, otherwise local thrombophlebitis occurs). The dose is always expressed as mg Sb: 2 x 10 mg/kg IM or slow IV infusion per day for at least 30 days. On an ampoule might be written 1500 mg/5 ml, which is 1500 mg calculated as the salt, not as stibium itself. This can lead to underdosing if one is not aware of this detail. As a dose is practically totally excreted and eliminated via the urine within 6 hours after administration, a twice daily administration would pharmacokinetically be more logical than an injection once daily. However, a single administration per day appears to suffice in practice. The dose should be reduced in patients with kidney failure. A maximum of 850 mg/day [10 ml Glucantime®] has been previously set due to

the risk of cardiotoxicity with higher doses. This limit has been contested and has been abandoned in the latest WHO guidelines. T-wave inversion and prolongation of the QT-time are indicative of threatening arrhythmia. The fever usually disappears after 1 week. The spleen begins to get smaller after 2 weeks but frequently requires 6 to 12 months to return to normal.

Antimony

Antimony is just below arsenic in the periodic table. It mimics the toxic effects of arsenic, which result from binding to adjacent thiol groups on enzymes, thereby impairing their function. Antimony is found in trivalent and pentavalent forms. Inhalation of stibine gas (SbH_3) causes massive haemolysis. Pentavalent antimonials (e.g. meglumine antimoniate, sodium stibogluconate) are used for treatment of leishmaniasis. One of their actions is to inhibit phosphofructokinase, the rate-limiting step in the parasites' glycolytic pathway.

Follow-up and response in the event of recurrence

Follow-up is necessary as a number of patients will relapse. This usually happens in the first 6 months after treatment. Upon recurrence of visceral leishmaniasis (relapse), higher doses of Glucantime® can be used for a longer time (2-3 months). Alternatively and preferably another drug or combination therapy can be used to treat relapses.

Cases of complete treatment unresponsiveness can occur. Splenectomy sometimes has to be carried out in cases of life-threatening anaemia or thrombocytopaenia. If possible pneumococcal vaccination should be given before the operation, and lifelong antimalarial prophylaxis is indicated thereafter if the patient stays in an endemic area.

Alternative treatments:

While antimonials have been the mainstay for treatment of visceral leishmaniasis for many decades, alternative options have been explored, mainly driven by the emergence of antimonial resistance in India, but also by their toxicity. Currently first line drugs entail antimonials, conventional amphotericin B and the lipid-containing formulations, paromomycin and miltefosine.

Amphotericin B is a polyene and has a fairly complex structure with a hydrophilic and a lipophilic component. The recommended dose of amphotericin B [Fungizone®] is 0.5-1 mg/kg/day IV, to be given over 6 hours; total dose max. 1-3 g. This drug is mainly used for the treatment of deep

mycoses, though it is also active against *Leishmania*. It is a rather toxic medication. Shivering, fever, nausea, vomiting, headache, anaemia, phlebitis at the site of the infusion, cardiotoxicity, kidney failure, hypokalaemia and hypomagnesaemia are frequent side effects. Side effects occurring shortly after administration can be reduced by cortisone IV or meperidine (pethidine), a morphine analogue. Administration of 500-1,000 ml physiological isotonic saline solution before starting the IV-drip reduces the risk of nephrotoxicity. The toxicity of the drug is reduced by pharmacological complexing with lipids prior to the administration. The drugs are then concentrated in the reticuloendothelial system and not in the kidneys so that a higher daily dose per kg of bodyweight can be administered and treatment time shortened (e.g. to 5 days). There are good indications that single-dose treatment (high dose; 10 mg/kg of the liposomal formulation) is useful, at least in the Indian subcontinent (India, Nepal, Bangladesh). In 1990 AmBisome® was developed as a first-choice drug. Several lipid formulations of amphotericin B are now available. They differ from each other in the type of phospholipid and the ratio of lipid to amphotericin B. Good results have been obtained with these lipid formulations. The price of these medications (AmBisome®, Amphotec®, Abelcet®) has come down, but is still high for the average rural farmer in a developing country.

Formulations of Amphotericin B

1. Fungizone®: Amphotericin B deoxycholate. Contains no lipids.
2. Emulsification of Fungizone® in Intralipid 20%: little reduction of toxicity
3. AmBisome®: L-AmB: incorporation in liposomes (vesicles).
4. Abelcet®: ABLC or Amphotericin B Lipid Complex. Microscopically small ribbon-like membranes formed by complexing with phospholipids.
5. Amphotec®: ABCD (= Amphocil®) Amphotericin B Colloidal Dispersion: AmB-cholesteryl sulphate forms disc-shaped structures.

Injectable aminosidine (paromomycin) is now also a first line drug. It is an aminoglycoside antibiotic. In 2007 the results of an Indian study showed that paromomycin IM, at a dose of 11 mg/kg/day x 21 days was noninferior to amphotericin B at a dose of 1 mg/kg IV every other day x 30 days. The combination with antimonials for 17 days was also found effective in East-Africa. Pain at the injection site, liver toxicity and ototoxicity were reported as side effects. Paromomycin for IM administration is licensed in India, and since 2012 also in Nepal. Combined with antimonials it is the first line regimen in East-Africa.

Miltefosine (Miltex®) was approved for use in India in 1992. It became more widely available in subsequent years. Miltefosine or hexadecylphosphocholine is a lecithin analogue (=phosphatidyl-choline analogue). In the molecule phosphatidylcholine is bound to a carbohydrate

component via an ether bridge instead of an ester. Miltefosine interferes with certain cellular signal cascades and with membrane synthesis, though its precise mode of action is still unknown. It was initially developed as an antineoplastic agent. In the 1990s it was also discovered that in vitro and in animal models it was active against *Leishmania* parasites. These organisms contain many ether lipids in the cell membrane. The main advantage of the compound is that it can be given orally, in contrast to the injectable antimony derivatives and amphotericin B. It cannot be given IV as this would lead to haemolysis. The molecule is fairly easy to produce and this should eventually bring down the price, which is quite high in the West.. The daily dose for adults is 100-150 mg, and for children 2.5 mg/kg/day. It should be given for 4 weeks. The half-life is several weeks. The cure rate was high in studies in India, although lower efficacy was found in East-Africa. Dose-dependent gastrointestinal discomfort often occurs and reversible hepato- and nephrotoxicity sometimes occurs. It is teratogenic and so cannot be given to pregnant women or women who want to conceive in 6 months after treatment. How quickly resistance to miltefosine will develop when used as monotherapy in the field is not yet clear. It is relatively easy to induce resistance in vitro. In this regard, it is of concern that success rates have been declining over the last years in the Indian subcontinent, although it is not yet well defined whether this relates to true parasite resistance, underdosing or evolving parasite fitness are also considered as alternative explanations. This has led to the use of liposomal amphotericin B (AmBisome) as first line treatment in the Indian subcontinent.

Combination therapy This is the suggested way forward to increase treatment efficacy, prevent the development of drug resistance, reduce treatment duration and possibly decrease cost. Pentavalent antimonials combined with paromomycin is now first line treatment in East-Africa. Other combinations including liposomal amphotericin B, paromomycin and miltefosine were found effective in India in phase III trials. Phase IV studies are ongoing.

Table: The main drugs currently used for treatment of visceral leishmaniasis.

Drugs	Regimen	Marketing ^a	Clinical efficacy	Resistance
Pentavalent antimonials	20 mg/kg iv or im daily for 28-30 days	Albert David (SSG); GSK (Pentostam®) Sanofi Aventis (Glucantime®)	35-95% (depending on geographic area)	As high as 60% (Bihar, India)
Amphotericin B	0.75-1 mg/kg iv for 15-20 doses (daily or alternate days)	Bristol Meyers Squibb (Fungizone®) Generic companies	> 97% all regions	Not documented

Liposomal Amphotericin B	10-30 mg/kg total dose iv; usually 3-5 mg/kg/dose single dose (10 mg/kg) in India	Gilead (AmBisome®)	Europe and Asia: > 95%; Africa: not fully established (higher dose required?)	Not documented
Miltefosine	2-2.5 mg/kg/d orally daily over 28 days (India only)	Paladin (Impavido®)	Asia: 94% (India) Africa: single field study (93% in HIV(-))	Readily obtained in lab isolates
Paromomycin sulphate	15 mg/kg im daily for 21 days (India only)	IOWH/Gland Pharma	Asia: 95% (India) Africa: 15 mg/kg: 64% (Sudan <50%) 20 mg/kg: 80% (Sudan)	Readily obtained in lab isolates

^a marketing authorization holder iv: intravenous; im: intramuscular; SSG: sodium stibogluconate

Table: The main drugs currently used for treatment of visceral leishmaniasis (continued).

Drugs	Toxicity	Cost/course	Issues
Pentavalent antimonials	Frequent, potentially severe; Cardiac toxicity, Pancreatitis, Nephro + hepatotoxicity	Generic ~ \$53 Branded ~ \$70	Quality control; Length of treatment; Painful injection; Toxicity; Resistance in India
Amphotericin B	Frequent Infusion-related reactions, Nephrotoxicity (in-patient care needed)	Generic price: ~ \$21	Need for slow iv infusion; Dose-limiting; Nephrotoxicity; Heat stability

Liposomal Amphotericin B	Uncommon and mild; Nephrotoxicity (limited)	Preferential price: \$280 (20mg/kg total dose) Commercial price: ~ 10x	Price; Need for slow iv infusion; Heat stability (stored <25° C)
Miltefosine	Common, usually mild and transient; gastro-intestinal (20-55%), Nephro + hepatotoxicity Possibly teratogenic	Preferential price: ~ \$74 Commercial price: ~ \$150	Price; Possibly teratogenic; Potential for resistance (half-life); Patient compliance
Paromomycin sulphate	Uncommon, Nephrotoxicity Ototoxicity Hepatotoxicity	~ \$15	Efficacy variable between and within regions; Potential for resistance (?)

Table. Treatment recommendations for visceral leishmaniasis per geographical region, as recommended by the WHO (in order of preference)

<i>L. Donovanii</i> - Indian subcontinent
1. Liposomal amphotericin B: 3-5 mg/kg/d iv over 3-5 days for total dose of 15 mg/kg or 10 mg/kg iv sd
2. Combination regimens (sequential co-administration)
Liposomal amphotericin B (5 mg/kg iv sd) + miltefosine (dosage as below) for 7 days
Liposomal amphotericin B (5 mg/kg iv sd) + paromomycin (dosage as below) for 10 days
Paromomycin + miltefosine (dosages as below) for 10 days
3. Amphotericin B deoxycholate 0.75-1 mg/kg/d iv, daily or on alternate days, for 15-20 doses
4. Miltefosine: children 2-11 years: 2.5 mg/kg/d; ≥12 years and < 25 kg body weight: 50 mg/day; 25-50 kg: 100 mg/day; > 50 kg: 150 mg/day; orally for 28 days
5. Paromomycin 15 mg (11 mg base)/kg/d im for 21 days

6. Pentavalent antimonials: 20 mg Sb ⁵⁺ /kg/d im or iv for 30 days in areas where they remain effective (including Nepal, Bangladesh and certain areas in India)
7. Rescue treatment in case of non-response: conventional amphotericin B deoxycholate or liposomal amphotericin B at higher doses
<i>L Donovanii</i> – East-Africa
1. Combination therapy: pentavalent antimonials + paromomycin for 17 days (dosages as above)
2. Pentavalent antimonials monotherapy as above
3. Liposomal amphotericin B 3-5 mg/kg/d iv over 6-10 days for total dose of 30 mg/kg
4. Amphotericin B deoxycholate as above
5. Miltefosine as above
<i>L infantum</i>
1. Liposomal amphotericin B 3-5 mg/kg/d iv in 3-6 doses for a total dose of 18-21 mg/kg
2. Pentavalent antimonials 20 mg/kg Sb ⁵⁺ /kg/d im or iv for 28 days
3. Amphotericin B deoxycholate 0.75-1 mg/kg/d iv, daily or on alternate days for 20-30 doses, total dose of 2-3 g

iv: intravenous; im: intramuscular; sd: single dose

The nitroimidazole: **fexinidazole** has potential as a safe and effective oral drug therapy for treatment of visceral leishmaniasis (see also treatment of Human African Trypanosomiasis). Both metabolites of fexinidazole (sulfone and sulfoxine) were active against *Leishmania donovani* amastigotes. Reliance on a single enzyme for prodrug activation may leave fexinidazole vulnerable to the emergence of drug resistance. Clinical studies are ongoing. One option under exploration in East-Africa is the combination of miltefosine and fexinidazole (both given orally).

Several other drugs mentioned below have also been explored historically but have not made it to first line treatment.

Pentamidine isethionate (4 mg/kg every 48 hours IM for 4 months).

Combination therapy with gamma-interferon was explored, based on the importance of Th1 immunity in achieving control of visceral leishmaniasis, but efficacy was only modest.

High-dose allopurinol (Zyloric®), e.g. 3 x 7 mg/kg/day (that is, 20 mg/kg/day), for 4-12 weeks was also effective in clinical studies.

Terbinafine (Lamisil®) is an antimycotic drug with some clinical activity.

Sitamaquine. Due to relatively low efficacy rates and safety issues, this has largely been abandoned.

Pamidronate a bisphosphonate drug typically used in the treatment of osteoporosis is effective against experimental cutaneous leishmaniasis. Several bisphosphonates have significant activity against *Leishmania donovani* in vitro, and several are potent inhibitors of bone resorption and in clinical use for the treatment of osteoporosis and Paget's disease. It is possible that currently approved clinical regimens of the drug are not high enough to cure human cutaneous leishmaniasis. Pamidronate could be a useful lead compound in the synthesis of new drugs against this disease.