Republic of Sudan
Federal Ministry of Health
Case Management Department

MANUAL FOR THE DIAGNOSIS AND TREATMENT OF LEISHMANIASIS

April 2017
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Acknowledgements

The National Leishmaniasis Control Programme (LCP), Federal Ministry of Health, Sudan, would like to acknowledge all the efforts spent on studying, controlling and reducing morbidity and mortality of leishmaniasis in Sudan, which culminated in the formulation of this manual in April 2004, updated in 2017.

We would like to express our thanks to all institutions, organizations, research groups and individuals for their support.
Preface

Leishmaniasis is a major health problem in Sudan. Visceral, cutaneous and mucosal forms of leishmaniasis are endemic in various parts of the country, with serious outbreaks occurring periodically. Sudanese scientists have published many papers on the epidemiology, clinical manifestations, diagnosis and management of these complex diseases. This has resulted in a better understanding of the pathogenesis of the various forms of leishmaniasis and has led to more accurate and specific diagnostic methods and better therapy. Unfortunately, many practitioners are unaware of these developments and still rely on outdated diagnostic procedures and therapy.

This document is intended to help those engaged in the diagnosis and treatment of patients with various forms of leishmaniasis. The guidelines are based on publications and experience of Sudanese researchers and are therefore evidence based. The guidelines were agreed upon by top researchers and clinicians in workshops organized by the Leishmaniasis Control Programme (LCP), National Ministry of Health, Sudan. We hope that they will be helpful to clinicians and other workers in the field of leishmaniasis.

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Sudan

April 2017
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>CL</td>
<td>Cutaneous leishmaniasis</td>
</tr>
<tr>
<td>DAT</td>
<td>Direct agglutination test</td>
</tr>
<tr>
<td>ICT</td>
<td>Immunochromatographic test</td>
</tr>
<tr>
<td>IFAT</td>
<td>Immunofluorescence antibody test</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LCP</td>
<td>Leishmaniasis Control Programme</td>
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<tr>
<td>LST</td>
<td>Leishmanin skin test</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PKDL</td>
<td>Post Kala-azar dermal leishmaniasis</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>rK28</td>
<td>Recombinant 28 antigen</td>
</tr>
<tr>
<td>rK39</td>
<td>Recombinant K39 antigen</td>
</tr>
<tr>
<td>SGOT</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>SSG</td>
<td>Sodium stibogluconate</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TOC</td>
<td>Test of cure</td>
</tr>
<tr>
<td>VL</td>
<td>Visceral leishmaniasis</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Objectives and Targets of the Manual:

- To provide a standardized and simplified guide for diagnosis and management of leishmaniasis;
- To promote evidence-based, safe and rational use of antileishmanial drugs;
- To serve as a training tool and reference material for health service providers, programme managers and researchers.

Targets:

- Health care workers (physicians, medical assistants, nurses, pharmacy personnel, laboratory technicians) providing care to people in endemic areas;
- LCP managers, health planners, and researchers;
- Organizations involved in leishmaniasis control.
Chapter 1

INTRODUCTION

History of the Leishmaniasis Control Programme

Visceral leishmaniasis (VL) is a vector-borne protozoal disease that is estimated to cause 200,000–400,000 cases annually. More than 90% of these cases are found in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan.

The Leishmaniasis Control Programme (LCP) was part of endemic disease administration, together with schistosomiasis, guinea worm, sleeping sickness, and zoonotic diseases. In February 1998, the LCP was designated as a separate programme, and a national programme coordinator was nominated. Since September 2001, the programme has been integrated with the National Malaria and Schistosomiasis Control Programmes within the Ministry of Health. Recently, the LCP became under the Neglected Tropical Disease Directorate within the MOH, with other control programs of neglected tropical disease.

Epidemiology of leishmaniasis in Sudan

Leishmaniasis is a group of diseases with a variety of clinical manifestations. There are four main clinical forms of leishmaniasis in Sudan: VL (kala-azar); post-kala-azar dermal leishmaniasis (PKDL); CL; and mucocutaneous leishmaniasis. VL is the most severe form, with up to 100% fatality in untreated cases. In population-based studies, incidence rates of 38/1000 per year, and case fatality rates as high as 20.5% have been observed (Zijlstra et al., 1994).

The disease is reported to be more prevalent among poor people, individuals with malnourishment, vagrants, farmers, labourers, water carriers, and those who live in remote areas, who have a limited capacity to meet the costs of the disease.
Disease burden

VL is among the most important health problems in Sudan, with >24 660 cases and 1193 deaths being reported during 1996–2001, and from 2002 to 2011 the number of reported cases was 29 700 and 1120 deaths in seven states. The number of reported cases is mainly a reflection of reporting rather than the actual disease transmission. Reports and published work from Sudan show that the disease affects mainly children with few adult cases.

Cutaneous leishmaniasis (CL) is present in the different states of Sudan, with the main foci in the northern state and North Darfur, and in 2011, 6000 cases of CL were reported, mainly.

Figure: 1 Map of VL (kala-azar) in Sudan based on cases reported in 2011 from 19 treatment centres. Cases are attributed to a population of 100 000.
**Treatment centres:**

In 2015, FMOH and KalaCore conducted assessment for the treatment centres and came up with 36 treatment centres distributed in ten states as follow:

**Gedarif state:** Gedarif teaching hospital, paediatric hospital, Maternity hospital, Um Alkher hospital, Bazora, Hawata hospital, Tabarak Alla hospital, Basonda hospital, Alhassan-Doka hospital, Kassab hospital, Goresha hospital and Almogran hospital.

**Sinnar state:** Azaza damos hospital, Sinnar hospital, Sinnar paediatric hospital, Aldinder hospital and Sinja hospital.

**Aljazera state:** Wad Madani hospital and Wad Madani paediatric hospital

**North Kurdfan state:** Alobied hospital and Um Rawaba hospital

**South Kurdufan state:** Kadugli hospital, Abu karshola hospital and Abu Gebiha hospital.

**White Nile:** Kusti hospital, Alsofi hospital and Algetaina hospital.

**Blue Nile:** Alruseris hospital, chinease frinship hospital and Aldamazen hospital

**Khartoum state:** Tropical medicine hospital, Jafer Ibn ouf hospital and Mohammed Alamin hospital

**North Darfur state:** Almalha hospital and Alfasher hospital.

**South Darfur state:** Nyala hospital.

**Figure:** 1 Map of VL treatment centres.
Parasites
Worldwide, over 20 pathogenic species of the *Leishmania* parasite are known. In Sudan, the parasite isolated from humans and sand flies that causes VL belongs to the *Leishmania donovani* sensu lato cluster. There are a few reports of isolation of *Leishmania archbaldi* and *Leishmania infantum* from humans and dogs in Gedaref State, eastern Sudan. The causative parasite for CL in Sudan is *Leishmania major* zymodeme LON-1 (El Hassan and Zijlstra, 2001).

Vectors
*Phlebotomus orientalis* is the primary vector for transmission of VL in Sudan. The sylvatic behaviour of adult *P. orientalis* and lack of knowledge of its resting and breeding sites are the main reasons to prohibit any plan to control this vector through spraying of insecticides. However, insecticide-impregnated bed nets and insect repellents remains the only choice for protection against the bites of *P. orientalis*. Observations on the bed time of people in VL-endemic areas imply that impregnated bed nets could potentially give more protection to children than adults against *P. orientalis* bites. *P. orientalis* bite around the mid-night and other sandflies bite early. the vector is unpredictable and highly susceptible to enviromental factors (temperature and humidity) and rainy season.

The vector of CL is *Phlebotomus papatasi*. 
Transmission cycles
There are two different transmission cycles:

- Anthroponotic transmission in which humans are the sole source of infection for the vector;
- Congenital transmission has been reported sporadically from some endemic areas. There are no reports on other routes of transmission such as sexual or transdermal.

Causative agent for leishmaniasis has two developmental stages

Amastigotes: In vertebrate hosts Ovoid, 2 to 4 m in size (also called LD bodies), Intracellular (inside macrophages), few present in peripheral blood. Spread all over the body through circulating macrophages. Also present in PMN cells and monocytes. Divide by binary fission.

Promastigotes:

Seen in vectors as well as cultures. Fully developed promastigotes are 15-20 x 1-2 micrometer in size. Infective form for humans Flagellated form.
Sandfly Stages

1. Sandfly takes a blood meal (injects promastigote stage into the skin)
2. Promastigotes are phagocytized by macrophages
3. Promastigotes transform into amastigotes inside macrophages
4. Amastigotes multiply in cells (including macrophages) of various tissues

5. Sandfly takes a blood meal (ingests macrophages infected with amastigotes)
6. Ingestion of parasitized cell
7. Amastigotes transform into promastigote stage in midgut
8. Divide in midgut and migrate to proboscis

= Infective Stage
= Diagnostic Stage
Chapter 2

CLINICAL FEATURES OF VISCERAL LEISHMANIASIS AND DIAGNOSIS

VL clinical features: main symptoms and signs

The main symptoms and signs of VL are:

- prolonged, irregular fever with or without rigors
- enlarged spleen, which is soft at the start of the disease and later it can become hard
- weight loss that progresses to wasting
- enlarged lymph nodes
- anaemia that is secondary to chronic illness, with iron-deficiency features
- Cough.

About half of the Sudanese VL patients present with hepatomegaly, nasal bleeding, diarrhoea and vomiting (see below table). Few patients show oedema or jaundice. Other signs and symptoms are insomnia, arthralgia, ascites and uveitis. Patients become gradually ill over a period of a few months and nearly always die if not treated.

Table 1

Occurrence of clinical features in patients with VL in Sudan

<table>
<thead>
<tr>
<th>Symptoms/signs</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Fever</td>
<td>95%</td>
</tr>
<tr>
<td>2- Splenomegaly</td>
<td>95%</td>
</tr>
<tr>
<td>3- Uncomfortable spleen</td>
<td>85%</td>
</tr>
<tr>
<td>4- Weight loss (wasting)</td>
<td>80%</td>
</tr>
<tr>
<td>5- Anaemia</td>
<td>75%</td>
</tr>
<tr>
<td>6- Lymph node enlargement</td>
<td>75%</td>
</tr>
<tr>
<td>7- Loss of appetite</td>
<td>70%</td>
</tr>
<tr>
<td>8- Cough</td>
<td>75%</td>
</tr>
<tr>
<td>9- Hepatomegaly</td>
<td>60%</td>
</tr>
<tr>
<td>10- Epistaxis</td>
<td>50%</td>
</tr>
<tr>
<td>11- Diarrhoea</td>
<td>40%</td>
</tr>
<tr>
<td>12- Vomiting</td>
<td>15%</td>
</tr>
<tr>
<td>13- Jaundice</td>
<td>5%</td>
</tr>
<tr>
<td>14- Oedema</td>
<td>5%</td>
</tr>
</tbody>
</table>

Source: adapted by permission of the publisher, from WHO, 1996
### Table 2

**Abnormal laboratory findings in VL patients**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>60–90%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>84%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73%</td>
</tr>
<tr>
<td>Albumin &lt;30 g/l</td>
<td>88%</td>
</tr>
<tr>
<td>Globulin &gt;30 g/l</td>
<td>98%</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>17%</td>
</tr>
<tr>
<td>Elevated SGOT/PT</td>
<td>22%</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>40%</td>
</tr>
</tbody>
</table>

*PT (Prothrombin Time); SGOT (aspartate aminotransferase).

Source: adapted, by permission of the publisher, from El-hag et al. (1994).

### Differential diagnoses

In Sudan, malaria is the most important disease with a similar presentation to VL. Therefore, malaria should be properly ruled out (and treated) before considering VL. Differential diagnosis should also consider enteric fever, schistosomiasis, haemoglobinopathy (especially sickle cell anaemia), malnutrition, tuberculosis (TB), brucellosis, hyper-reactive malarial splenomegaly (formerly known as tropical splenomegaly syndrome) and AIDS.

### Diagnosis of visceral leishmaniasis (VL):

**Clinical diagnosis**

*Clinically suspect case*

Any patient presenting with fever of ≥2 weeks duration, with one of the following signs: splenomegaly, weight loss and/or lymphadenopathy, who lives in or has travelled to endemic area...
Confirmed case
There are two accepted ways of confirming VL in a clinically suspected case: either by parasitology or serology.

Laboratory diagnosis
After taking a proper history and performing a thorough clinical examination, parasitological or serological tests are required to decide who should be treated (see the national recommended diagnostic algorithm below).

Parasitological diagnosis
Microscopic examination of Giemsa-stained spleen, bone marrow or lymph node aspirates to detect amastigotes remains the reference standard in VL diagnosis. However, these methods are either invasive or insensitive. It takes <1 h from sample collection to obtain the result.

The sensitivity of lymph node aspiration is 52–65%, whereas the sensitivity of bone marrow aspiration can reach up to 75% (Kager et al., 1983; Siddig et al., 1988; Zijlstra, 1998). Splenic aspiration sensitivity is 90–95%. Negative slides do not prove absence of the parasite, and low parasite density can be missed microscopically.

Lymph node aspiration is safe, easy and can be done by paramedical staff, compared with bone marrow aspiration, which is painful and needs specific and sterile needles, and trained personnel. Spleen aspiration is the most sensitive procedure, but it may be hazardous. It needs an experienced physician and should be performed in hospital, where blood transfusion is available because bleeding is a life-threatening complication.

Parasitological methods require highly trained laboratory personnel and the results are dependent on the quality of microscopic examination and reagents.

Serological diagnosis
Several immunological blood tests that identify specific antibodies against *Leishmania* are available: immunofluorescence antibody test (IFAT), ELISA, direct agglutination test (DAT) and recombinant K39 antigen (rK39) immunochromatographic test or (rK 28) (ICT) (useful in field settings). Leishmaniasis Control Program selected two serological tests (DAT and rK39/rK28 ICT) that can be used for diagnosis of VL in Sudan.

Direct agglutination test
The DAT is simpler than many other tests but its drawbacks include:
• prolonged incubation time (18 h)
• requirement for microtitre plates and micropipettes
• Requirement for well-trained laboratory personnel.

Moreover, the DAT (as for all serological tests for antibody detection) suffers from two major limitations.

Antibodies can remain detectable up to several years after cure because of asymptomatic infections. A significant proportion of healthy people living in endemic areas with no history of VL are positive for *Leishmania* antibodies.

Therefore, the DAT cannot distinguish between active VL and subclinical and past infection, and such tests cannot be used for diagnosis of relapse or for evaluation of cure.

<table>
<thead>
<tr>
<th>DAT</th>
<th>Freeze dried</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive:</td>
<td>≥ 1:3200</td>
</tr>
<tr>
<td>Borderline (BL):</td>
<td>1:1600; 1:800; 1:400</td>
</tr>
<tr>
<td>Negative:</td>
<td>≤ 1:200</td>
</tr>
</tbody>
</table>

**rK39-based immunochromatographic test:**
rK39 is a cloned antigen of 39 amino acid repeats of a gene found in *Leishmania chagasi*. A meta-analysis of 13 studies evaluating the rK39 ICT showed excellent diagnostic performance (sensitivity and specificity estimates of 93.9% and 95.3%, respectively). The overall sensitivity was lower in studies from East Africa than in those from South Asia. Several brands of the rK39 ICT have been evaluated. Higher values for both sensitivity (90%) and specificity (99%) have been obtained with the rK39 ICT (IT-LEISH) manufactured by BioRad (previously DiaMed) the good diagnostic performance of IT-LEISH has been confirmed in a recent tropical disease research multicenter study with 87.2% sensitivity and 96.4% specificity in East Africa. Also rK28 is another antigen antibody based test which is evaluated in Sudan. The test is easy to use in the field, reproducible, rapid (10–20 min) and inexpensive, therefore, the diagnosis can be established at the primary health care level. However, as an antibody detection test, the rK39/rK28 ICT cannot be used for the diagnosis of relapse and as a test of cure.
Nucleic-acid-based assays
Polymerase chain reaction (PCR) is usually highly sensitive for detection of *Leishmania* infection, but this does not imply it will be useful for the confirmation of acute VL disease in patients in an endemic area, because many carriers of the infection in the area will be PCR positive without developing VL disease.

**National Diagnostic Algorithm of clinical suspect of VL**
Chapter 3

TREATMENT OF LEISHMANIASIS

Before starting anti Leishmaniasis drug, the patient must be tested for HIV. The basic investigations required are HB, HBV, HCV, RFT (at least Blood Urea), ECG (Day1 and day7), and Hcg. VL patient must be admited during the treatment course with proper follow up by clinician, NO ambulataroy treatment nor empircal treatment.

First-line treatment for visceral leishmaniasis
First-line treatment comprises combination of sodium stibogluconate (SSG; Albert David, Kolkata, India) and paromomycin sulphate (PM; Gland Pharma, Hyderabad, India). SSG is a pentavalent antimony compound and paromomycin sulphate is an aminoglycoside antibiotic.

SSG&PM is recommended by WHO and its efficacy is better than SSG alone, also it has other benefit:

- reduced duration of treatment is more economical (44US$ versus 55.8 US$),
- reduced potential risk of resistance to SSG,
- reduced long exposure to SSG toxicity.

Other alternative options for first line treatment for VL
• In some clinical settings where PM is not available or contraindicated, SSG can be used alone for 30 days duration.
• Other types of pentavalent antimonials can be used, such as meglumine antimoniate (Glucantime).

**Treatment regimens**

SSG: 20 mg/kg/day for 17 days as a single daily dose, (WHO, 2010). No upper limit should be set for the daily dose, which should be determined by the patient’s body weight.

PM: 15 mg/kg/day (11 mg/kg paromomycin base) for 17 days as a single daily dose, (WHO, 2010). The two drugs should be prepared in separate syringes.

For all patients, proper history should be taken with full medical examination. Specific examination must be done like hearing assessment by tuning fork and whisper test to assess contra-indication to paromomycin use (risk of hearing loss).

There is no trough concentration (amount of drug following the last dose), therefore, if treatment is interrupted for >5 days, it should be resumed from Day 1.

**Route of administration**

SSG is administered by intramuscular (IM) with proper follow up to avoid abscess. A vial of 30 ml solution contains the equivalent of 100 mg/ml pentavalent antimony. It is recommended to administer it by IM injection.

PM is administered by the IM route only. An ampoule of 2 ml solution containing 375 mg/ml paromomycin base.

**Sodium stibogluconate**

**Toxicity/side effects**

• Clinical: injection site pain, vomiting, nausea, anorexia, arthralgia, myalgia, headache, fatigue, renal function impairment, cardiac toxicity and pancreatitis;
• Laboratory: elevated amylase (biochemical pancreatitis), elevated liver enzymes (biochemical hepatitis), elevated renal function tests, leukopenia, anaemia and thrombocytopenia;
• Electrocardiographic (ECG) changes are dose dependent and the most common are T-wave inversion and prolonged QT interval.
**Treatment of side effects**

- Patients with nausea or vomiting should continue eating and drinking but in small amounts;
- Treat vomiting with oral promethazine or other antiemetics for 2 days;
- Patients who vomit too much should be given oral rehydration salt or milk;
- Stop SSG for 2–5 days until vomiting is resolved;
- Consider injection of metoclopramide or promethazine;
- Patients taking tinidazole or metronidazole should be asked about vomiting and given antiemetics, and if necessary, the drug should be stopped;
- The most common cause of death is concomitant disease such as pneumonia, malaria or dysentery;
- Patients with concomitant diseases should be treated carefully.

**Contraindications**

Contraindications to SSG include: Cardiac disease, liver disease (jaundice), renal failure, age >45 years, HIV/AIDS, pregnancy, and infancy

**Pregnant women and neonates**

The data on the safety of pentavalent antimonials in pregnancy are confined to case reports, which indicate that they are relatively safe. However, recent published work indicates some reservations for using SSG in pregnant women and infants. There was some excretion of antimony in breast milk following administration of SSG to one woman. More evaluation is required before pronouncing on the safety of antimony in breast-feeding infants.

**Paromomycin sulphate**

The bioavailability of PMS is high (approaching 100%) following IM injection but it is negligible following oral administration; thus the IM route is required to treat a systemic disease such as VL. The half-life of PMS in humans is 2–3 h. It is not metabolized; it is excreted unchanged in the urine, thus, accumulation can occur in patients with diminished renal function.

PMS should be stored below 30°C and protect from light. It should not be frozen.
Toxicity/side effects

The most common adverse effects are injection site pain, transient elevation of alanine aminotransferase and aspartate aminotransferase, and increased blood alkaline phosphatase, creatinine and bilirubin. Toxicological studies have been conducted in animals. At high doses, paromomycin exhibits nephrotoxicity, ototoxicity and neuromuscular blockade. No cases of overdose have occurred in clinical trials of IM PMS. General supportive care is indicated. The effectiveness of renal dialysis as a treatment of overdose has not been formally studied.

Contraindications

- Patients who have shown hypersensitivity to Paromomycin or other aminoglycosides.
- Discontinue use if an allergic reaction occurs.
- Relatively contraindicated in patients with impaired renal function.
- Patients with pre-existing hearing impairment.

Pregnant women and neonates

Reproductive studies in rats and rabbits indicate that PMS is not teratogenic but does affect fertility and implantation. Aminoglycosides can cross the placenta, thus, PM may cause foetal injury when administered to pregnant women. It is therefore contraindicated during pregnancy. PM can be recovered in breast milk. The absorption of PM is negligible after oral administration, thus, it is expected that breast-fed infants would have no systemic exposure to PM.

Second-line treatment of visceral leishmaniasis

*Liposomal amphotericin B (AmBisome)*

AmBisome is administered at a dose of 3mg/kg/daily days for 10 to 14 days. 3-5 mg/kg per dose for 6-10 days up to total of 30 mg/kg as initial dose please see annex

Given on alternate days: 1, 3, 5, 7, 9, 10, for special group eg renal problem or heart disease to avoid fluid overload; see annex for calculation.
**Indications**

- lack of response or relapse after SSG–PMS or SSG monotherapy
- Contraindication to SSG or PM.
- SSG-induced toxicity
- age >45 or <2 years
- HIV co-infection
- Pregnancy
- Severely ill patients

**Route of administration**

*For the first dose Hypersensitivity test should be done which is by:*

Taking 0.25ml of reconstituted AmBisome in 1 ml disposable syringe and dilute it up to 10 ml with 5% DA for test. intravenous inject slowly 1ml per minute then wait for 30 minutes.

AmBisome comes in vials of 50 mg and needs to be reconstituted in 12 ml distilled water and diluted in 5% dextrose (at a concentration of 1 ml in 20 ml 5% dextrose) before administration by IV infusion over 30–60 min. The drug should be reconstituted using gloves and gowns. The reconstituted drug should be protected from light during the infusion session. Do not dilute with saline solutions or mix with other electrolytes or drugs.

**Storage**

Prior to mixing, AmBisome should be stored at 2–8°C and protected from exposure to light. Do not freeze the drug. The mixture of AmBisome and 5% dextrose may be stored for 15 h at 2–8°C and an additional 6 h at room temperature. Short interruption of the cold chain will not damage the drug.

**Side effects**

The major side effect is renal failure, usually reversible, which can be mostly prevented by providing adequate hydration. A frequent but benign side effect is the occurrence of chills and fever during or after infusion. In the event of occurrence of chills and fever give Paracetamol and go ahead with the AmBisome. Fever and chills can be partially prevented
by infusing AmBisome slowly (over 2 hours). Patient often feel a low backache if the infusion is going too fast.

**Pregnant women and neonates**

AmBisome appears safe during pregnancy and is recommended as first-line treatment.

**Contraindications**

AmBisome is contraindicated in patients who have shown hypersensitivity to amphotericin or the lipid content of AmBisome.

**Other second-line drugs for treatment of leishmaniasis**

*Amphotericin B deoxycholate*; Amphotericin B deoxycholate is sometimes referred to as conventional amphotericin B. Amphotericin B is a mixture of antifungal polyene antibiotics produced by some strains of *Streptomyces nodosus*.

**Dose**

Amphotericin B is given at a dose of 1 mg/kg every other day for 30 days (total 15 mg/kg), or 0.5 mg/kg daily for 30 days. It should be given initially at a test dose of 0.1 mg/kg.

**Route of administration**

IV infusion should be given as a colloidal complex with sodium deoxycholate, at a concentration of 0.1 mg/ml in 5% glucose over 2–4 h. Amphotericin B is infused in 1 litter 5% dextrose over 12 h, to decrease infusion-related side effects (e.g., fever and chills).

**Side effects**

These side effects apply to the conventional form only: headache, nausea, vomiting, chills, fever, malaise, muscle and joint pain, diarrhoea and gastrointestinal cramps, hypertension, hypotension, cardiac arrhythmia (including ventricular fibrillation), cardiac arrest, skin rashes, anaphylactoid reactions, blurred vision, tinnitus, hearing loss, vertigo, liver disorders, peripheral neuropathy, convulsions, nephrotoxicity (which occurs in almost all patients receiving amphotericin B), hypokalaemia, hypomagnesaemia, nephrocalcinosis, anaemia, and thrombophlebitis at the injection site.
Pregnant women and neonates

There are case reports of successful treatment of fungal infections in pregnant women with amphotericin B, without any adverse effects on the infant. However, care should still be exercised.

Drugs under investigation

Miltefosine

Miltefosine was developed as an antineoplastic drug. It is the first oral drug with demonstrated efficacy against VL but clinical trials are not yet complete. The drug has been extensively studied in India, where it is registered. No enough data to recommend. Miltefosine for Sudanese patients, More research among Sudanese patients is highly recommended.

Pentamedine:

Pentamedine is used as prophylaxis in other country, No enough data to recommend Miltefosine for Sudanese patients, More research among Sudanese patients is highly recommended.

Supportive treatment for patients with visceral leishmaniasis

Care under direct medical supervision and observation

• Nutritional support.
• Multivitamins.
• Iron sulphate/gluconate and folic acid.
• Tinidazole for parasitic infections.
• Malaria prophylaxis in special circumstances.
• Care for concurrent infection (e.g., malaria, pneumonia, TB and HIV/AIDS).
• Blood transfusion is not generally needed; haemoglobin increases with successful treatment. Blood transfusion should be undertaken if the setting is optimal.
for donor screening and one has the ability to deal with any complications that may arise.

**Nutrition protocol for visceral leishmaniasis patients**

The overall objectives in nutritional care for patients with VL are to assist the recovery period and improve the response to treatment. The specific objectives focus on:

- supporting all patients with nutritional support during treatment
- reducing the incidence of concomitant illness/infection
- Treating severe and moderate acute malnutrition.

All patients with VL should receive adequate nutritional support. This can be done through general food distribution, which must be appropriate in quality and quantity. The quality can be improved through supplementation of food items.

**Follow-up after treatment**

Follow-up at the end of treatment, at 6 months post-treatment, and at any time whenever symptoms return is important to detect treatment failure.

**Criteria of cure**

Primary VL: clinical cure with no fever, absence/reduction in the size of the spleen, weight gain, good appetite, and increase in haemoglobin and albumin levels.

**Case definition according to follow-up**

Cases can be defined as follows:

- **Initial Cure**: A patient that showed improvement of signs and symptoms at end of treatment

- **Initial treatment failure**: A positive TOC (parasitological failure) and persisting clinical signs/symptoms. There are two types: slow-responders and non-responders

- **Non-responder**: patients with persistent clinical symptoms and signs and a positive parasitology aspiration after completion of treatment (after 17 days of
combination therapy or 30 days of SSG treatment or full dose Ambisome) patients who do not show any decrease in parasite load are also classified as non-responders.

- **Slow responder:** Patients who show a slow clinical response and decrease but not a disappearance of parasite load on lymph node or bone marrow aspirate examination after completion of therapy. (After 17 days of combination therapy or 30 days of SSG treatment or full dose Ambisome).

- **Definitive cure:** patients who have an initial cure and show no sign of relapse within 6 months.

- **Discontinuation due to drug toxicity:** Discontinuation of treatment due to SSG/PM-related drug toxicity

- **Defaulter:** A patient that took less than 14 doses of SSG/PM or less than a total dose of 25mg/kg of Ambisome.

- **Relapse:** a patient with clinically and parasitologically confirmed VL within 6 months of successful treatment of VL.

- **Referred out:** Any patients referred to other hospital for further management.

- **Death:** Patient that died before, during the treatment of kala azar.

- **SAE:** any severe adverse effect related to the VL drug, which is supposed to reported

**Test of cure (TOC)**

TOC is a parasitological test (lymph node or bone marrow aspiration) performed at the end of treatment to assess the parasitological response to therapy. If the TOC is performed too early (<28 days), parasites may still be present and a diagnosis of non-response or slow response could be wrongly made. This is particularly important now that shorter treatment regimens are administered (i.e. SSG/PM 17 days, Ambisome 10 days). Therefore, the interpretation of a positive TOC made earlier than day 28 must take into account the presence or absence of clinical and biological signs of non-response.

TOC is NOT mandatory for all cases but it’s indicated in the following situations:
• Primary Kala-azar patients who show no clinical improvement at the completion of first line therapy (persistence of fever, Hb not increasing and/or no regression of the spleen)
• Relapsed kala azar patients who received second line therapy.
• In all HIV-VL co-infected patients.
• Non-responders shifted to another anti-leishmanial treatment.
• Slow responders during the extended course of treatment (weekly).

TOC is not necessary for primary VL if the patient improved clinically (No kala-azar symptom, gain weight, Hb increase and decrease in spleen size).

Treatment of non-responders and relapses

Initial non-responders:
Consider second-line drugs (e.g., AmBisome). **Do not repeat combination therapy (SSG+PM):** instead switch to another antileishmanial drug. In case there are no others drugs are available, one can stop PM and continue alone with SSG for first relapse up to 60 doses.

First relapse: For any patients treated before by SSG alone should be receive SSG/PM and for any patient treated by SSG/PM will be treated with AmBisome.

Second and third relapse: AmBisome (dose as above) Patients should be examined for risk factors for TB and HIV.
Chapter 4

OTHER TYPES OF LEISHMANIASIS

Cutaneous leishmaniasis:
Cutaneous leishmaniasis (CL) in Sudan is caused by *L. major*. The disease is endemic in many parts of the country.

The vector is *P. papatsasi* and the animal reservoir is probably the Nile rat *A. niloticus*.

Clinically, patients usually present with papules, nodules, or noduloulcerative lesions, mainly on the exposed parts of the skin. In 20% of cases, the parasite disseminates through the lymphatics, producing sporotrichoid-like lesions.

Diagnosis is confirmed by the demonstration of parasites in slit smears in 50–70% of cases and in histological sections in 70%. CL is a self-limiting disease; therefore, treatment is confined to patients with severe disease (El-Hassan & Zijlstra, 2001).

Epidemiology

Cutaneous leishmaniasis in the Sudan

CL is reported to prevail in many regions of Sudan and, four major outbreaks of CL have been reported: the first started in 1976–1977 in the region of Shendi – Atbara north
of Khartoum, the second in 1985 in and around El–Gerrsa in the White Nile area, and the third and last major epidemic took place in Khartoum province with about 10000 recorded cases in 1985-1987. The most recent outbreak occurred in south Kordofan Abukarshola locality in 2014 where 718 cases were reported. The outbreak affected different age groups. During the last two years an outbreak of CL occurred in the capital Khartoum following the heavy rainy season with thousands of individuals affected.

The Parasite

More than 20 different species of Leishmania can cause disease in humans. In the region, L. tropica causes anthroponotic cutaneous leishmaniasis whereas L. major, and less frequently L. infantum, cause zoonotic cutaneous leishmaniasis.

In Sudan most of the diagnosed cases are caused by L. major with but some cases are reported to be caused by Leishmania donovani.

The vector

The vector is P. papatasi.

Reservoir

The Nile rat A. niloticus is suspected to be the reservoir for the parasite.

Transmission of leishmaniasis

Leishmaniasis is transmitted by the bite of female sandflies. When the sandfly bites infected skin it makes a pool. With their mouthparts, which have cutting and saw-like edges, they scratch the tissue of the dermis, which contains several macrophages full of amastigotes, and mix them with blood. By sucking the blood from these pools, they suck not only blood but also damaged tissue of the dermis containing macrophages with amastigotes.

In the midgut of the sandfly, amastigotes change to promastigotes with flagella and multiply by binary fission. It takes about 5–7 days, depending to the temperature of the environment, for promastigotes to almost fill the midgut and change to their infective
form (metacyclic), which migrate to the anterior part of the gut and proboscis. At this stage, the sandfly is infective and when it bites for feeding it first injects some saliva (to prevent the blood from clotting) along with promastigotes in its mouthparts into the dermis of the new host. Promastigotes injected by this bite change to amastigotes, which are ingested by the macrophages of the dermis, the cells in which they live and multiply.

In cutaneous leishmaniasis, it takes several weeks or months until the lesion at the site of injection becomes apparent.

Factors affecting transmission

Population movements:

Epidemics of cutaneous leishmaniasis are often associated with migration and the introduction of non-immune people into areas with existing transmission. Prediction of such outbreaks depends on the availability of ecological information and on evaluation of development areas before implementation of projects or population movements.

Socioeconomic factors:

Poverty increases the risk for leishmaniasis in many ways. Poor housing and sanitary conditions (e.g. lack of waste management, open sewerage) may increase sandfly numbers, as well as their access to humans. Crowding of a large number of people into a small space may attract sandflies. Economically driven migration may result in non-immune individuals entering areas with transmission.

Environmental risk factors:

Large numbers of patients with cutaneous leishmaniasis have been reported when suburbs extend into formerly uninhabited lands with a high density of rodents. In some foci of anthroponotic leishmaniasis, rural-to-urban migration accompanied by poor-quality suburban housing can increase the frequency of the disease. In some epidemiological situations, deforestation and destruction of natural habitats can reduce transmission of cutaneous leishmaniasis. However, in some cases, deforestation appears to have increased rather than decreased human infection. Cutaneous leishmaniasis is a climate-sensitive disease, occupying a characteristic “climate space” that is strongly affected by changes in rainfall, atmospheric temperature and humidity.
Clinical description

Appearance of one or more lesions, typically on uncovered parts of the body. The face, neck, arms and legs are the commonest sites. At the site of inoculation, a papule appears which can develop to a papule and enlarged to become an indolent ulcerated nodule or plaque.

The sore remains in this stage for a variable time before healing and typically leaves a depressed scar. Other atypical forms may occur. In some individuals, certain strains can disseminate and cause mucosal lesions. These sequelae involve nasopharyngeal tissues and can be disfiguring.

Laboratory criteria for diagnosis

• Positive parasitology (stained smear or culture from the lesion).

• Mucocutaneous leishmaniasis only: positive serology (indirect immunofluorescent antibody test, enzyme-linked immunosorbent assay).

• Polymerase chain reaction (more sensitive than microscopic examination).

Case classification by WHO operational definition

• **Probable case**: a probable case of cutaneous leishmaniasis is a person showing clinical signs (skin or mucosal lesions) without parasitological confirmation of the diagnosis (positive smear or culture) and/or, for mucocutaneous leishmaniasis only, serological diagnosis.

• **Confirmed case**: a confirmed case of cutaneous leishmaniasis is a person showing clinical signs (skin or mucosal lesions) with parasitological confirmation of the diagnosis (positive smear or culture).

• **Cured case**: complete re-epithelialization before Day 45.

• **Relapse case**: reappearance of a nodule, plaque or ulceration after cure.

• **Treatment failure**: increase of a nodule, plaque or ulceration within 14 days of treatment, or lack of complete re-epithelialization within 45 days of treatment starting.

Differential diagnosis must include:
infectious and non-infectious conditions. Therefore it is mandatory to obtain a parasitological confirmation of the diagnosis before engaging in a systemic, potentially highly toxic antileishmanial treatment. The same procedure is recommended before engaging in a local treatment.

Differential diagnosis of cutaneous leishmaniasis (pictures of all types will be added)

- Impetigo
- Paronychia
- Venous leg ulcer
- Verruca
- Neuropathic ulcer
- Zona
- Verruca
- Psoriasis
- Sarcoidosis
- Blastomycosis
- Chromoblastomycosis
- Cutaneous tuberculosis
- Mycetoma
- Brulli ulcer

Treatment:
Cutaneous leishmaniasis is not a life-threatening condition and severe complications are infrequent. However, as superficial secondary infections may complicate ulcerated cutaneous leishmaniasis, it is important to clean lesions. Cutaneous leishmaniasis due to L. major is associated with a self-cure rate above 50%–75% at 4–6 months. The recommended drug or treatment approach in cutaneous leishmaniasis should not induce life-threatening complications; however, in severe cases, the risk–benefit ratio is different.
The treatment decision is based first on the risk–benefit ratio of the intervention for each patient (for the recommended step-wise approach to choosing the most appropriate treatment option, see diagram).

To determine which treatment is most appropriate, it is important to collect the clinical information on the following five aspects:

- Size of lesion: papule (<1 cm), nodule (<4 cm) or plaque (≥4 cm) (add photos).
- Number of lesions.
- Location of lesions on the body.
- Evolution of the lesions: duration, aggravation (active lesion), improvement (self-curing);
- Immunological and general health status of the patient: immunocompromised, diabetes, heart, liver or kidney trouble.

In all patients, lesions should be washed with clean water and soap, then the lesion should be covered by a dressing (gauze and tape) and changed three or four times per week. This facilitates healing and prevents the creation of a sticky crust.

Bacterial superinfection is a rare complication in cutaneous leishmaniasis. However, if lesions show obvious signs of clinically significant bacterial superinfection, i.e. a red, swollen and tender zone extends beyond the cold infiltrated borders of the leishmaniasis lesion itself (a complication rarely associated with fever), it is then justified to initiate oral antibiotics effective against common streptococci and staphylococci.

If the bacterial superinfection appears in cases treated with intralesional antimonials, the injection must be postponed and systemic antibiotics should be prescribed. When superinfection is managed, intralesional antimonials can be resumed.

Specialized advice (9)

Step-wise algorithm for the treatment of cutaneous leishmaniasis
IL, intralesional; Sb, pentavalent antimony. *See situation 1 in text.

(1) Self-curing lesions show flattening or reduction in the surface of the ulceration and/or induration.

(2) Washing the lesion, wound dressing and follow-up will be performed in all situations.

(3) Lymphatic dissemination per se does not influence treatment decision. However, when it increases the number of lesions requiring therapy it may justify the use of systemic therapy.

(4) Most lesions of limbs, trunk, cheek, upper-cheek, chin and front can be injected, including those close to large joints. Injections in ears, fingers, toes are usually very painful. Injections in lesions of the eyelids, nose and lips can sometimes be performed by very experienced health care providers. In children, premedication facilitates the procedure.

(5) See Annex 2 and Annex 3 for information about the different formulations and the practical aspect of treatment administration.

(6) In patients aged over 50 years, the risk of severe adverse events related to systemic Sb therapy is probably higher than in younger patients, justifying specialized advice and very close follow-up.

(7) See Annex 4 for information about the different formulations and the practical aspect of treatment administration and follow-up.

(8) Fluconazole has been proposed to treat L. major cutaneous leishmaniasis but its efficacy is variable. Itraconazole has been tested in cutaneous leishmaniasis due to L. tropica. Where available, topical paromomycin can be used simultaneously on a large number of lesions. Liposomal amphotericin B have been used in tertiary care centres.

(9) In complex situations, decision must be discussed on a patient by patient basis.

**Situation 1**

The patient:

1. Has lesions that are limited in size (papules, nodules or ulcerated nodules all <4 cm); and

2. Has less than four lesions; and

3. Has lesions that are not potentially disfiguring or disabling (i.e. not on face, fingers or toes); and

4. Is infected with L. major (or the lesion is already self-curing); and
5. Is not immunocompromised and does not suffer unbalanced diabetes.

In this situation, the recommendation is to wash lesions and put a dressing on the lesion without specific antileishmanial therapy. It is important to make sure that the patient adheres to this option; otherwise he or she will probably look for other kinds of interventions and will lose confidence. It is also important to provide a clear explanation about the benefits and lack of risk of this approach:

- Cutaneous leishmaniasis induces no risk of general disease and there is no risk of transmission to family members.
- There is a reasonably high probability of cure in the next few months.
- This approach avoids the discomfort created by the specific antileishmanial treatment.

A schedule for follow-up is established and communicated to the patient at 14, 30 and 45 days, with a final visit at 180 days. It is important to clearly mention the possibility for the patient to come back to receive specific antileishmanial therapy if the evolution is not satisfactory.

**Situation 2**

The patient: has all the features defined in Situation 1 but was not cured despite the care provided as described in Situation 1;

or:

1. Has lesions <4 cm; and
2. Has less than four lesions for which he or she asks for treatment; and
3. Has lesion(s) located in sites compatible with local treatment (see Fig. 9); and
4. Has one or more active lesion due to L. tropica or L. infantum; and
5. Is not immunocompromised and does not suffer unbalanced diabetes.

In this situation, one of the following therapeutic options can be used:

- Topical paromomycin ointment twice daily for 20 days (if L. major);
• Cryotherapy (liquid nitrogen -195°C) plus intraregional pentavalent antimonials
• Thermotherapy
• Intraregional antimonials alone: 1–5 ml, twice weekly for 3–4 weeks until complete cure. The same follow-up schedule as in Situation 1 is recommended.

**Situation 3**

The patient: has all features defining Situation 1 or 2 but was not cured despite the care provided as described in Situations 1 and 2; or:

1. Has a lesion ≥4 cm (plaque); or
2. Has four or more lesions requiring immediate therapy; or
3. Has lesion(s) located in sites not compatible with local treatment; or
4. Is immunocompromised or suffers unbalanced diabetes.

In this situation the recommended treatment is systemic pentavalent antimonials with appropriate elimination of contraindications and appropriate follow-up.

**In complex situations** (different from Situations 1–3 defined above), the decision must be discussed on an individual basis. The following treatments can be discussed.

• Fluconazole, orally 200–600 mg/day for 4–6 weeks, has been proposed to treat L. major cutaneous leishmaniasis but the efficacy is variable.

• Itraconazole has been tested in cutaneous leishmaniasis due to L. tropica in adults. Liposomal amphotericin B (20 mg/kg cumulative dosage in 4–7 slow infusions) have been used at tertiary care centres.

It is also important to bear in mind that allergic reactions can appear when using any of the different medicines or materials during the treatment of cutaneous leishmaniasis.
Annexes

Annex (1) parasitological diagnosis.
Annex (2) Standard operating procedure for intralesional injection of antimony.
Annex (3) Standard operating procedure for thermotherapy.
Annex (4) Systemic treatment of cutaneous leishmaniasis with pentavalent antimonials. (Dosage and precautions for sodium stibogluconate)

**Mucosal leishmaniasis:**
Mucosal leishmaniasis is a chronic infection of the upper respiratory tract and/or oral mucosa, which is caused mainly by *L. donovani*. The disease occurs in areas of the country that are endemic for VL, particularly among Masalit and other closely related tribes in western Sudan. The condition may develop during or after an attack of VL, but in most cases it is a primary mucosal disease.

The diagnosis is established by demonstration of parasites in smears or biopsies, by culture or animal inoculation. Most patients yield positive results in the DAT and leishmanin skin test (LST). Patients respond well to treatment with SSG (Pentostam) (El-Hassan & Zijlstra, 2001).

*Treatment of mucosal leishmaniasis*

Single doses of 10–20 mg/kg/day of SSG are given for a minimum of 4 weeks. Relapse should be treated with the same drug given for at least twice as long as the original treatment. Only when this fails should alternative treatment be given.

**Post Kala-azar Dermal Leishmaniasis (PKDL):**
PKDL is a known complication of VL. In the majority of cases, dermal lesions develop several months after the clinical cure of VL, but sometimes PKDL occurs during or even before treatment. However, cases have been reported in the absence of a history of VL. About 55% of successfully treated VL patients develop PKDL.
The lesions of PKDL start on the face as small scattered hypopigmented macules and papules. The rash can become nodular and spread to the trunk and limbs. Lesions are symmetrical and not itchy. A grading system is used to describe the spread of the skin lesions.

- Grade 1: scattered macular, papular or nodular rash on the face with some lesions on the upper chest and upper arms.
- Grade 2: dense macular, papular or nodular rash covering most of the face and extending on the chest, back, and upper arms and legs.
- Grade 3: dense macular, papular rash, covering most of the body, including hands and feet. In grade 3, crusting, ulcers, scaling and spreading to the mucosa of the lip and the palate occur. It is referred to as PKDL with mucosal involvement (or combined PKDL and post kala azar mucosal leishmaniasis). Lesions are often restricted to sun-exposed areas (whole body in children, face and collar distribution for men, and face for women).

Parasites can be detected in skin smears, but not in all cases. Parasites have also been detected in the normal skin in patients with VL. PKDL might persist for up to 10 years. It is speculated that PKDL patients could form a reservoir of the parasite in the community. Bed nets may be indicated to prevent transmission.

PKDL is distinct from CL, which consists of one or more ulcers caused by other species of *Leishmania*. PKDL can easily be confused with diffuse leprosy.

**Treatment of PKDL:**

Spontaneous healing occurs in mild cases (grade 1 or mild grade 2).

The indications for treatment are:

- Grade 3 and advanced grade 2 lesions
- Persistence of lesions for >12 months
- Concomitant anterior uveitis or mucosal lesions.

Treat until the lesions are definitely improving and not until the lesions have disappeared. Once healing begins during treatment, it usually continues off treatment. There are no parasitic criteria for cure because of the difficulties of demonstrating the parasite in the lesions. Follow-up is monthly until full resolution of lesions. It is advisable to take pictures of PKDL patients (after obtaining consent) at admission to ensure proper follow-up of the clearing of lesions.
The following drugs can be used to treat PKDL:

- **SSG&PM** for 17 days (SSG: 20 mg/kg/day for 17 days as a single daily dose)
- **PM** 11 mg/kg paromomycin base for 17 days

- AmBisome at a dose of 2.5 mg/kg/day for 20 days has been used successfully in some patients (Hashim et al., 1995; Musa et al., 2005).
- SSG at a dose of 20 mg/kg/day for 60–90 days is effective (El Hassan & Zijlstra, 2001). It is advised to continue treatment until 4–7 days after clinical cure (lesions have regressed and are no longer palpable, but discoloration is still visible). Approximately 4–8 weeks of treatment are needed, but longer courses are common.
HIV and leishmaniasis are both expanding due to the increasingly overlapping geographical distribution of the two causative pathogens (in Asia, east Africa, South Africa and southern Europe) the number of cases with co-infection is expected to rise. IV drug users represent the main population at risk.

HIV infection and VL influence each other reciprocally. HIV has caused an increase in VL cases. HIV patients with VL have a poor prognosis, and VL stimulates replication of HIV (Davidson, 1997).

**Clinical features of Leishmania/HIV co-infection**

The diagnosis of VL in patients co-infected with HIV can be particularly difficult. The usual clinical features of VL (splenomegaly, pancytopenia, fever and weight loss) are not always present or may be hidden by other opportunistic infections mimicking the same symptoms. Patients may have atypical VL with slight or no splenomegaly and only non-specific symptoms of fever, weight loss and malaise.

VL may be rapidly progressive, resembling bacterial sepsis. Alternatively, VL may have unusually slow progression with a few non-specific symptoms, and some patients with VL may be entirely asymptomatic.

HIV/Leishmania co-infected patients may have predominantly gastrointestinal involvement with symptoms of diarrhoea and weight loss. Leishmania parasites can be detected in biopsies of the oesophagus, duodenum and rectum. The larynx may also be involved, either alone or with gastrointestinal involvement.

**Diagnosis of visceral leishmaniasis in HIV-positive patients**

In AIDS patients, the cells responsible for the immune response are destroyed, impairing the capacity of the immune system to react to invasion by the leishmaniasis parasite. Consequently, the serological test for detection of Leishmania antibodies (IFAT or ELISA) is negative in 20–40 % of patients with HIV and VL co-infection. It is expected that DAT titres in Africa will be lower in such cases as well. The diagnosis is better by lymph node/bone
marrow aspirate, and not DAT alone. Parasites are abundant in lymph nodes/bone marrow, and microscopy of bone marrow aspirates yields a diagnosis in 91–97% of cases.

In 50% of HIV/VL patients, the buffy coat (white cell concentrate) of peripheral blood is positive. Sensitivity of culture of the buffy coat can reach 90%. About 80% of HIV/Leishmania co-infected patients usually have another AIDS-defining opportunistic infection, and 90% have CD4+ count <200/mm³ at the time of diagnosis. This may not be the case in Africa where the causative species is *L. donovani*, which is probably more virulent than *L. infantum*.

**All VL patients must be screen for HIV, and the Bone Marrow is recommended test for diagnosis**

*Treatment of HIV/Leishmania co-infection*

All VL patients should be counselled and tested for HIV because first-line antileishmanial treatment in HIV-positive patients is different. The response to antimonials, AmBisome or other anti-leishmaniasis drugs is both slow and less satisfactory in HIV/Leishmania co-infected patients. The median survival among HIV/VL patients is about 12 months. These patients have a huge parasite load and lack cell-mediated immunity to assist in parasite clearance.

Patients with VL/HIV co-infection should be treated with AmBisome.

**Failure to clear parasites and treatment of relapse**

A positive TOC in a patient with HIV/Leishmania co-infection should be followed by further treatment. If patients do not have relief of the symptoms of VL by 30 days, they will not benefit from a longer course of treatment. Thus, if HIV infection is suspected in patients with a positive TOC, an HIV test should be preformed.

Relapse of VL in known HIV patients should only be treated if symptoms are present. If no symptomatic relief occurs after 1 week, treatment should be stopped and palliative care initiated. Thus, if HIV infection is suspected in patients who have relapsed, an HIV test should be performed.

**Prognosis of HIV/leishmaniasis**
Thirty percent of HIV/VL patients will die during or within 1 month after treatment using drug rather than AmBisome. The mean survival with optimal treatment is only 12 months. Only 16% will survive for >3 years. Death is seldom due to VL alone. A sterile cure cannot be achieved by any drug, and relapse is almost inevitable.

Public health implications of HIV/leishmaniasis

HIV/Leishmania co-infected patients must be considered as highly infectious reservoirs of Leishmania in areas of active transmission because of the presence of amastigotes in the blood. The reservoir of VL in Africa is probably humans, so drug-resistant transmission can occur.

There is a clear correlation between the severity of immunosuppression and the percentage of sandflies becoming infected. Every VL patient in the should sleep under a mosquito net, and every HIV-positive patient should be sleeping under an impregnated bed net, whether or not they have VL.

Annex 1: outline of the new treatment protocol of leishmaniasis

1-Treatment of Visceral Leishmaniasis:

A- First-line treatment of VL is SSG and Paromomycin sulphate (PM) injection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>Route of administration</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSG</td>
<td>20 mg/kg single dose</td>
<td>17 days</td>
<td>IM/IV</td>
<td>Cardiac disease, liver disease (jaundice), renal failure, age &gt;45 years, HIV/AIDS, pregnancy, and infancy</td>
</tr>
<tr>
<td>Paromomycin sulphate (PM)</td>
<td>15 mg/kg single dose</td>
<td>17 days</td>
<td>IM only</td>
<td>Patients who have shown hypersensitivity to Paromomycin or other aminoglycosides Relatively contraindicated in patients with impaired renal function. Patients with pre-existing hearing</td>
</tr>
</tbody>
</table>
B- Second-line treatment of Visceral Leishmaniasis:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>Route of administration</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmBisome (liposomal amphotericin B)</td>
<td>3-5 mg/kg per day, up to total dose of 30 mg/kg.</td>
<td>6–10 days Alternate day (1, 3, 5, 7, 9, 11.)</td>
<td>IV only</td>
<td>Patients who have shown hypersensitivity to amphotericin or the lipid content of AmBisone</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>1 or 0.5 mg/kg/day</td>
<td>Every other day for 30 days Daily for 15 days</td>
<td>IV only</td>
<td>Patient with renal disease.</td>
</tr>
</tbody>
</table>

2-Treatment of Cutaneous Leishmaniasis

Step-wise treatment decision in cutaneous leishmaniasis due to

**L. major or L. tropica or L. infantum**

Step-wise treatment decision in cutaneous leishmaniasis due to

**L. major or L. tropica or L. infantum**
3- Mucosal leishmaniasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight/age</th>
<th>Dose/day</th>
<th>Duration</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSG</td>
<td>All new cases</td>
<td>20 mg/kg single dose</td>
<td>Minimum of 4 weeks</td>
<td>IM/IV</td>
</tr>
<tr>
<td>SSG</td>
<td>Relapse</td>
<td>20 mg/kg twice</td>
<td>Minimum of 4 weeks</td>
<td>IM/IV</td>
</tr>
</tbody>
</table>

4- Post Kalaazar Dermal Leishmaniasis (PKDL)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight/age</th>
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5- Leishmania/HIV co-infection

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Annex 2: Other tests for visceral leishmaniasis

rK28-based
A new, synthetic, multiepitope polyprotein, rK28, was obtained by fusing *L. infantum* k9 gene with single repeat units of k39 and k26 genes. This was followed by development and evaluation of two new rK28-based RDT prototypes.

rK28-LF RDT was developed by EASE MedTrend (Shanghai, China) and evaluated in Bangladesh. It had more favourable results (98.1% sensitivity, 92.5% specificity) compared to Kalazzer Detect (88.7% sensitivity, 100% specificity).

A second prototype test of rK28 (K28-DPP) was developed by Chembio Diagnostic Systems (Medford, NY, USA) and evaluated in Sudan. K28-DPP RDT proved to be superior and provided a sensitivity of 95.9% and specificity of 100% while the Kalazar Detect yielded a sensitivity of 86.3% and specificity of 96.4%. Moreover, the results of a recent TDR multicentre study proved that the new rK28-based RDTs have great potential to simplify VL disease confirmation at the point-of-care (unpublished data).

Latex agglutination test (KAtex)
The KAtex latex agglutination test was developed to detect heat-stable, low-molecular-weight carbohydrate antigen in urine (Attar et al., 2001). It is a simple, rapid and economical test, and is most suitable for use in remote areas.

In a multicenter study in east Africa (Ethiopia, Kenya and Sudan), KAtex showed good specificity but moderate to very low sensitivity (Boelaert et al., 2008). A field evaluation of the test in Sudan indicated that the test had a sensitivity of 95.2% and good agreement with microscopy but poor agreement with serological tests and a specificity of 100% (El-Safi et al., 2003). In addition, the test was also positive for the two confirmed VL cases co-infected with HIV. One of the advantages of the test is its ability to distinguish active from past infections. Accordingly, it can be used as a TOC and for diagnosis of relapse. However, the need to boil
the urine before testing to avoid false-positive reactions is a limitation. Work to improve the format of this urine antigen detection test is ongoing.

**Leishmanin skin test**

LST is a test that measures the delayed hypersensitivity type IV reaction in terms of induration of the skin in response to intradermal injection of *Leishmania* antigens:

- values ≥5 mm are considered to be positive
- it is typically negative during active primary VL
- it is positive in 80% of cases after 3–6 months following successful treatment
- it is positive in 50% of PKDL patients and nearly 100% of those with active CL, particularly at the advanced phases
- it has great value in field epidemiological surveys
- it has a special place in diagnosis to augment serology.

**ANNEX 3: DEFINITIONS**

**Cutaneous leishmaniasis**

Ulcers, macules, papules or nodules of the skin caused by leishmaniasis. Atypical forms are frequent. No involvement of other organs.

**Primary visceral leishmaniasis**

A patient who is diagnosed with VL for the first time has primary VL. There is no previous history of treatment of VL. Informal, incomplete treatments in the villages do occur and should be asked for explicitly.

**Post kala-azar dermal leishmaniasis**

PKDL is a cutaneous manifestation caused by the same parasite that causes VL and usually occurs several weeks after recovery from VL.

**Relapse**
A patient with a diagnosis of VL who has previously been treated successfully for VL.

**Reinfection**

A person who has VL more than once is considered to have a relapse rather than reinfection. The term reinfection is not used with VL patients. We assume that reinfection occurs but does not lead to clinical disease because of immunity after successful treatment.

**Test of cure**

The TOC is aspiration (usually of the spleen) to obtain proof of cure (to demonstrate the absence of parasites). A smear is made on a slide and stained with Giemsa. A TOC is performed for patients with primary VL between days 25 and 30. A positive TOC indicates that the patient has not yet been fully cured. It is possible that in patients who improve clinically, the parasites in the smear are reduced in number but are still detectable (slow responders).

**Initial cure**

Patients who improve clinically and have a negative TOC at discharge (after the first treatment).

**Definite cure**

Patients who have an initial cure and show no sign of relapse within 6 months.
ANNEX 4: Aspiration of lymph node, spleen and bone marrow

**Lymph nodes**

Lymph node aspiration is commonly taken from less hazardous clear lymph groups (e.g., inguinal or trochlear). The nodes are grasped between the thumb and finger after sterilization. A 21-gauge needle is attached to a 5-ml syringe and introduced, pushing the needle in and out to force the cells into the needle. A few drops of the aspirated fluid are placed onto a slide, smeared thinly, dried, fixed with methanol, stained with Giemsa, and examined.

**Spleen**

Spleen aspiration is the simplest, fastest and most reliable procedure for detection of *Leishmania* parasites. However, it carries a risk of bleeding, visceral puncture and splenic rupture, therefore, it requires expertise (physician) and should be performed in hospital with ready access to blood and an operating theatre.

Contraindications for spleen aspiration are: impalpable spleen, bleeding tendency, untrained staff, jaundice and late pregnancy.

**Technique**

- Sterilization of the site and equipment.
- A 21-gauge needle attached to a 5-ml syringe is inserted in the midline of the spleen. The needle is inserted quickly to the full needle depth (3 cm). A vacuum is created by pulling the plunger back and the needle is removed immediately. The speed ensures that no tearing occurs. The content of the syringe is deposited on a slide; a thin smear is made; and the slide is stained with Giemsa and examined.
- Puncture is performed at expiration, especially in children.
- No local anaesthesia is given.
- Sedation is recommended in restless or crying child (lymph node or bone marrow aspiration is preferred).
- Patient must be observed for 24 h.
Bone marrow

Bone marrow aspirate is usually taken from the sternum or iliac crest under local anaesthesia, with a sterile bone marrow aspirate needle attached to a 10-ml syringe. This smears are formed immediately on at least three slides, fixed with 100% methanol, dried labelling, and stained with Giemsa. Examined fewer than 100 magnifications (1000 field).

Annex 5: SOP for Preparation of AmBisome (reconstitution and dilution), Sudan

Procedure:

- Choose appropriate room for preparation of AmBisome and wash your hands with soap.
- Wear a pair of gloves.
- Take 12 ml of distilled water (in a 20 ml syringe, if available).
- Remove the rubber cap of the AmBisome vial and push the distilled water into the vial.
- Shake the vial immediately for 30 seconds until complete dispersion of the AmBisome.
- Allow bubbles to dissipate before use.
- Follow the same instruction for the next vial to be reconstituted using the same syringe; calculate the total number of vials based on body weight according to the Table given below.
• **Hypersensitivity test:** take **0.25ml** of reconstituted AmBisome in 1 ml disposable syringe and dilute it up to **10 ml** with **5% DA** for test.

  AmBisome is NOT compatible with saline and must not be reconstituted with saline or administered through an intravenous line that has previously been used for saline unless first flushed with 5% dextrose solution. Do NOT mix AmBisome with other drugs or electrolytes

  • Calculate the volume of 5% DA to dilute the whole dose of AmBisome according to the patient’s body weight using the tables.

  • Now hang the 500ml pack of 5% DA on an infusion stand.

  • Fix an infusion set with the 5%DA bottle/pack. Keep the required volume of 5% DA in the bottle/pack and discard the excess amount of 5%DA in a bowl.

  • Take another syringe to pull the reconstituted AmBisome from the vial, set a syringe filter on it.

  • Wash the pack/bottle surface with a ball of cotton soaked with chlorohexidine at the site of injecting the reconstituted AmBisome.

  • Inject the drug into that 5%DA solution.

  • Use one syringe filter for one vial of AmBisome.

  • Inject the total volume of reconstituted AmBisome in that 5% DA solution in the same manner.

  • Follow strict aseptic precaution from preparation site to infusion to the patient.

**Responsible person**

Qualified and trained staff nurse is responsible for the task but the whole procedure should be closely observed by the duty physician.

**Glossary/ Definition:**

• 5% DA: 5% dextrose in aqua

• kg: kilogram
AmBisome dosage in East Africa:

5 mg / dose for 6 – 10 d

Total dose up to 30 mg / kg

Regimen:

3 mg/kg/day for 10 days

Calculation:

Dosage in ml = dosage in mg × 19 = ml of Dextrose 5%

4

Rate for infusion: weight in Kg x 2,375

Reference: Leaflet provided with the AmBisome vial
AmBisome doses (~30 mg/kg divided in 10 doses)

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First line Treatment is SSG & PM for 17
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ANNEX 6: REFERENCES


Thomson, M. and Ashford R. Consultancy report on entomological and parasitological investigations in Leer and Duar, West Upper Nile, South Sudan, July 1990.

Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA. England.


