

4: TREATMENT OF VL AND SIDE EFFECTS

4.1 **What are the criteria, dependent on available resources, for the initiation of treatment?**

Other causes of the clinical picture, such as malaria, should be excluded (see section 2).

Ideally, all VL cases should be confirmed parasitologically. In field conditions, however, clinical features and a positive serological test for *Leishmania* (DAT test; see section 3) or, to a lesser degree, a positive formol gel test (see section 3) and, if available a negative leishmanin test justifies starting treatment (Slide 35)(the leishmanin skin test is negative during active VL).

In remote areas where neither parasitological or serological diagnosis is possible a trial of treatment may be necessary, if malaria or other causes have been excluded. A response to antimonials should be seen within a week to ten days, with a fall in temperature, increased feeling of well-being and an increased appetite.

When clinical (symptomatic) VL occurs (see 2.1 and 2.2 above) it is not benign or self-limiting and must be treated, as it is usually fatal if appropriate treatment is not given.

4.2 **How should treatment with antimonials be given? What are the side effects and contra-indications? How much does the treatment cost?**

Treatment

The World Health Organization recommends treatment with pentavalent antimony at 20 mg pentavalent antimony/kg/day for 30 days. Previously, an upper limit of 850 mg pentavalent antimony/day was advised, but more recently this has been revised, and there is no upper limit on the daily dose of 20 mg pentavalent antimony/kg. Treatment may be given as a once daily intramuscular injection (which is preferable for children) and in adults a larger volume of pentavalent antimony may require intravenous injection or infusion. Intravenous injection should be given over 5 - 10 minutes and infusion should be diluted in 50 - 100 ml of 5 % dextrose solution. In severely wasted children, the intramuscular injection may have to be divided among multiple sites. The following three antimonial preparations are currently available:

- (1) Pentostam (sodium stibogluconate) is available from Wellcome, U.K. It contains 100 mg pentavalent antimony/ml.

- (2) Glucantime (meglumine antimoniate) is available from Rhône-Poulenc, Rorer/Specia, France and Rhodia Farma, Brazil: it contains 85 mg pentavalent antimony/ml.
- (3) Sodium antimony gluconate (identical to sodium stibogluconate) is available in India, from Albert David Limited, Delhi, from Stibanate Company Limited, Calcutta and from Anoco Pharmaceuticals, Patna: it contains 100 mg pentavalent antimony/ml.

Side effects to antimony treatment

In clinical practice minor side effects are common, moderate side effects are uncommon and severe side effects very rare. The commonest side effects are pain at the injection site, muscle pain (myalgia), joint pain (arthralgia), loss of appetite and nausea. These symptoms are relatively mild and myalgia and arthralgia may be controlled by paracetamol. QT segment changes may occur on the ECG, and therefore in ideal circumstances ECG monitoring before treatment and weekly during treatment should be performed, but clinically important arrhythmias or heart failure are very unusual. In ideal circumstances weekly monitoring of hepatic and renal function and amylase should be undertaken, though these rarely give rise to symptomatic illness.

There are no absolute contra-indications to pentavalent antimony treatment, and even severely ill patients should respond. Pentavalent antimony is not contra-indicated in pregnancy. If underlying cardiac, renal or hepatic disease is present, the patient should, ideally, be carefully monitored during treatment and other drugs should be considered.

Cost

The cost of treatment is very high: for a 60 kg patient the cost of Pentostam will be approximately \$150; Glucantime would cost about \$120 and sodium antimony gluconate approximately \$16.

Other aspects of treatment

There may be considerable non-drug costs in the treatment of VL: hospital admission, additional food, transport, and loss of income from the carers. In ideal circumstances, all patients should be treated in hospital.

In practice, the economic burden of hospital treatment means that, in countries that have less funds allocated for health care, uncomplicated VL cases may be treated by daily injections at a dispensary or in the home by visiting health workers, and selected cases referred for hospitalization. Criteria for referral to hospital include: severe anaemia (haemoglobin less than 5 grams/100 ml), severe or prolonged diarrhoea, severe wasting,

or non-response to treatment.

Simultaneous infections with malaria, HIV or tuberculosis should be suspected if the clinical response is poor, and patients who have tuberculosis and VL must be referred to hospital for simultaneous treatment. Unresponsive or relapsed cases should always be referred to hospital.

4.3 **How should unresponsive or relapsed cases be treated?**

Patients who are unresponsive to a course of pentavalent antimony or who relapse after treatment should never be retreated without parasitological confirmation of the diagnosis, and response to treatment must be monitored parasitologically. This requires that the patient be referred to a specialist centre.

Patients who have been referred for a relapse or unresponsive VL should always be investigated for concomitant infection with tuberculosis (by sputum smear, and, if available, by chest x-ray), malaria (by microscopy of Giemsa stained blood films), amoebic dysentery or amoebic liver abscess, or HIV. Occasionally, empirical treatment for typhoid fever may also be required.

Notes on second courses of treatment:

- (a) In many cases, the exact dose, duration and quality of pentavalent antimony used for the first course may not be known, particularly if the treatment was done in a remote area. In these circumstances a supervised course of pentavalent antimony, 20 mg/kg daily for 30 days should be given.
- (b) If the patient is clinically unresponsive to a supervised course of pentavalent antimony after two weeks of treatment, or is parasitologically unresponsive at the end of treatment (with bone marrow or other aspirates still positive for parasites after 30 days of treatment) then a second line drug or drug combination should be used (see below).
- (c) *The practice of using intermittent courses of pentavalent antimony with drug-free periods in between is illogical and should be discouraged. It may lead to the emergence of pentavalent antimony-resistant disease.*

Second-line drugs

- (a) Amphotericin B (Fungizone, Squibb). A suitable regimen is 0.5 mg/kg by intravenous infusion daily, or on alternate days, until a total dose of 20 mg/kg

has been given. In some areas a lower total dose has been successful, for example in India a total dose of 7 mg/kg is reportedly successful. The major side effect of amphotericin B is renal impairment, and renal function should be monitored weekly during treatment. Renal impairment can be reduced by pre-hydrating the patient with an infusion of normal saline. If a rise in urea and creatinine occur, the interval between doses should be lengthened. Other side effects include fever and anaemia.

- (b) Aminosidine (paromomycin; Gabromicina, Farmatalia). Aminosidine is an anti-leishmanial aminoglycoside which may be synergistic with pentavalent antimony. A suitable regime is pentavalent antimony 20 mg/kg daily for 30 days plus aminosidine at 15 mg/kg daily for 30 days. The two drugs are given by separate injections in two separate sites. Aminosidine may cause renal impairment and urea or creatinine should ideally be monitored weekly during treatment. It might also affect the auditory nerve and cause high-tone deafness.
- (c) Other drugs which have been used in repeated relapses and unresponsive cases are: Pentamidine isethionate, 4 mg/kg on alternate days for 11 weeks; pentavalent antimony + allopurinol at 20 mg/kg/day in divided doses; liposomal amphotericin B (AmBisome), total dose 20 - 30 mg/kg given over 10 - 20 days; pentavalent antimony + gamma-interferon. Pentamidine may cause hypoglycaemia, diabetes, renal impairment and pancreatitis. AmBisome is effective with very little toxicity but is very expensive. Experience has shown that it can be given in 5 or more doses of 3 - 4 mg/kg over a 10 day period, with excellent results.

4.4 **What supportive measures are required during treatment?**

Patients should receive adequate nutrition. Vitamin supplements and iron may be added.

Treat dysentery with antibiotics and hydration.

Treat pneumonia with antibiotics.

Maintain oral hygiene to prevent mouth infections (cancrum oris) and rapidly treat cancrum oris, should it occur, with metronidazole and penicillin.

Maintain skin hygiene and treat skin sepsis.

Treat malaria and/or tuberculosis if present.

Very occasionally, blood transfusion may be required for severe anaemia or bleeding due to thrombopenia.

Vitamin K may be of benefit in severe epistaxis.

4.5 **How can cure be evaluated?**

At the end of treatment (day 30) clinical assessment should show weight gain, a regressing spleen, and the patient should have been without fever for the last two -three weeks. The haemoglobin and white blood cell count should be rising.

Parasitological confirmation of cure is not routinely necessary and may be reserved for cases where response is in doubt.

Parasitological confirmation of cure is essential, however, in the treatment of relapses.

After treatment the patient should be reviewed at 1, 3, 6 and 12 months. Patients should be told to report if they develop symptoms of VL or a skin rash (PKDL).

Good clinical progress would be: no recurrence of fever; weight continuing to rise; spleen size continuing to regress. In addition, the haemoglobin should be rising.

The leishmanin skin test should become positive in 80 % of patients 12 months after successful treatment.

A persistently enlarged spleen is no cause for concern provided the patient's other symptoms are improving, and residual enlargement of the spleen may persist for months or years after successful treatment.

Lymphadenopathy, which is common in some places, e.g. Sudan, India, may persist for months or years after successful treatment.

Relapse

After a complete course of effective treatment in immunocompetent patients less than 5 % of patients will relapse.

Clinical features of relapse are a fever, weight loss, and an enlarging spleen size.

Relapse of VL is most likely to occur within the first 3 months after treatment, and is most unlikely after 12 months.

4.6 **How is post-kala azar dermal leishmaniasis (PKDL) treated?**

PKDL is treated with pentavalent antimony, in the same dose and by the same routes as VL. A dose of 20 mg pentavalent antimony/kg/day for 4 months or longer is used in Indian PKDL. In African (Ethiopia, Kenya and Sudan) PKDL 2 to 3 months of treatment may suffice. Once lesions improve clinically treatment may be stopped, as PKDL very rarely relapses.

4.7 **What minimum or special equipment and services are required for treatment?**

Adequate supplies of pentavalent antimony, sterile syringes and sterile needles are required for treatment of uncomplicated VL at a dispensary or in the home by a visiting health worker.

Hospital services with access to parasitological and serological diagnosis (and if possible leishmanin skin test) are required for treatment of unresponsive or relapsed cases (see section 3 and relevant appendices). Additional hospital services are required to support patients with HIV co-infection or other co-infections (see 4.3 above).