Visceral Leishmaniasis

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Abstract

Pentavalent antimonials (Sb^V) have been the sheet anchor of therapy for leishmaniasis for >75 years. In the early 1980s, it was realized that a significant subset of patients with visceral leishmaniasis were not responding to Sb^V in the state of Bihar, India. Revised recommendation using ten times more drug provided a transient reprieve; however, a large proportion of patients in India and to some extent in Nepal remained unresponsive to Sb^V. Diverse studies have suggested emergence of Sb^V refractory strains in India. Attempts to find a marker of unresponsiveness have failed so far. Alternative therapeutic options include conventional amphotericin-B or its lipid formulations, oral miltefosine, and paromomycin and short course multidrug therapy. In the Indian subcontinent, the only recommended monotherapy is a single dose of liposomal amphotericin-B (L-AMB, dose 10 mg/kg) which is efficacious, safe, and ensures complete compliance. Multidrug therapy has high efficacy, short course, less toxicity, and prevents development of resistance. If these scarce antileishmanial drugs are to be protected from going down the lane of Sb^V, multidrug, short course, affordable treatment of VL should be evolved with access to all.

7.1 Introduction

Visceral leishmaniasis (VL) (Fig. 7.1), also known as "Kala-azar," is typically caused by parasites belonging to the *L. (L.) donovani* complex, which includes two species: *Leishmania (L.) donovani*, the causative organism of VL in the Indian subcontinent (ISC) and Africa, and *Leishmania (L.) infantum* [(*L. (L.) chagasi*)], which causes VL in the Mediterranean basin and Central and South

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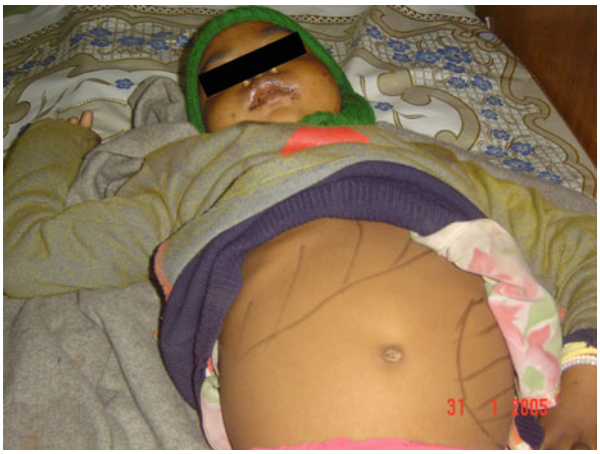

Fig. 7.1 A child with visceral leishmaniasis with hepatosplenomegaly

America. Approximately 0.2–0.4 million VL cases and 0.7–1.2 million CL cases occur each year. In 2015 more than 90% of global VL cases occurred in seven countries: India, Bangladesh, Sudan, South Sudan, Kenya, Brazil, and Ethiopia [1].

The number of VL cases is highest in the ISC. The World Health Organization (WHO) has targeted VL for elimination from this region as a public health problem by 2020. A memorandum of understanding was signed by India, Bangladesh, Nepal, and later Bhutan and Thailand to eliminate Kala-azar from this region. Elimination has been defined as bringing the annual incidence of Kala-azar to less than one case per 10,000 population at block PHC (Primary Health Centre) level in India and Bangladesh and district level in Nepal and Bhutan. Currently, Nepal has eliminated the disease at district level and sustained the situation for the past 2 years. Bangladesh has achieved the elimination target in 90% of endemic upazilas. India has achieved the target in more than two thirds of endemic blocks [2].

VL is the systemic and most severe form of leishmaniasis, characterized by prolonged fever, splenomegaly, lymphadenopathy, hepatomegaly, pancytopenia, progressive anemia, and weight loss. If untreated, VL is uniformly fatal. Some patients with VL may develop a chronic form of dermal leishmaniasis characterized by indurated nodules or depigmented macules, which is called post-Kala-azar dermal leishmaniasis (PKDL). PKDL is quite common (occurring in >50% patients with VL) in Sudan, where it may occur concurrently with VL and heals spontaneously in most patients [3]. In the ISC, it affects only a small proportion of patients, 6 months to several years after an episode of VL, and treatment is necessary [4]. Patients with PKDL serve as an important reservoir of infection.

Natural transmission of leishmaniasis is carried out by female sand flies. In South Asia and the Horn of Africa, the predominant mode of transmission is anthroponotic and patients with Kala-azar or post-Kala-azar dermal leishmaniasis (Fig. 7.2) and those with asymptomatic infection may be the reservoirs for driving transmission [5–8]. In the Mediterranean, the Middle East, and Brazil, the disease is zoonotic, with the domestic dog as the most important reservoir host sustaining transmission [6].

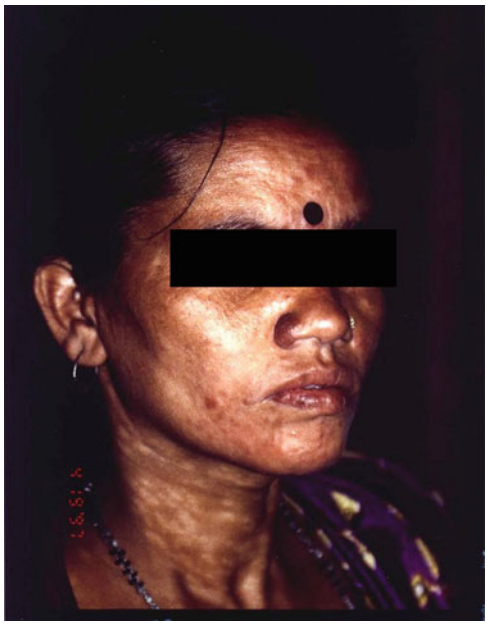

Fig. 7.2 A patient with post-Kala-azar dermal leishmaniasis with multiple nodules on the face

7.2 Visceral Leishmaniasis: The Challenges

7.2.1 Increase in the Risk Factors for Leishmaniasis

Environmental changes like deforestation, urbanization, and migration of nonimmune people to endemic areas have led to the increase in the incidence of leishmaniasis. Migration from nonendemic to endemic areas is a major risk factor for the spread of VL as these people, on their return, can spread the disease in a nonimmune population. This issue is exemplified by the severe epidemic in Southern Sudan which led to the death of 100,000 patients [9]. In the ISC, VL is associated with low socioeconomic status. Even when free drugs are available, patients cannot afford the costs of transportation to the hospital and of hospitalization. Thus, untreated VL and PKDL cases harbor the parasite and disseminate it [10].

The HIV/AIDS pandemic has modified the natural history of leishmaniasis [11] (see Chap. 6). Both diseases exert a synergistic detrimental effect on the cellular immune response because they target similar immune cells [12, 13].

HIV infection increases the risk of developing VL in areas of endemicity, reduces the likelihood of a therapeutic response, and greatly increases the probability of relapse [14–17]. At the same time, VL promotes the clinical progression of HIV disease and the development of AIDS-defining conditions. These factors make HIV/VL co-infected patients a potential source for spreading drug-resistant parasites [11, 18]. Furthermore, transmission of the infection via needle sharing in HIV/VL co-infected patients in southern Europe threatens to convert an apparently zoonotic

disease into the anthroponotic form [11, 19, 20]. HIV-VL co-infection has been reported from more than 35 countries. Initially, most of these cases were from southwestern Europe, but the number of cases is increasing in sub-Saharan Africa especially Ethiopia, Brazil, and South Asia [19, 21, 22]. In the hyperendemic region of Bihar, India, 1.8–4.5% of VL patients were HIV-positive [23, 24]. There was an increase in the incidence of VL/HIV co-infection from 0.32/100,000 in 2007 to 1.08/100,000 in 2010 in northern Brazil [25]. In Ethiopia HIV co-infection ranged from 10.4% to 40% among VL patients from different centers [26, 27].

Most people with leishmanial infection do not develop into clinical disease. These asymptomatic infections are defined differently in studies as either a positive serological test, polymerase chain reaction (PCR), or leishmanin skin test (LST) in individuals who are otherwise in a healthy condition. In prospective studies, the ratio of incident infection to clinical disease varies from 1:2.4 in Sudan [28], 4.1–5.6:1 in Kenya [29] and Ethiopia [30], 4.1–8.9:1 in the ISC [31–33], 18:1 in Brazil [34], to 50:1 in Spain [35]. A mathematical modeling study based on data from the ISC has shown that transmission of *L. (L.) donovani* is predominantly driven by asymptomatically infected hosts [36]. A detailed description can be found in Chap. 4. Thus, in the era of elimination of VL in the Indian subcontinent, the current challenge is to find out which subset of asymptomatics have the highest risk of developing into clinical VL and sustaining transmission.

7.2.2 Challenges in the Diagnosis of VL

The diagnosis of VL is complicated by the fact that its clinical features are shared by a number of commonly occurring diseases like malaria, typhoid fever, tuberculosis, etc. The sequestration of parasites in the spleen, bone marrow, or lymph nodes is a challenge, and demonstration of parasites necessitates embarking upon invasive procedures which are difficult to perform in the prevailing field conditions (Fig. 7.3). Additional details on challenges in VL diagnosis can be found in Chap. 4.

Molecular techniques such as PCR can be used for the diagnosis of VL, but these techniques remain restricted to referral hospitals and research centers, despite efforts to simplify them.

Antigen-based tests like the latex agglutination test detecting a heat-stable, low-molecular-weight carbohydrate antigen in the urine of VL patients have demonstrated a good specificity but only low to moderate (48–87%) sensitivity in East Africa and the ISC [37–40].

Antibody-based tests, though widely used, have drawbacks. Antibodies remain detectable up to several years after cure; therefore, VL relapse cannot be diagnosed by serology [41, 42]. In endemic areas, a significant proportion of healthy individuals with no history of VL are positive for antileishmanial antibodies owing to a group of patients with asymptomatic infections. The seroprevalence in healthy populations varies from $<10\%$ in low to moderate endemic areas [29, 43, 44] to $>30\%$ in high-transmission foci or areas where household contacts are common

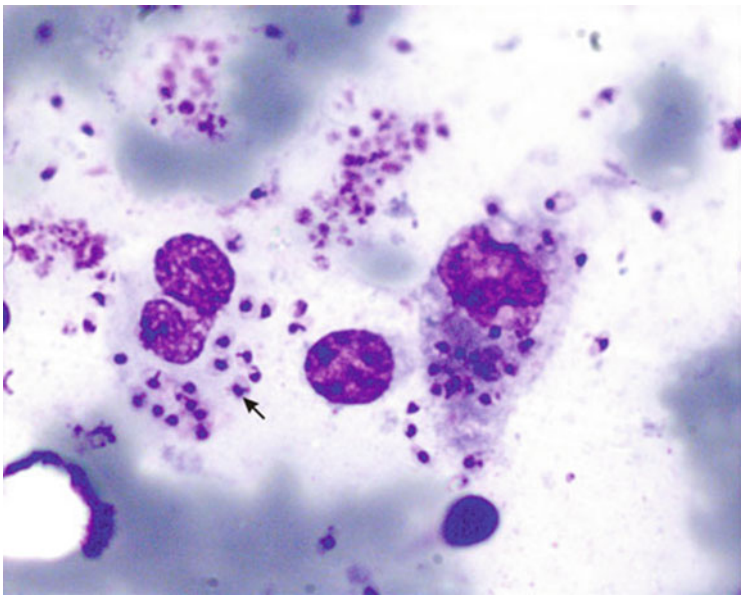

Fig. 7.3 Microphotograph showing two infected macrophages with multiple amastigotes

[45–47]. Another drawback is that over 40% of HIV co-infected individuals have no detectable specific antibody levels against *Leishmania* [11].

The direct agglutination test (DAT) and the rK39-based immunochromatographic test (ICT) are the two serological tests which have been extensively validated in the field. In a meta-analysis performed by [39], DAT had a demonstrated sensitivity of 94.8% (95% confidence intervals (CI), 92.7–96.4) and specificity of 97.1% (95% CI, 93.9–98.7), respectively. The performance of DAT was not influenced by region or by species of *Leishmania*. Its main drawbacks are cumbersome procedure, the regular quality control of antigen, the need for the storage of the antigen at 2–8 °C once it has been dissolved, and the prolonged incubation time needed for performing the assay. rK39 is a 39-amino acid repeat that is part of a kinesin-related protein in *L. (L.) chagasi* and is conserved within the *L. (L.). donovani* complex [48]. Immunochromatographic strip tests (ICTs) based on rK39 are easy to perform, rapid, and cheap and yield reproducible results. A meta-analysis that included 13 validation studies of the rK39 immunochromatographic test (ICT) showed sensitivity and specificity estimates of 93.9% (95% CI, 87.7–97.1) and 95.3% (95% CI, 88.8–98.1), respectively [39]. However, this test shows regional variation and has been shown to be less accurate in East Africa [49–51]. Another format of rK39 ICT has been reported with higher sensitivity and specificity in Africa [52]. There is an urgent need to develop a sensitive, easy-to-use, noninvasive antigen-detection test for the diagnosis of primary VL (particularly in HIV co-infected patients), which would also diagnose relapses.

7.2.3 Challenges in VL Treatment

Over the years there have been many challenges in the treatment of VL. The number of antileishmanials is small. All of them except miltefosine (MIL) have to be administered parenterally. The duration of treatment is long, drugs are toxic, and hospitalization is required for monitoring. As new therapies have been developed for VL, e.g., L-AMB, oral MIL, and paromomycin, the standard pentavalent antimonials (Sb^V) have been rendered obsolete in some regions.

7.2.3.1 Antimonials

First indications of drug resistance came from unconfirmed reports from the four most affected districts in North Bihar of about 30% patients not responding to the prevailing regimen of Sb^V [53]. An expert committee of the Government of Bihar recommended that Sb^V should be used in two 10-day courses with a 10-day interval [54]. Aikat et al. [55] followed these recommendations and described only 1% patients' refractory to Sb^V therapy. However, only a few years later, Thakur et al. [56] randomized patients to receive Sb^V 20 mg/kg (maximum 600 mg) either for 20 days or longer in case of partial or delayed response and demonstrated that 86% of patients were cured in the former group.

Surprisingly, the cure rate with 10 mg/kg for 20 days was much lower compared with earlier results. In the same year, the WHO [57] expert committee recommended Sb^V to be used in doses of 20 mg/kg up to a maximum of 850 mg for 20 days and a repetition of the same regimen for 20 days in cases of treatment failures. Four years later, [58] again reviewed the WHO recommendations and published a report of a clinical trial in which Sb^V at 20 mg/kg (max. 850 mg) for 40 days cured 97% of patients, while 20-day treatment at the same doses cured only 81% of patients. Three years later, the same group reported a further decline in cure rate to 71% after 20 days of treatment at the same doses [59]. Furthermore, by the early 1990s, extending the therapy to 30 days could cure only 64% of patients in a hyperendemic district of Bihar [60]. Five years later, in a bigger study, 156 patients were randomized in three groups for treatment either with (a) Sb^V alone for 30 days or (b) Sb^V plus interferon-γ (IFN-γ) for 15 days or (c) Sb^V plus IFN-γ 30 for days. Only 36% of patients were cured with Sb^V alone, and addition of IFN-γ improved the cure rate to 42% and 49% in groups b and c, respectively [61].

Between 1994 and 1997, a study was conducted to document the level of Sb^V resistance in the hyperendemic region of Bihar and to determine whether therapeutic failure had spread to the neighboring state of Uttar Pradesh (UP). At Bihar and UP sites, 209 and 111 patients were treated, respectively. The results demonstrated that only 35% of patients could be cured at Bihar, and of these, primary unresponsiveness was seen in 52% patients, whereas another 8% relapsed after an initial cure. In UP, on the other hand, 98% were cured initially and one (1%) relapsed.

Thus, it was apparent from the study that Sb^V continued to be effective in the state of UP, but in North Bihar, where most of the disease occurred, it was ineffective in most patients [62]. There were reports of antimony resistance spreading to the Terai regions of Nepal, especially from the district adjoining the hyperendemic areas of

Bihar, where up to 30% of the patients were unresponsive, though in eastern Nepal a 90% cure rate had been reported [63]. These studies confirmed that a high level of antimony resistance existed in Bihar, whereas it was still effective in surrounding areas.

There had been speculations whether Indian *L. (L.) donovani* had become truly refractory to Sb^V or resistance occurred because of the inadequate doses being used in Bihar. In a study to determine whether acquired drug resistance was present in Bihar, *L. (L.) donovani* isolates were taken from responders and nonresponders. In vitro amastigote-macrophage assay showed that isolates from patients who did respond to sodium stibogluconate treatment were threefold more sensitive, with 50% effective doses (ED_{50}) ~2.5 mg Sb^V/mL compared to isolates from patients who did not respond (ED_{50} ~7.5 mg Sb^V/mL) [64]. The significant differences in amastigote sensitivity supported the concept of acquired resistance in Bihar.

The reasons behind the appearance of resistance were that (a) Sb^V was freely available and (b) both qualified medical practitioners and unqualified quacks prescribed the drug. This unrestricted availability of the drug led to widespread misuse. Most patients (73%) consulted unqualified practitioners first [65]. It was a common practice to start with a small dose and gradually build up to the full dose over a week; it was also advocated to have drug-free periods to minimize the toxicity, especially renal toxicity. It was common for physicians to split the daily dose in two injections to be given twice a day. These practices resulted in the buildup of a subtherapeutic blood level and increased tolerance of parasites to Sb^V. In a study to detect the factors leading to antimony resistance in Indian VL, it was observed that only 26% of the patients were treated according to the WHO guidelines, 42% did not take the drug regularly, and 36% stopped the drug on their own initiative. Almost half of the patients, receiving pentamidine as a second-line drug, had not received adequate antimony treatment before being labeled as refractory to Sb^V. These facts indicate large-scale misuse of antileishmanial drugs in Bihar, contributing to development of drug resistance [65]. Moreover, there were several manufacturers of Sb^V in India, and not all produced consistent quality products, resulting in occasional batches being substandard and toxic, adding to the problems associated with Sb^V therapy and serious toxicity and deaths related to the drug [66].

Another reason for the increasing frequency of *Leishmania* resistant to Sb^V in India while parasites still remained sensitive in the rest of the world could be that transmission in Bihar is anthroponotic. In this type of life cycle, once Sb^V resistance gets established, it spreads exponentially through the population and organisms, is sensitive to the drug, and gets eliminated quickly, whereas drug-resistant parasites continue to circulate in the community.

7.2.3.2 Other Antileishmanial Drugs

Pentamidine was the first drug to be used in patients, refractory to Sb^V, and, initially, high cure rates were reported [67]. But its efficacy declined over the years, and a decade later, it cured only approximately 70% of patients [59, 68, 69]. Its use in VL was ultimately abandoned due to its decreased efficacy and serious toxicities.

AMB-B is a polyene antibiotic used predominantly as an antifungal drug, but it also has excellent antileishmanial activity. Due to the high affinity of AMB-B for 24-substituted sterols, aqueous pores are formed in the plasma membrane leading to increased membrane permeability and killing of *Leishmania*. In Sb^V refractory regions in India, it has been used extensively with excellent results [70, 71]. AMB-B has excellent cure rates (~100%) at a dose of 0.75–1 mg/kg for 15–20 daily or alternate days intravenous infusions; however, most of the patients experience infusion reactions (e.g., fever, chills, and thrombophlebitis) and, occasionally, serious toxic episodes (e.g., hypokalemia, nephrotoxicity, myocarditis, and even death). It was recommended as a first-line drug by the Indian National Expert Committee for Sb^V refractory regions [72] (NVBDCP). The need for infusions, hospitalization for prolonged periods, high cost of the drug, requirement for close monitoring, and high incidence of adverse events (occasionally serious) constitute important drawbacks that prevented its implementation at the primary health-care level in Bihar. Clinical resistance to AMB-B is rare.

Lipid-associated amphotericin-B (L-AMB) preparations are as effective as conventional AMB-B and have negligible adverse reactions. The dose requirement of L-AMB varies in different geographical regions; while for patients in the ISC a small dose induces high cure rates, a higher dose is needed for patients from the Mediterranean region and Brazil [73–75]. It is possible to administer high doses of L-AMB over a short period with high cure rates [76]. Although its high price precluded its use in the developing countries, it was the drug of choice for VL in Mediterranean. However, a preferential pricing agreement with WHO (agreement between Gilead and WHO of 14 March 2007) reduced the price of L-AMB (AmBisome®) for endemic regions to $20 (now $18) per 50-mg vial [77]. The preferential pricing made L-AMB a feasible option for the treatment of VL in the endemic region.

MIL, an alkyl phospholipid, is the first oral agent approved for the treatment of leishmaniasis. At the recommended doses (100 mg daily for patients weighing 25 kg and 50 mg daily for those weighing <25 kg for 4 weeks), cure rates were 94% for VL [78]. Its limitations are high cost, need for monitoring for gastrointestinal side effects, and occasional hepatic toxicity and nephrotoxicity. As it is teratogenic, women of child-bearing potential have to observe contraception measures for the duration of treatment and an additional 3 months. Furthermore, it has a long-terminal half-life, which ranges between 150 and 200 h. About four half-lives are required to reach more than 90% clearance of the plateau levels (at steady state). Thus, subtherapeutic levels may remain for several weeks after a standard course of treatment. This fact may lead to the quick emergence of resistance. Free availability and quick recovery (within 10 days, most patients feel better) coupled with the high cost of the drug may motivate patients to prematurely discontinue treatment, and suboptimal compliance will ultimately lead to the emergence of parasite resistance [79]. Due to its oral advantage, this drug was chosen for the elimination program in India, Nepal, and Bangladesh [77, 80]. However, after a decade of use of the drug in the ISC, the relapse rate doubled and its efficacy appeared to have declined [81]. Another recent study from India revealed a cure rate of only 92.6% at 12 months [82]. While in Nepal the results were worse, with relapse rate of 10.8% at 6 and of 20.0% at

12 months [83]. In Bangladesh, a phase IV study showed a cure rate of only 85% [84]. Its efficacy was low in a study from Ethiopia where the final cure among non-HIV-infected patients 6 months after treatment in the MIL group was only 75.6% [85]. The dwindling efficacy of MIL monotherapy in the ISC is a matter of great concern, and it has been replaced with other therapies for the elimination initiative. A complementary explanation of this situation is given in Chap. 4.

Paromomycin, an aminoglycoside-aminocyclitol antibiotic, has been used for the treatment of VL in a parenteral formulation and CL in both topical and parenteral formulations. In a phase III trial in the ISC, paromomycin was shown to be non-inferior to AMB-B and was approved by the Indian government in August 2006 for the treatment of patients with VL [86]. Clinical resistance with this drug in VL has not been reported.

However, following a 60-day parenteral course for treatment of CL in two *L. (L.) aethiopica* cases, isolates taken from relapsed patients were three- to fivefold less susceptible to the drug—after treatment—than isolates taken before treatment in an amastigote-macrophage assay [87]. The advantages of this agent include its cost, approximately US $10 per patient [88]. The disadvantages are the need for intramuscular injection, monitoring of serum transaminases, and the existence of inadequate data regarding its use in pregnancy.

7.3 Control of Visceral Leishmaniasis

7.3.1 Free Distribution of Drugs

The high cost of the antileishmanial drugs coupled with their easy, over-the-counter availability often leads to underdosing and incomplete treatment. This has been the major factor for antimony resistance, and this reason could lead to resistance to another drug like MIL too. Considering that majority of the population cannot afford to purchase and complete a full course of treatment, it is recommended that antileishmanials should be made available free of cost to be distributed through public and/or private health-care providers like antitubercular and antiretroviral drugs, and antileishmanial drugs should be withdrawn from the open market.

7.3.2 Monitoring Therapy

The appearance of Sb^V resistance in the anthroponotic cycle in Bihar suggests that resistance could also expand to other antileishmanial drugs as well. A similar potential for resistance to originate exists in East Africa, another anthroponotic focus of VL with intense transmission, where poverty, illiteracy, and poor health-care facilities are common.

A recent study demonstrated that even in 2008, critical flaws remained in VL case management in the primary health-care services in Bihar, like obsolete use of antimonials with high failure rates and long patient delay. After reviewing the

visceral leishmaniasis 191 records of all 150 patients sampled and interviewing 139 patients or their guardian, it was concluded that 81% of patients had first presented themselves to unqualified practitioners, the median delay before reaching the appropriate primary health-care facility was 40 days (IQR 31–59 days), and 48% of VL patients were still being treated with Sb^V out of which 40% needed a second treatment course [89]. Similar concerns were raised for MIL when in a phase IV trial in India, involving domiciliary treatment with MIL and weekly supervision, showed doubling of the relapse rates in one of the clinical centers [79]. These findings suggest that monitoring therapy is imperative to prevent emergence of resistance. The directly observed treatment strategy (DOTS) for tuberculosis has been a big success, and either a parallel or integrated with DOTS system could be organized for leishmaniasis. This will lead to better compliance, completion of the treatment course, and ultimately, prevent resistance.

7.3.3 Combination Therapy

The growing resistance of the parasite to antileishmanial drugs suggests that the currently used monotherapy needs to be reviewed. Multidrug combination therapy has been used successfully in tuberculosis, leprosy, and malaria. The rationale behind combination therapy is increased activity through use of compounds with synergistic or additive activity, preventing the emergence of drug resistance; lower dose requirement, thereby reducing chances of toxic side effects and cost; and increased spectrum of activity.

A randomized, noncomparative, group sequential, triangular design study assigned 181 subjects to treatment with 5 mg/kg of L-AMB alone (group A; 45 subjects), 5 mg/kg of L-AMB followed by MIL for 10 days (group B; 46 subjects) or 14 days (group C; 45 subjects), or 3.75 mg/kg of L-AMB followed by MIL for 14 days (group D; 45 subjects). When it became apparent that all regimens were effective, 45 additional, nonrandomized patients were assigned to receive 5 mg/kg of L-AMB followed by MIL for 7 days (group E). All 226 subjects had initial apparent cure responses. Nine months after treatment, final cure rates were high (>95%) and similar in all multidrug groups. These results suggest that single infusion of L-AMB (in most instances, administered in an outpatient setting) followed by a brief self-administered course of MIL could be an excellent option against Indian Kala-azar [90]. The preferential pricing opened the prospect of combining lower total doses of L-AMB in other combination regimens [77]. In another study in the ISC, three-drug combinations (single injection of 5 mg/kg L-AMB and 7-day oral MIL or 10-day 11 mg/kg intramuscular paromomycin or 10 days each of MIL and paromomycin) were used. All the combinations showed an excellent cure rate and were non-inferior to the standard treatment [91].

Combination therapy provides shorter duration treatment with much improved compliance that will prevent the emergence of resistance. Since the pipeline for the antileishmanial drugs is nearly empty, it is imperative to protect and prolong the effective life of the existing drugs. In the recent guidelines published by the WHO,

this combination therapy has been made one of the preferred treatment for VL in the ISC [92].

7.3.4 Novel Therapy

Liposomal AMB is one of the safest and most efficacious among antileishmanials. With the decrease in the price of L-AMB (AmBisome®) for endemic regions [77], an open-label study in India comparing the efficacy of single-dose L-AMB at a dose of 10 mg per kilogram of body weight to conventional AMB, at 1 mg per kilogram, given every other day for 15 doses was conducted. Cure rates at 6 months were similar in the two groups: 95.7% (95% CI, 93.4–97.9) in the liposomal-therapy group and 96.3% (95% CI, 92.6–99.9) in the conventional-therapy group [93]. The low-dose requirement, preferential pricing, excellent efficacy, a single-day hospitalization, no safety concerns, and monitoring requirement make a single infusion of the liposomal preparation an excellent option for the ISC. All these factors led WHO to recommend this treatment as one of the best option for this region [92]. The single dose ensures 100% compliance and therefore decreases the chances of resistance. To test the feasibility in primary health centers, a study was done in Bangladesh where the cure rate at 6 months was 97% [94].

Encouraged by the success of the single-dose L-AMB therapy in the ISC, a randomized controlled trial was done to compare the efficacy and safety of single dose of L-AMB 7.5–10 mg/kg body weight or multiple doses, 7 times 3 mg/kg on days 1–5, 14, and 21 in East Africa. However, the trial was terminated after the third interim analysis because of low efficacy of all the regimens [95].

7.3.5 Monitoring Drug Resistance

Ideally, parasite resistance should be monitored, rather than relapses or unresponsiveness.

It will also permit the identification of key intracellular targets and parasite defense mechanisms, which can then be exploited to rationally develop analogues of existing drugs that would not be affected by the most common defenses. Analysis of genetic markers that determine high antileishmanial resistance, performed systematically for every parasite isolate that shows low antileishmanial sensitivity, would facilitate the tracking of the level of resistance in affected populations. At present, there are no molecular markers of resistance available for the currently used antileishmanial drugs, and the only reliable method for monitoring resistance of isolates is the technically demanding in vitro amastigote-macrophage model. Development of drug resistance markers and tools easy to use in the field should be encouraged. See Chaps. 4 and 15 for a detailed discussion of this topic.

7.3.6 Management of PKDL

Patients with PKDL serve as an important reservoir of infection, and in ISC, treatment is essential. In India, AMB-B 60–80 doses over 4 months or MIL for 12 weeks are the recommended regimens. However, the inordinately long regimens especially for patients without any physical handicap lead to frequent noncompliance. Better and shorter and acceptable options need to be developed [96].

7.3.7 Management of HIV/VL Co-infection

Another potential source for the emergence of drug resistance is the HIV/VL co-infected patients. These patients have high parasite burden and a weak immune response, respond poorly to treatment, and have a high relapse rate. Therefore, they are the ideal candidates to harbor drug-resistant parasites. All antileishmanial therapies are less effective in HIV-positive patients. There is a high mortality rate due to concurrent illness, complications, and drug toxicity. Pentavalent antimonials (Sb^V) and AMB-B are more toxic to HIV patients, who require close monitoring for pancreatitis, cardiotoxicity, and nephrotoxicity [22]. In Ethiopia, MIL was found to be less effective than Sb^V in co-infected patients, and side effects were worse in these patients [52]. The best option for these patients is L-AMB. Secondary prophylaxis to prevent relapses has been reported in several publications, but more evidence from clinical trials is needed to establish a beneficial effect [22]. Initiation of HAART (highly active antiretroviral therapy) dramatically decreases the incidence of VL co-infection. Therefore, HAART in combination with antileishmanials should be advocated strictly in these patients. A detailed description of this topic can be found in Chap. 6.

7.4 Vector Control

Vector control is an important strategy for decreasing the spread of VL. Residual insecticide spraying of houses and animal shelters was shown to be efficacious in India [97], where the vector (*Phlebotomus argentipes*) is restricted to areas in and around the home. However, in Sudan and other endemic countries in East Africa, transmission occurs mainly outside villages [98]. Therefore, indoor residual spraying for disease control is unlikely to be as efficient in this region. Case-control studies conducted in Bangladesh and Nepal demonstrated that sleeping under a nonimpregnated bed net during the warm months was a protective factor against VL [99, 100]. The mass distribution of insecticide-treated nets (ITNs) in Sudan was accompanied by a 27% reduction in the incidence of VL in an observational study [101]. A recent study showed that VL was associated with housing conditions like living in a thatched house or in a house with damp floors, which suggests that improving living conditions could decrease the incidence of VL [102].

7.5 Conclusion

Inventory of antileishmanial agents is very small; emergence of drug resistance and decreased efficacy of some drugs is further complicating the control of leishmaniasis. A better understanding of the mechanisms of action of the drugs and unraveling the puzzle of drug resistance mechanisms with easy-to-use markers of resistance may pave the way for more rational use of drugs. Directly observed therapy given free, in treatment centers manned by trained personnel, will go a long way in controlling the disease as well as drug resistance.

Combination chemotherapy is rapidly emerging as the norm for treating several infective disorders like malaria, tuberculosis, HIV, etc., and its application is strongly advocated for VL. Novel therapy like single-dose L-AmB which ensures complete compliance has revolutionized the treatment of VL in the ISC. Strict monitoring of these novel drug therapies is required to ensure their efficacy at field level.

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