and in Mediterranean/American regions, ≥20 mg/kg. The daily dose is flexible (1–10 mg/kg). In a study in India, a single dose of 10 mg/kg cured infection in 96% of patients. Adverse effects of liposomal AmB are usually mild and include infusion reactions, backache, and occasional reversible nephrotoxicity.

PAROMOMYCIN

Paromomycin (aminosidine) is an aminocyclitol-aminoglycoside antibiotic with antileishmanial activity. Its mechanism of action against *Leishmania* has yet to be established. Paromomycin is approved in India for the treatment of VL at an IM dose of 11 mg of base/kg daily for 21 days; this regimen produces a cure rate of 95%. However, the optimal dose has not been established in other endemic regions. Paromomycin is a relatively safe drug, but some patients develop hepatotoxicity, reversible ototoxicity, and (in rare instances) nephrotoxicity and tetany.

MILTEFOSINE

Miltefosine, an alkylphosphocholine, is the first oral compound approved for the treatment of leishmaniasis. This drug has a long half-life (150–200 h); its mechanism of action is not clearly understood. The recommended therapeutic regimens for patients on the Indian subcontinent are a daily dose of 50 mg for 28 days for patients weighing <25 kg, a twice-daily dose of 50 mg for 28 days for patients weighing ≥25 kg, and 2.5 mg/kg for 28 days for children 2–11 years of age. These regimens have resulted in a cure rate of 94% in India. However, recent studies from the Indian subcontinent indicate a decline in the cure rate. Doses in other regions remain to be established. Because of its long half-life, miltefosine is prone to induce resistance in *Leishmania*. Its adverse effects include mild to moderate vomiting and diarrhea in 40% and 20% of patients, respectively; these reactions usually clear spontaneously after a few days. Rare cases of severe allergic dermatitis, hepatotoxicity, and nephrotoxicity have been reported. Because miltefosine is expensive and is associated with significant adverse events, it is best administered as directly observed therapy to ensure completion of treatment and to minimize the risk of resistance induction. Because miltefosine is teratogenic in rats, its use is contraindicated during pregnancy and (unless contraceptive measures are strictly adhered to for at least 3 months after treatment) in women of childbearing age.

MULTIDRUG THERAPY

Multidrug therapy for leishmaniasis is likely to be preferred in the future. Its potential advantages in VL include (1) better compliance and lower costs associated with shorter treatment courses and decreased hospitalization, (2) less toxicity due to lower drug doses and/or shorter duration of treatment, and (3) a reduced likelihood that resistance to either agent will develop. In a study from India, one dose of liposomal AmB (5 mg/kg) followed by miltefosine for 7 days, paromomycin for 10 days, or both miltefosine and paromomycin simultaneously for 10 days (in their usual daily doses) produced a cure rate of >97% (all three combinations). In Africa, a combination of Sb^V and paromomycin given for 17 days was as effective and safe as Sb^V given for 30 days.

PROGNOSIS OF TREATED VL PATIENTS

Recovery from VL is quick. Within a week after the start of treatment, defervescence, regression of splenomegaly, weight gain, and recovery of hematologic parameters are evident. With effective treatment, no parasites are recovered from tissue aspirates at the posttreatment evaluation. Continued clinical improvement over 6–12 months is suggestive of cure. A small percentage of patients (with the exact figure depending on the regimen used) relapse but respond well to treatment with AmB deoxycholate or lipid formulations.

VL IN THE IMMUNOCOMPROMISED HOST

HIV/VL co-infection has been reported from 35 countries. Where both infections are endemic, VL behaves as an opportunistic infection in HIV-1-infected patients. HIV infection can increase the risk of developing VL by severalfold in endemic areas. Co-infected patients usually show the classic signs of VL, but they may present with atypical features due to loss of immunity and involvement of unusual anatomic locations, with, for example, infiltration of the skin, oral mucosa, gastrointestinal tract, lungs, and other organs. Serodiagnostic tests are commonly negative. Parasites can be recovered from unusual sites such as bronchoalveolar lavage fluid and buffy coat. Liposomal AmB is the drug of choice for HIV/VL co-infection—both for primary treatment and for treatment of relapses. A total dose of 40 mg/kg, administered as 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38, is considered optimal and is approved by the FDA, but most patients experience a relapse within 1 year. Pentavalent antimonials and AmB deoxycholate can also be used where liposomal AmB is not accessible. Reconstitution of patients' immunity by antiretroviral therapy has led to a dramatic decline in the incidence of co-infection in the Mediterranean basin. In contrast, HIV/VL co-infection is on the rise in African and Asian countries. Ethiopia is worst affected: up to 30% of VL patients are also infected with HIV. Because restoration of the CD4+ T cell count to >200/μL does decrease the frequency of relapse, antiretroviral therapy (in addition to antileishmanial therapy) is a cornerstone for the management of HIV/VL co-infection. Secondary prophylaxis with liposomal AmB has been shown to delay relapses, but no regimen has been established as optimal.

POST–KALA-AZAR DERMAL LEISHMANIASIS

On the Indian subcontinent and in Sudan and other East African countries, 2–50% of patients develop skin lesions concurrent with or after the cure of VL. Most common are hypopigmented macules, papules, and/or nodules or diffuse infiltration of the skin and sometimes of the oral mucosa. The African and Indian diseases differ in several respects; important features of post–kala-azar dermal leishmaniasis (PKDL) in these two regions are listed in Table 251-2, and disease in an Indian patient is depicted in Fig. 251-4.

In PKDL, parasites are scanty in hypopigmented macules but may be seen and cultured more easily from nodular lesions. Cellular infiltrates are heavier in nodules than in macules. Lymphocytes are the dominant cells; next most common are histiocytes and plasma

TABLE 251-2 CLINICAL, EPIDEMIOLOGIC, AND THERAPEUTIC FEATURES OF POST–KALA-AZAR DERMAL LEISHMANIASIS: EAST AFRICA AND THE INDIAN SUBCONTINENT

Feature	East Africa	Indian Subcontinent
Most affected country	Sudan and South Sudan	Bangladesh
Incidence among patients with VL	~50%	~2–17%
Interval between VL and PKDL	During VL to 6 months	6 months to 3 years
Age distribution	Mainly children	Any age
History of prior VL	Yes	Not necessarily
Rashes of PKDL in presence of active VL	Yes	No
Treatment with sodium stibogluconate	2–3 months	2–4 months
Natural course	Spontaneous cure in majority of patients	Spontaneous cure in minority of patients

Abbreviations: PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.