

# Elimination of Accelerating Kala-Azar with Early Diagnosis and Effective Management

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## Abstract

For the past few decades, Kala Azar has been a serious clinical and community medical issue in India. As HIV infection rates rise, kala-azar cases are expected to rise and take on more unusual forms. Many States, including Bihar, are severely impacted. There are currently a number of immunological assays that may be used for diagnosis that are both more accurate and precise compared to the aldehyde test. Drug resistance is a problem in the medical management of kala azar, as it is in many other illnesses nowadays. New medications and delivery methods are on the market. According to recent findings, Kala azar often appears in HIV-positive individuals prior to the onset of AIDS. The leishmanial genus apart from *L. donovani* could be among the infecting organisms due to the unusual appearance. The optimal method for illness control is maintained by combining medication tolerance avoidance, patient diagnosis and medication, and sandfly management.

**Key Words:** Kala azar, Leishmaniasis, HIV, diagnosis, Treatment.

## Introduction:

"kala-azar" arises from India which means "black fever," denoting the darkening of the skin that occurs as the illness worsens. There is significant clinical and epidemiological variability within the large spectrum of leishmaniasis disorders.

Human leishmaniasis can manifest in mainly 3 forms: cutaneous Leishmaniasis, mucocutaneous Leishmaniasis, and visceral Leishmaniasis. Leishmaniasis, a disease caused by intracellular protozoan parasites of the *Leishmania* genus, affects several species. The disease is endemic in 88 countries, including 72 developing nations and 13 industrialized ones. Ninety percent of visceral leishmaniasis (VL) cases are found in just five countries: Bangladesh, India, Nepal, Sudan, and Brazil. Meanwhile, ninety percent of cutaneous leishmaniasis (CL) cases occur in seven countries: Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia, and Syria. First of all Though *L. aethiops* is additionally linked to MCL, *L. Brasiliense*'s is the New World organism most commonly responsible for this condition. (2,3).

The original infection ultimately goes away from a cutaneous lesion, but years later, respiratory and oral mucosal involvements happen, causes inflamed oral cavity, nose, oropharynx, and trachea. Illness that progresses slowly is hard to cure and frequentl returns. Malnutrition and respiratory impairment can potentially result in mortality from a protracted illness (4). Without particular treatment, it may be deadly and present with fever, cachexia, hepatosplenomegaly, and blood cytopenia. Since anthroponotic VL foci were the source of (9)recurrent and lethal epidemics, VL is more important than CL. Alternatively, the name may have come from the word "kal," which means "death" and denotes the fatality of illness (5,6,7).

## Epidemiology:

Leishmaniasis, a neglected tropical disease, primarily affects impoverished populations across more than 90 countries in Asia, Africa, the Middle East, Central America, and South America. The incidence of cutaneous leishmaniasis (CL) ranges from 700,000 to 1.2 million cases each year, with around 95% of cases occurring in the Americas, the Mediterranean basin, the Middle East, and Central Asia (9) . The number of visceral leishmaniasis (VL) cases is estimated to be fewer than 100,000 annually, a significant decrease from earlier estimates of 400,000 cases (8). Countries like Brazil, China, Ethiopia, India, Kenya, Nepal, Somalia, and Sudan contribute to over 95% of the cases reported to the World Health Organization (WHO)(9) .

Risk factors for leishmaniasis include poverty, population migration, malnutrition, poor hygiene, and immunosuppression(9) .

The disease is transmitted by over 70 species of phlebotomine sand flies, which belong to the Diptera family Psychodidae. These flies are divided into the Phlebotomus genus in the Old World and the Lutzomyia genus in the New World, and they spread more than 20 identified species of the Leishmania parasite (10) .Leishmaniasis has geographically divided itself into distinct species across the Old and New Worlds. The "Old World" includes regions like Asia, the Middle East, Africa, and Southern Europe, while the "New World" encompasses areas such as Mexico, Central America, South America, and the United States.

Worldwide, sandflies may be found, and tropical varieties may finish their life cycle all year round [11]. Warmer months are when organisms in subtropical regions finish their life cycles [11]. The sandflies are greatest at night, flying softly and frequently going unnoticed by their target [11].

Due to immigration or travel from other nations, the common CL cases are found in the USA [8]. Nonetheless, the WHO declared that leishmaniasis was prevalent in the United States in 2015 [12]. Moreover, of the 69 new cases of leishmaniasis that were found in Texas in a recent investigation, 41 (or59%) were autochthonous CL who had never left the country [13]. The frequency and geographic range of leishmaniasis are expected to rise with climatic changing.

### Life Cycle:

The Leishmaniasis is transmitted to humans and other animal hosts by the female phlebotomine sand fly, which is mostly active at night. The life cycle of the Leishmania parasite involves two main stages: the promastigote and the amastigote (11,15). The promastigote stage, equipped with a flagellum, allows the parasite to move within the sand fly's intestines. When the sand fly feeds on a mammalian host's blood, it injects the promastigote into the skin. Once inside, the promastigote is engulfed by the host's mononuclear cells, where it transforms into the amastigote form(11,15).The amastigotes then multiply within the host's reticuloendothelial system, potentially leading to asymptomatic conditions or severe illness, depending on the host and parasite interaction. These amastigotes can spread through the body via the bloodstream and lymphatic system, causing mucosal and visceral diseases. Recent research indicates that the Leishmania RNA Virus (LRV1) co-infects certain species like Leishmania Viannia guyanensis and L. V. braziliensis, triggering a hyperimmune response through toll-like receptors. This response can lead to mucosal damage and metastatic infection (16,17) .

### Clinical Features:

VICERAL LEISHMANIASIS	POST KALA -AZAR DERMAL LEISHMANIASIS	CUTANEOUS LEISHMANIASIS	MUCOSAL LEISHMANIASIS
Fever, weight loss, fatigue, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia	Skin lesions (always starts on face) 6 months following VL	Skin lesions on extremities and face:Painless papules which progress to nodules then ulcers	Nasal secretions, nasal obstruction, pain, epistaxis. Destructive lesions in nose, oropharynx. Initially involves nose and mouth, can progress to include pharynx and larynx

**Table 1-2-3. John E. Bennett RD MBBJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases: 8th ed. Philadelphia: Elsevier/Saunders, [2015]; 2015.**

**Diagnosis:**

Immunological tests are widely used in the detection of kala azar which includes:-

- a) Indirect fluorescent antibody (IFA) test using amastigote or promastigote antigens. This test remains positive even 12-15 years after cure has been achieved (24).
- b) Direct agglutination test using promastigote antigen.
- c) Detection of anti-66 kDa antibodies in a micro enzyme linked immunosorbent assay (ELISA) is highly sensitive and specific in confirming kala azar (25).
- d) Indirect haemagglutination and immunoblot testing (26).
- e) Monoclonal antibody spot test is a simple test which is more sensitive than bone marrow smear examination (27).
- f) Amplification of kinetoplast DNA using polymerase chain reaction is a highly sensitive test (28).
- g) Detection of 72-75 kDa and 123 kDa fractions of Leishmania antigen in urine may be used to diagnose kala azar (29).

Because such immune-related tests are more accurate and precise than the traditional aldehyde test, they are especially helpful in population screening and the identification of subclinical illnesses (30).

SEROLOGICAL TESTS-it includes.

DISEASE	DIAGNOSTIC METHOD	REMARKS
CUTANEOUS LEISHMANIASIS	Biopsy, scraping, aspirate	Sensitivity depends on the pathologists experience and the caliber of the material. Acquire from the the bottom and ulcers edge.
VISCERAL LEISHMANIASIS	(a) Culture, isolation, aspirate and histology  (b) Peripheral blood  (c) Rapid diagnostic Test	Highest delicate for identification of VL when comparing lymph nodes and bone marrow aspirates.  Molecular examination of blood in vitro culture, useful in HIV patients diagnosis.  Helpful in detection of antibodies against various VL antigens.  Results available in 20-25 min.  Easy to perform, quick and cheap particularly helpful in underserved areas.

		Sensitivity varies depending on region and parasite species.  Can cross react with other infections- for example chagas disease.
MUCOSAL LEISHMANIASIS	Biopsy and aspirate	Helpful in ML diagnosis.

**Table- from Aronson et al. CID, PAHO, urza et al., Berman at a**

Through Culture, Microscopy specimen detection is crucial because direct evidence is desired (34, 35). Due to its sensitivity compared to microscopy or culture, PCR-based procedures are not standardized and are only available in large medical facilities or hospitals. Biopsies, aspirates, or scrapings can be used to obtain tissue.

In CL, the less disruptive edge of the ulcer ought to be extracted for histology, and the cleaned base of the ulcer ought to be taken for PCR and culture (35).

Sensitivity in VL depends on the location of tissue gathering, with biopsy of spleen producing the largest percentage of viable varieties. However, from this technique hemorrhage may cause fatality. Consequently, despite its reduced sensitivity (50–80%), Tissue specimen is mostly collected from bone marrow. Other sources are Liver, lymph nodes, and blood particularly in immunocompromised hosts (32, 36).

Giemsa-stained tissue is used to detect amastigote stages under a microscope, help in the diagnosis of various leishmaniasis. (37, 35). Giemsa dye gives rise to blue staining of the cytoplasm and red to purple staining of the nucleus and kinetoplast (33). Intracellular fungal infections, in contrast to amastigotes, lack a kinetoplast and exhibit positive staining with periodic acid Schiff, mucicarmine, or silver (38).

Cultivation of tissues that are infected is one of the additional techniques for direct diagnosis. Schneider's Drosophila medium together with 30% lethal bovine serum, are cultured for 3 to 4 weeks at 25 °C, helps in the identify the nature of parasite. Wet preparations from positive cultures are used to identify promastigote stages under a microscope (38).

Molecular amplification test, which uses PCR, is crucial for pauciparasitic syndrome diagnosis, including ML. Currently, confirmation of the leishmania species is advised to inform management choices (34). Furthermore, awareness of the Leishmania species increases the likelihood of developing mucocutaneous illness, which is why prompt medical intervention is advised (35)

Microscopy, culture, and molecular testing are the methods used for direct parasitological diagnosis; nevertheless, they are not always accessible or reliable sources of maté. As supplemental methods for serologic diagnosis, indirect immunologic tests, such as Western Blot, ELISA, immunofluorescence, and direct agglutination of IgG, can also be performed. These serologic tests can be useful in diagnosing ML and VL, but they are usually not helpful in instances with CL (32).

Antigen testing is additionally offered to help the diagnosis in alongside antibody tests. CL is identified with the use of immunochromatography, a new immunologic technique for ulcerative skin lesions, which allows for the quick identification of *Leishmania* species antigen (34). Additionally, ELISA urine antigen assays with an accuracy of more than 90% have been established (39, 40).

The Montenegro, also known as the Leishmanin Test, is a form of intradermal skin test that mimics the Mantoux skin test for tuberculin in that it causes a delayed hypersensitivity reaction. The exam is not publicly accessible. Individuals with ML and CL may have positive test findings (31, 32).

### **Treatment of Kala Azar**

The main objective for kala-azar treatment is to eradicate the parasite in less harmful, and effective medications. For kala azar first line treatment is pentavalent antimonial; the second line of treatment is pentamidine and amphotericin B. Lately, the latter are likewise being utilized as first-line medications (44). Unfortunately, because medication resistance is so common, treating kala azar is difficult. About a quarter of a million instances of kala azar that are refractory to sodium stibogluconate (SSG) have been reported in Bihar alone.

### **Pentavalent Antimonials**

They work by preventing the parasite from oxidizing fatty acids and metabolizing glycolysis. Among them, ureastibamine was created for the first time in India by Brahmachari and was presumably the most widely utilized of its kind earlier in the century (42). Meglumine antimonate and sodium stibogluconate formulations are already on hand.

It was abundantly evident during the 1980 pandemic that the standard stibogluconate has been given for 6 days at the dose of 10 mg/kg body weight which is insufficient. According to WHO in 1984 – the dose is 20 mg/kg body weight daily, or up to 850 mg/day for 20 days, and in case of recurrence twice dose has been given. It is now advised to take the medication for at least 30 straight days (43).

### **Pentamidine**

It contains a polyamine that prevents the DNA of the kinetoplast from functioning. It is administered IV or by gradual injection on alternate days at a dosage of 4 mg/kg BW Daily in situations when antimonial is not working. Although pentamidine resistance was initially noted in the pandemic of 1991, studies using 10–12 injections showed a 98.8% cure rate with no relapses. Relapse may occur even after 20–33 doses, according to recent research (41). Hypoglycemia, temporary hyperglycemia, long-term insulin-dependent diabetic mellitus, and cardiac arrhythmias are among its adverse effects. Slow infusion of pentamidine is recommended to reduce the possibility severe hypotension.

### **Amphotericin B Deoxycholate**

It is the most common antifungal medication. It increases the permeability of membranes by decreasing the formation of sterols. Initially, it was administered intravenously on alternate days at a dose of 0.5 mg/kg BW, 14 infusions has been given. Although this dosage is safe and effective, it is linked to a higher risk of recurrence. A high dosage is one that is particularly effective, with a entire collective dose is 1-3 grams; yet, it was discovered to be more hazardous. As of right now, 0.75 mg/kg BW given every other day for a total of 15 infusions is the suggested dosage (44). It is administered to individuals who are HIV positive (47), resistant to pentamidine (46), and antimonial (45). The most common adverse reactions are thrombophlebitis, malaise, chills, and renal toxicity.

### **Additional Medications**

For at least four weeks, allopurinol, a xanthine oxidase inhibitor, is administered alongside antimonial treatments at a dosage of 50 mg/kg body weight per day. Its use in combination with antimony compounds is limited.

It has also been found that oral administration of sulphadiazine, trimethoprim, and metronidazole for 12-25 weeks is effective (48). For pregnant patients, tinidazole can be used as a substitute for metronidazole.

Oral roxithromycin at a dose of 300 mg twice daily for 21 days has shown to be as effective as sodium stibogluconate(49).

Sodium aurothiomalate has also shown excellent therapeutic effects when administered as an initial dose of 10 mg, followed by 20 mg intramuscularly on alternative days, for a complete of 250 mg (45) .

Ketoconazole is being used in the treatment of kala-azar with promising results, working by disrupting the parasite's cell membrane (18). However, it may cause adverse effects such as gastrointestinal symptoms, hepatotoxicity, QT prolongation, hair loss, agranulocytosis, and decreased adrenal corticosteroid production.

Clofazimine, INH, rifampicin, and fluoroquinolones are a few other medications with antileishmanial properties.

### **New Strategies**

Recombinant human gamma interferon, or IFN-gamma, functions by stimulating secondary cytokines, activating infected macrophages, and boosting the cytotoxic potential of T and NK cells. It was applied subcutaneously for 30 days at a dosage of 100 micrograms/m<sup>2</sup> of body surface area in conjunction with sodium stibogluconate. Early parasite clearance and a reduction in drug resistance were the outcomes (51).

Leishmaniasis is being treated with liposomal medication formulations of sodium stibogluconate, amphotericin B, and pentamidine. It is anticipated that this new technique would reduce the length of medication therapy to just three days (52).

### **Kala Azar Elimination Grade In India**

The National Vector Borne Disease Control Programme (NVBDCP) (2) is in charge of organizing the eradication effort in India. (a) Early detection and complete management of disease; (b) cohesive vector management ; (C) supervision, monitoring, investigation, and estimation; (d) enhancing the human resource capacity in health sector; (e) social mobilization with communication for behavioral effect; (f) program supervision are all included in the plan of this program.

The process for addressing kala-azar being identifying and documenting cases in the village, using this data effectively for planning disease prevention and management strategies.

When a person in a endemic area presents with a fever that lasts for 2 weeks with an enlarged spleen, and a laboratory confirmation is available, liposomal amphotericin B is administered as a single dose of 10 mg/kg or a combination therapy is used, which includes paromomycin and miltefosine for ten days (53, 54).

The illness incidence has decreased dramatically, albeit very slowly, thanks to this early diagnostic technique; it went from 13869 in 2013 to 3145 in 2019. Four States accounted for roughly 60% of the cases recorded in 2019 (55). Among these were Bihar, which had the highest number of cases (2416). (56).

Moreover, 821 cases of post-kala-azar dermal leishmaniasis (PKDL) were registered and these cases were identified as a significant source of transmission in the municipal community (55).

In this context, elimination means achieving and sustaining a target of fewer than one case per 10,000 people at the district or sub-district level in all endemic areas for 3 consecutive years (57). The progra was implemented in three stages: an attack to lower instances below 1/10,000 for three years, from 2017 to 2019, a maintenance of cases below 1 per10,000 people from 2017 to 2019, and a maintenance of cases below this threshold through 2020 (58). Nepal has sucessfully maintained this status (59). The government currently has to significantly improve program execution to eradicate kala-azar in these states and across the rest of the country.

### **Steps To Eliminate Kala Azar**

According to the NVBDCP, 54 districts are mostly affecting from kala-azar, (55).There are various steps to eliminate the kala – azar:

**STEP 1-** Every epidemic blocks must actively organize an investigative team to conduct active case discovery. Anyone with a fever lasting longer than 15 days, their condition should be checked and sent to the district hospital right once for treatment.

**STEP 2-** Treatment ought to begin very early, and confirmation testing ought to be conducted. Full health facilities should be offered at the block level, according to the Health Ministry's higher authorities. This team will be responsible for the block's health and will frequently provide to the blocks health officials.

**STEP 3-** The human-vector-human chain of infection should be stopped and broken by using residual pesticide spraying. For the purpose of covering every home and livestock shed in the villages, the spraying activities need to be done twice a year. To make sure that these procedures are performed correctly or not, the health authorities should regularly monitor and oversee these procedures.

**STEP 4-** There should be social mobilization programs along with education campaigns for community involvement to decrease the frequency of kala-azar.

**STEP 5-** For the Kala-azar Elimination Program to be successful, program management—which includes appropriate supervision, monitoring, and evaluation—must be carried out. Offices at the federal, state, and local levels must closely coordinate on matters of strategy, planning, and policy. In a few more years, kala-azar may be eradicated from India if all these steps are done.

### Conclusion

Leishmaniasis, also called as kala azar, is a complicated condition which is challenging to identify and manage. Improvements in early diagnosis, vaccination research, therapy, appropriate care planning, and reporting might significantly reduce the disease's morbidity and mortality. And through social mobilization along with educational campaigns especially in rural areas helps in decreasing the frequency of Leishmaniasis.

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