New therapies for visceral leishmaniasis

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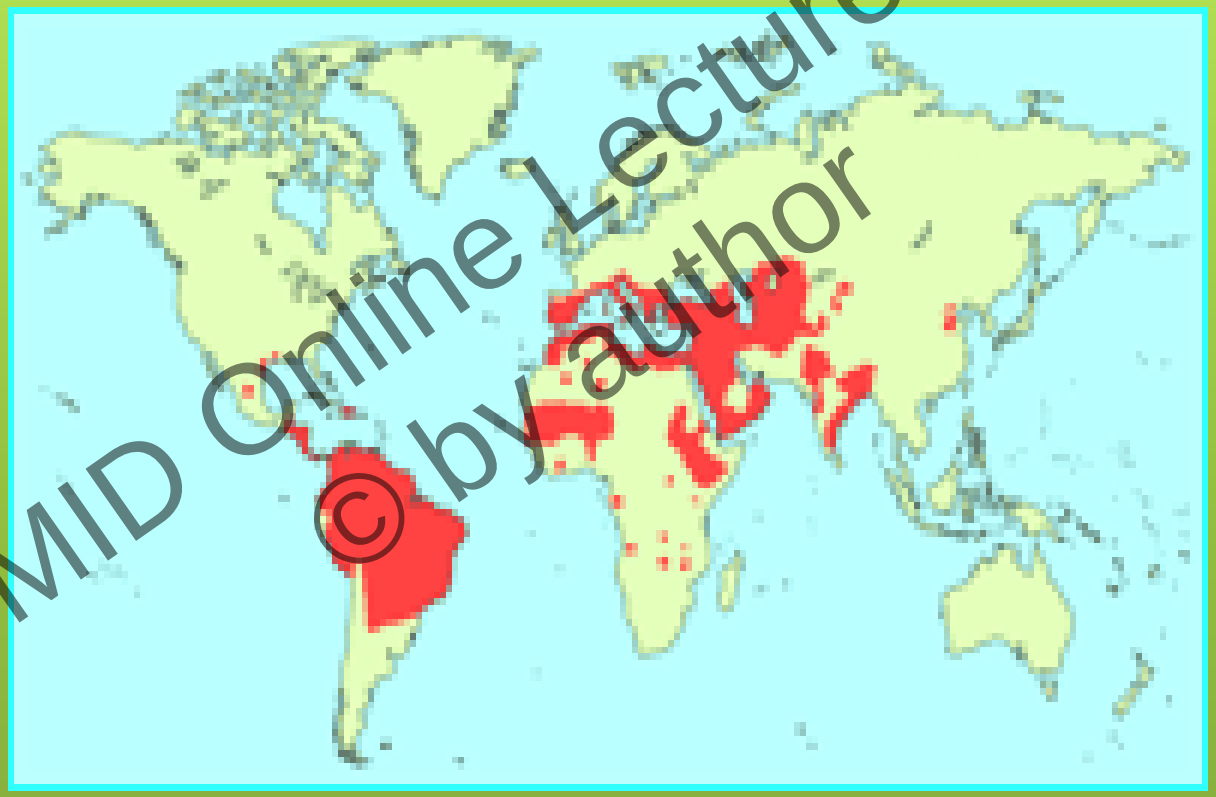
Visceral leishmaniasis

- Systemic disease, involving the reticuloendothelial system
- Infection due to the complex of ***Leishmania (L.) donovani***, which includes -- ***L. (d.) donovani*** in India, Asia and subsaharan Africa and -- ***L. (d.) infantum/ chagasi*** in the Mediterranean, Central Asia and S. America.

Epidemiology

- Endemic in 88 countries, including the Mediterranean
- 500.000 cases/year globally
- HIV infection changed the epidemiology
- Before 1985, 70% of VL in Europe was in children < 15 years old
- After the AIDS epidemic, 70% of cases in adults

Endemic Areas for Leishmaniasis



BMJ 2003;326:378

Table 4. Reported and estimated incidence of visceral leishmaniasis in the Mediterranean

Country	Reported cases/year	Estimated cases/year
	Reported VL cases/year Years of report	Estimated annual VL incidence
Albania	114	140 to 210
Algeria	111	130 to 200
Greece	42	50 to 80
Italy	134	160 to 240
Morocco	152	300 to 610
Spain	117	140 to 210
Tunisia	89	110 to 160
Turkey	29	60 to 120

[a]Underreporting considered moderate (2–4-fold).
doi:10.1371/journal.pone.0035671.t004

Alvar J, Vélez ID, Bern C, Herrero M, et al. (2012) Leishmaniasis Worldwide and Global Estimates of Its Incidence. PLoS ONE 7(5): e35671. doi:10.1371/journal.pone.0035671

Transmission

- With the female fly
  - Phlebotomus in the Old World
  - Lutzomyia in the New World

Transmission

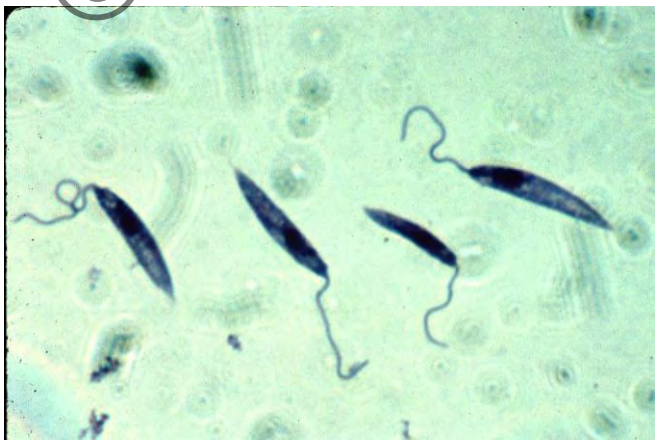
Rarely by:

- Blood transfusion
- Infected transplanted organ
- Sharing of needles
- Accident in the laboratory

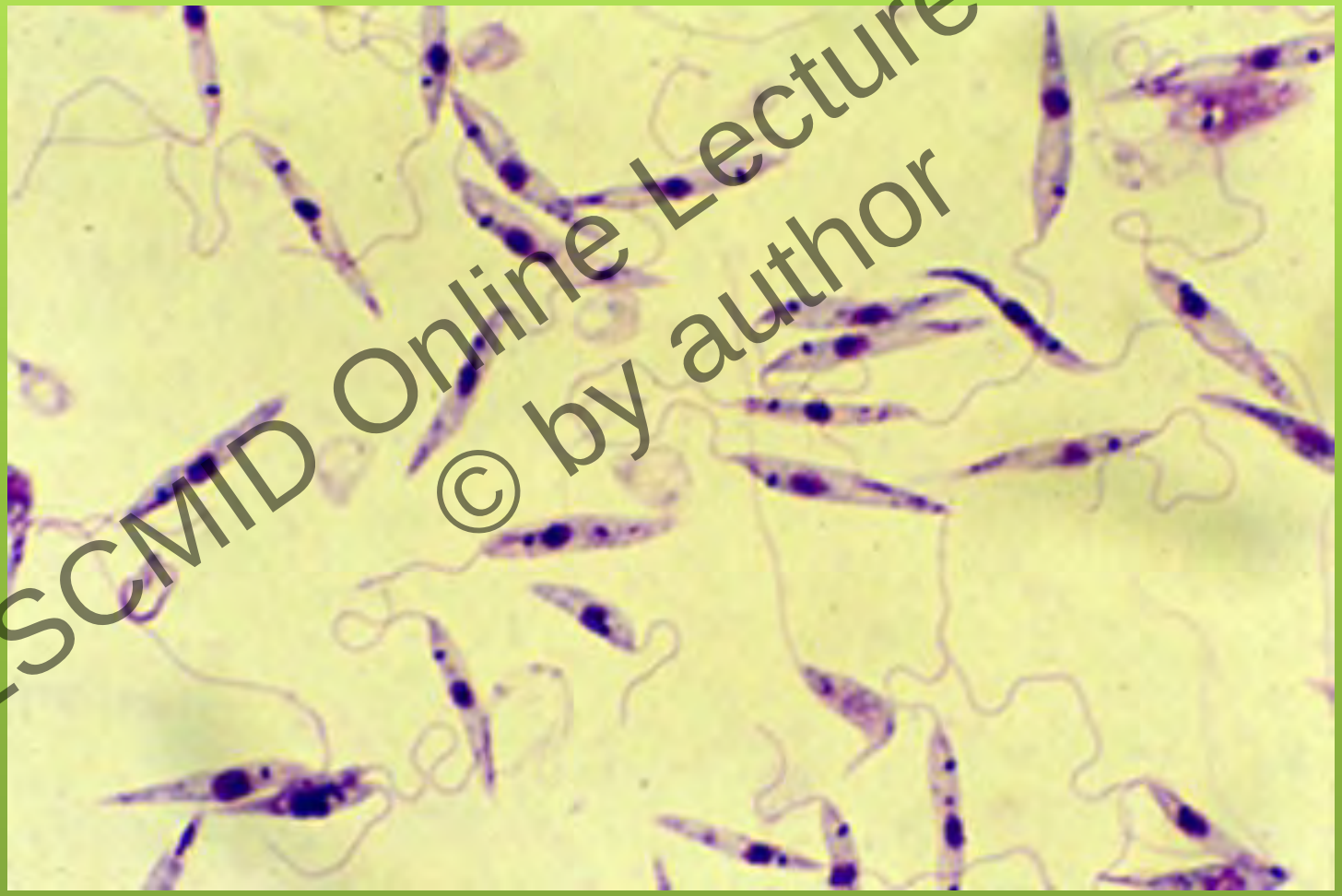
Cycle of life

Leishmania exists in two forms

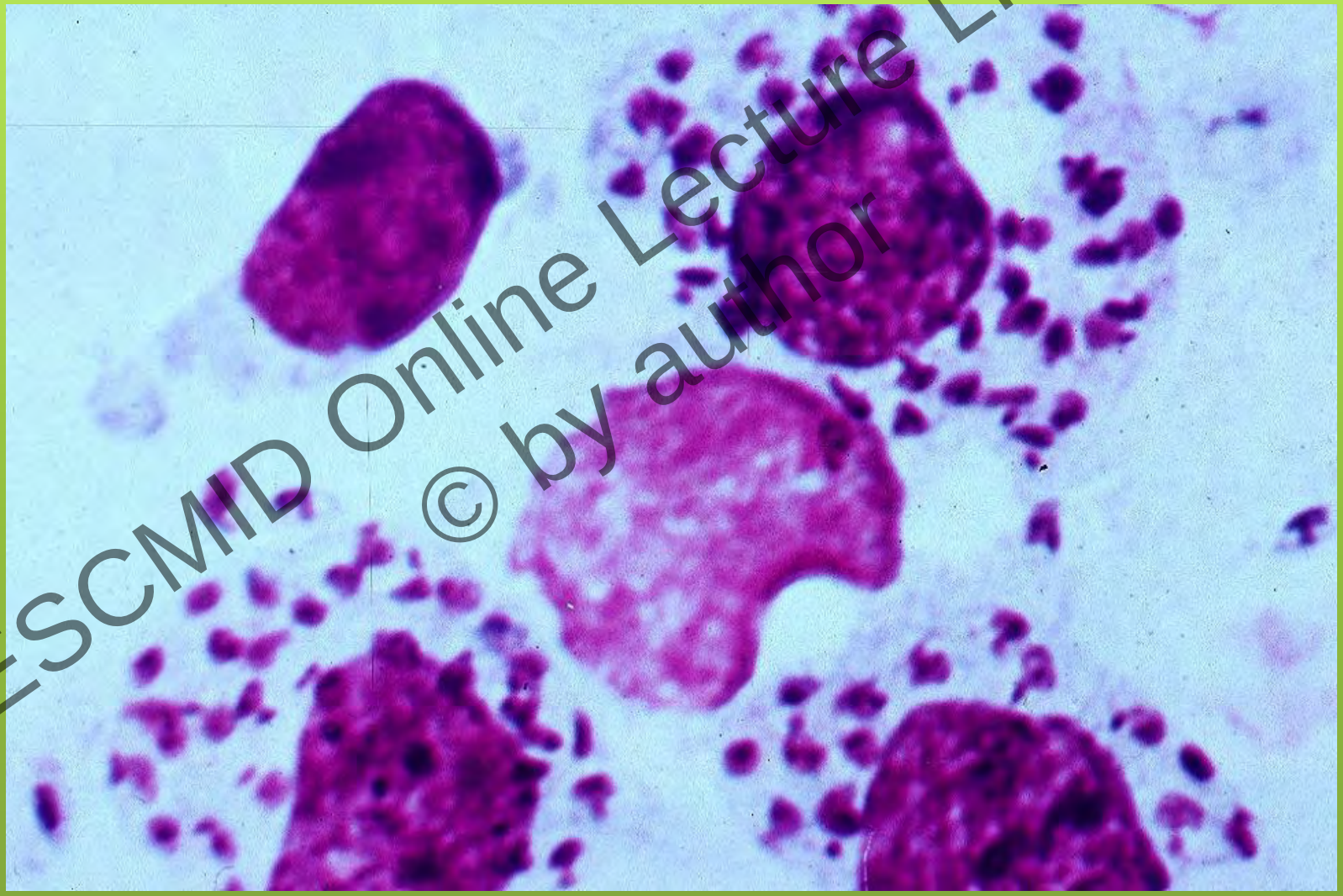
- Amastigote in the macrophages of mammalian hosts
- Promastigote in the gut of the sandfly vector

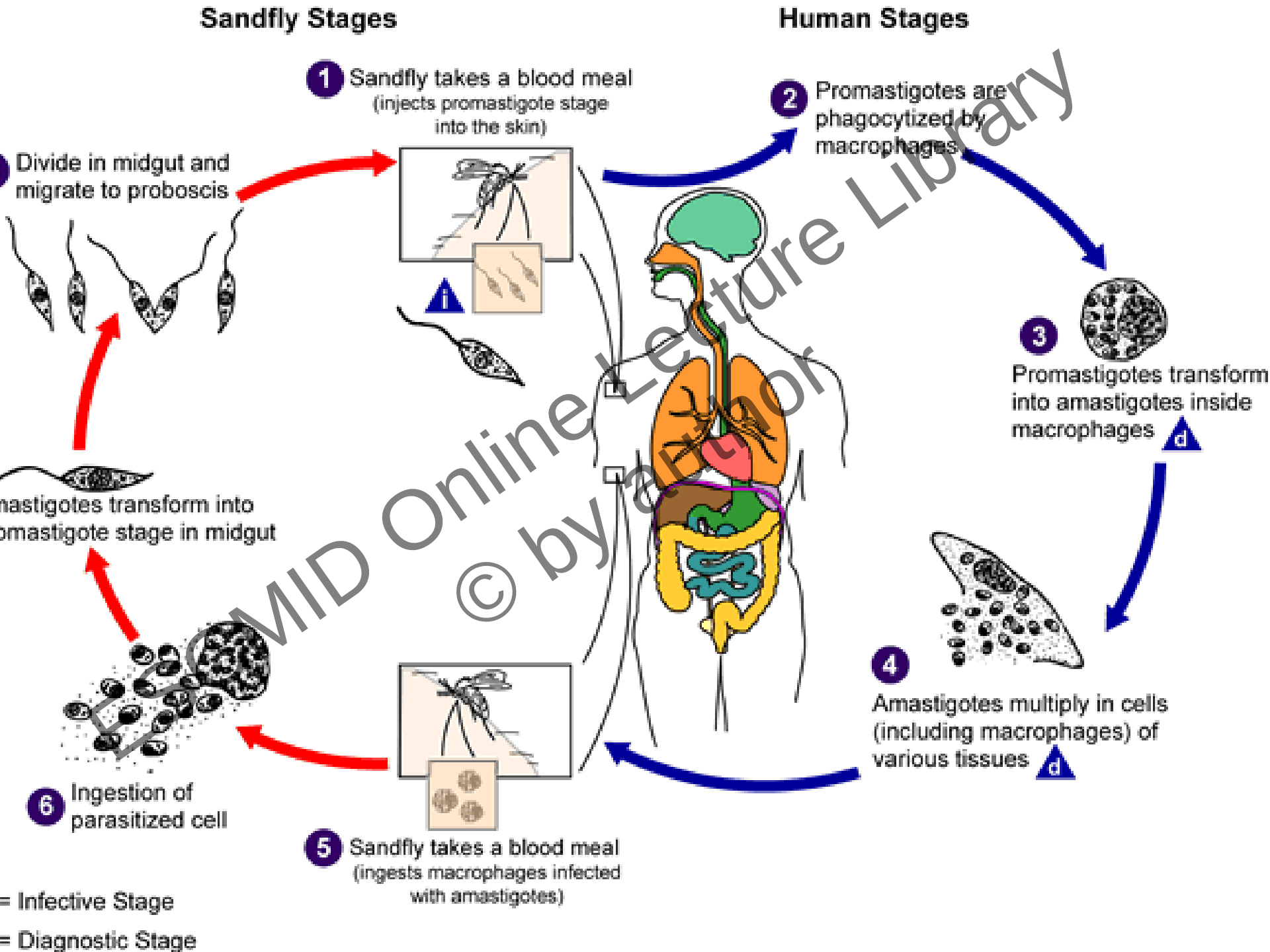


Leishmania infantum: Promastigotes



Amastigotes





Clinical presentation

- Often asymptomatic
- Depends on the type of the parasite and the immune status of the host
- Incubation time: 4-6 months, may vary from 10 days to more than 3 years
- Classical presentation known as "kala-azar"

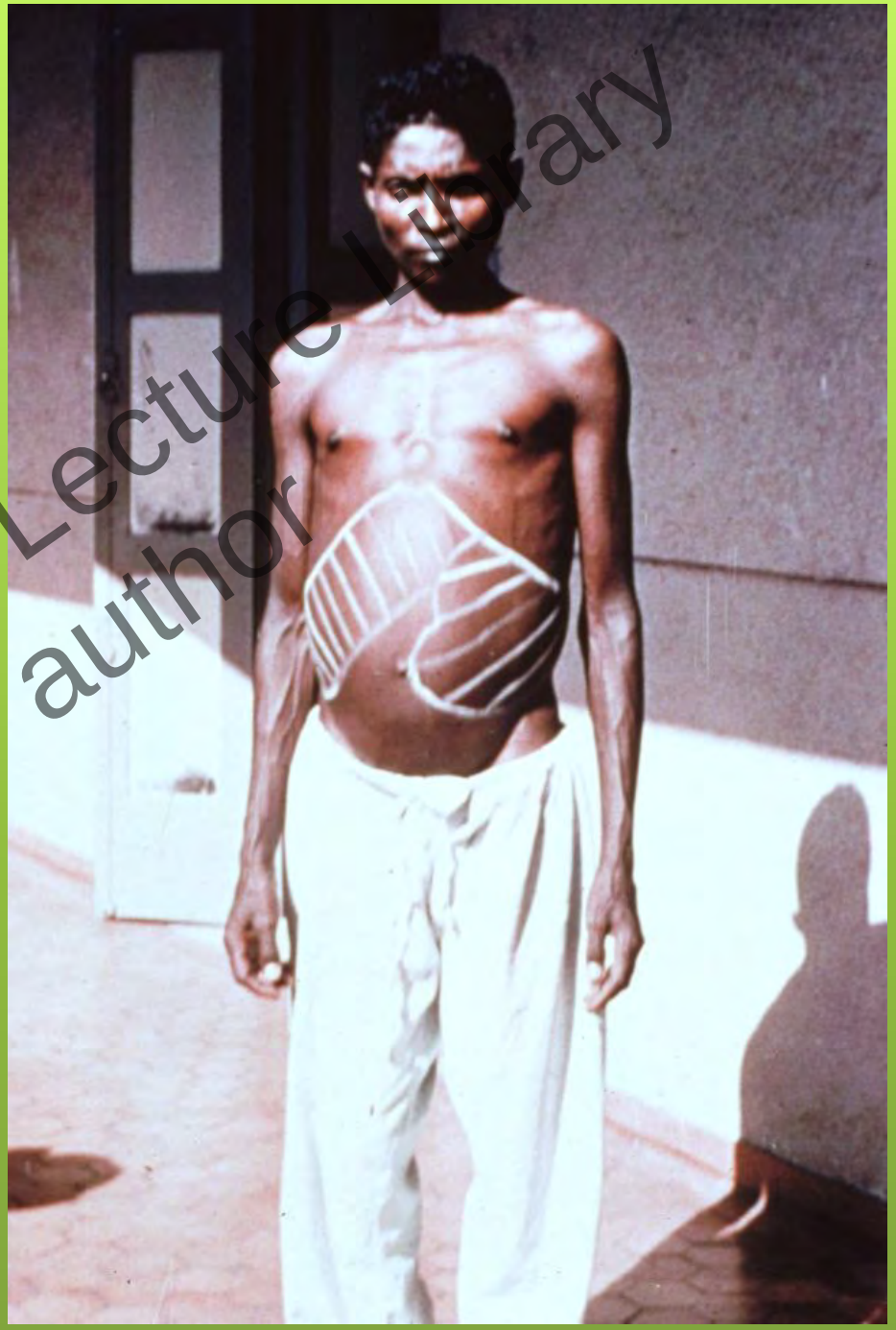
Clinical Presentation

- Hepatosplenomegaly
- Fever
- Cachexia
- Pancytopenia
- Hypergammaglobulinemia

Clinical Presentation

As the disease progresses:

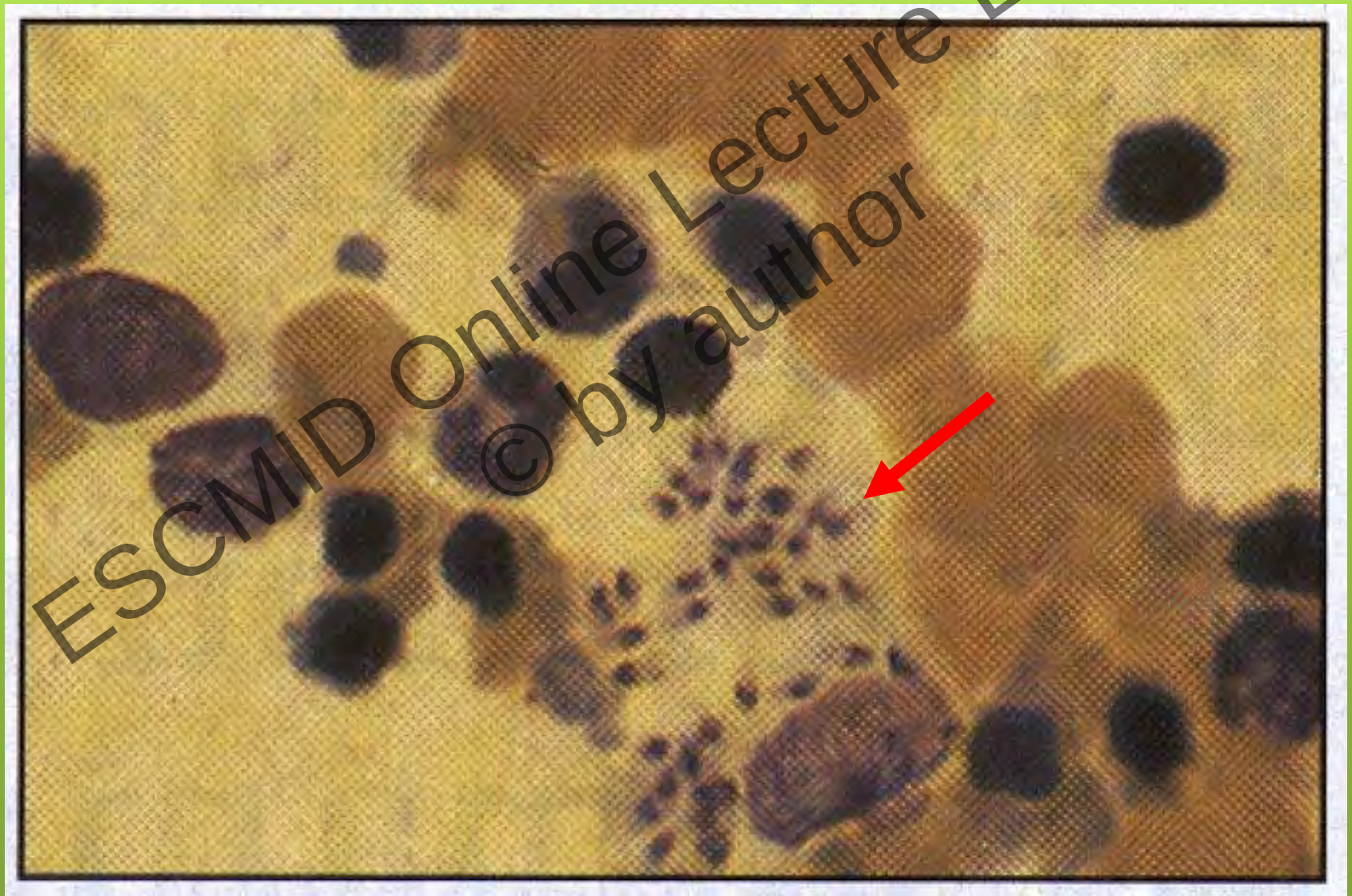
- Hepatic dysfunction, jaundice, ascites
- Hemorrhagic complications
- Bacterial infections
- Immunosuppressed patients (HIV) may present with symptoms from the stomach, the esophagus, the intestine, the skin, the CNS or the lung.



Diagnosis

- Clinical presentation
- Identification of parasite in the macrophages of the reticuloendothelial system (bone marrow, spleen, liver or lymph nodes) with direct microscopy, culture or DNA testing
- Antibodies in serum
  - Indirect fluorescent antibody tests (IFA)
  - ELISA
  - Direct agglutination test (DAT)

Bone marrow aspirate



Treatment

- Fatality is 80-90%, if untreated.
- Available drugs:
  - Pentavalent salts of antimony
  - Liposomal Amphotericin B
  - Amphotericin B deoxycholate
  - Miltefosine
  - Paromomycin

Pentavalent antimony compounds

- **Meglumine antimoniate** (Glucantime- 1.5g meglumine antimonate= 425 mg pentavalent antimony)
- **Sodium stibogluconate** (Pentostam)
- Used to be the drugs of choice. Today, 1st choice in East Africa
- High resistance in India and Nepal
- Common relapse
- Not for immunocompromised

Pentavalent antimony compounds

Adverse events

- Hepatotoxicity
- Pancreatitis
- Cardiotoxicity
- Prolonged QT on EKG, inversion of T waves, arrhythmia

Liposomal amphotericin B

- AmBisome is the only drug approved by FDA for the treatment of VL
- Four European studies (348 patients), with total cumulative doses >18mg/kg, showed cure rates of 98 to 100%

Clin Infect Dis. 1996;22(6):938
Q J Med. 1994;87(2):75
J Pediatr. 1997;131(2):271
Clin Infect Dis. 2003;36(5):560

Liposomal amphotericin B

- An expert panel convened by the **WHO** in 2005 concluded that a total cumulative dose of 20 mg/kg is adequate to achieve high cure rates in immunocompetent VL patients in all regions of the world, regardless of the specific dosing schedule

Clin Infect Dis. 2006;43(7):917

Liposomal amphotericin B

- WHO recommends liposomal amphotericin B for the treatment of VL in the Mediterranean, Middle East, Central Asia and S.America, as well as for India, Bangladesh, Butan and Nepal.
- For East Africa and Yemen WHO recommends pentavalent salts of antimony as first line treatment.

Clin Infect Dis. 2006;43(7):917

Liposomal amphotericin B

Adverse events

- Nephrotoxicity
- Hypokalemia
- Infusion related toxicity

Amphotericin B deoxycholate

- Cheap
- More toxic than liposomal ampho B

Miltefosine

- The only oral agent
- Effective drug for treatment of VL
- 2.5mg/kg/day orally for 28 days
- Teratogenic
- Vomiting and diarrhea
- Transaminase elevations may require suspension of treatment

Paromomycin (aminosidine)

- Aminoglycoside antibiotic
- Binds to 30S ribosomal subunit
- Used in India and East Africa
- Clinical trials are currently underway to determine the optimum dose

Combination therapy

- To prevent the development of acquired resistance
- To establish shorter treatment courses with high efficacy to improve compliance and decrease treatment costs
- Recommendations do not exist

Combination therapy

- Liposomal ampho B (1 dose of 5mg/kg) + miltefosine for 7 days
- Liposomal ampho B + paromomycin for 7 days
- Miltefosine +paromomycin for 10 days
- Liposomal ampho B+ salts of antimony
- Salts of antimony + paromomycin

Liposomal Amphotericin B for the Treatment of Visceral Leishmaniasis

Caryn Bern,[1] Jill Adler-Moore,[2] Juan Berenguer,[3] Marleen Boelaert,[5] Margriet den Boer,[6] Robert N. Davidson,[7] Concepcion Figueras,[4] Luigi Gradoni,[8] Dimitris A. Kafetzis,[10] Koert Ritmeijer,[6] Eric Rosenthal,[11] Catherine Royce,[12] Rosario Russo,[9] Shyam Sundar,[14] and Jorge Alvar[13]

Clinical Infectious Diseases 2006; 43:917–24

Use of combination antileishmanial drug regimens should be promoted to prevent the development of resistance to existing drugs. Well-conducted trials of specific combinations are urgently needed. A regimen would be considered effective if it produces an initial parasitologic and clinical cure in ⩾95% of patients and a definitive cure at 6 months in ⩾90% of patients.

Immunocompetent patients

- Preferred therapy in Mediterranean, Middle East, Brazil
- Liposomal amphotericin B
  - 3 mg/kg IV on days 1-5, 14 and 21; or
  - 3 mg/kg/day x 7-10 days; or
  - 10 mg/kg/day x 2 days

Alternative therapy

- Amphotericin B deoxycholate 0.75-1.0 mg/kg IV every other day for 30 days; or
- Antimony salts 20 mg/kg IV or IM daily x 28 days

Int J Antimicrob Agents. 2005;25(1):26
Clin Infect Dis 2003; 36:560-6.

HIV-VL co-infection

- Liposomal amphotericin B 2-4 mg/kg IV daily x 10 days; or
- Interrupted schedule (e.g. 3-5 mg/kg on days 1-5, 10, 17, 24, 31, 38) to achieve total dose of 20-60 mg/kg
- Secondary prophylaxis: Liposomal amphotericin B 4 mg/kg every 2 to 4 weeks

Assessment of response to treatment

- Response to treatment is generally assessed clinically, based on resolution of fever, decrease in spleen size, and weight gain.
- Serological tests are not useful tests of cure as they remain positive for months to years after treatment.

Thank you!