Treatment Challenges in Cutaneous Leishmaniasis

Factors Affecting Therapeutic Response

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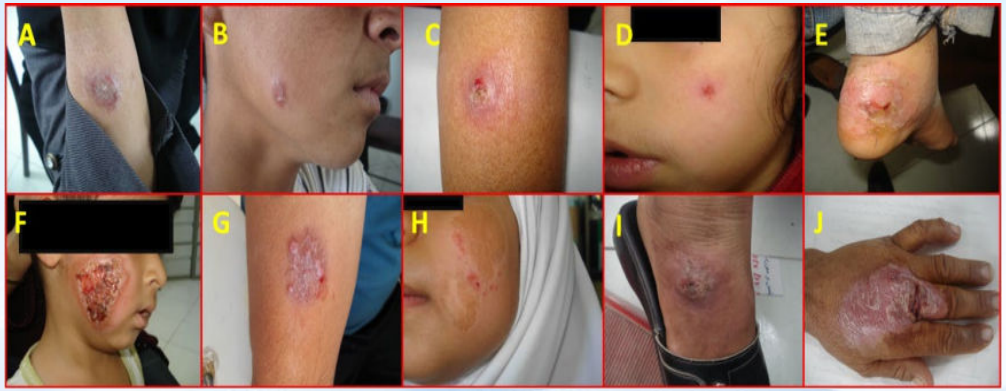
CONTENT

1 Cutaneous Leishmaniasis Overview

2 Treatment Resistance Factors

3 Parasite-Related Resistance Mechanisms

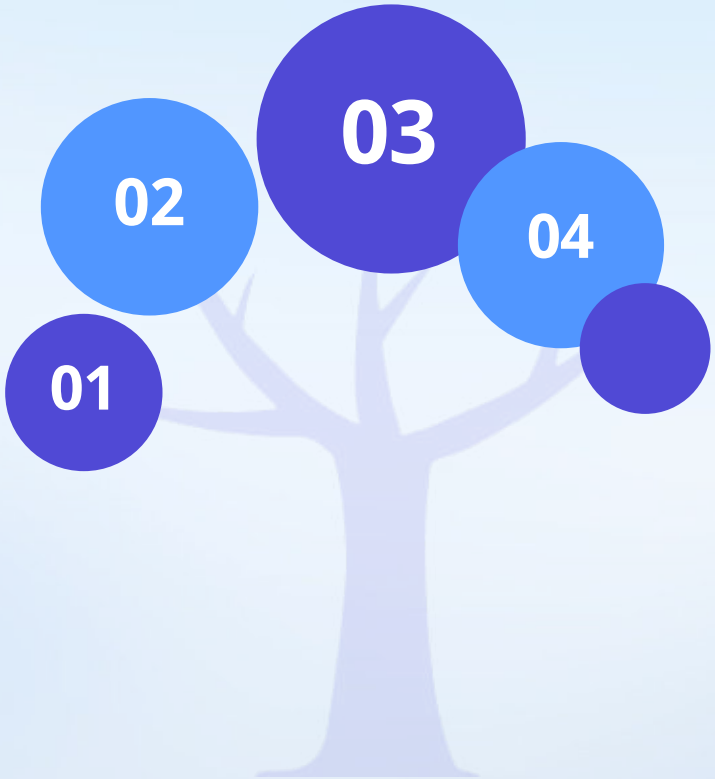
4 Strategies



01

Cutaneous Leishmaniasis Overview

Overview



Leishmaniasis Prevalence

Affects over 1 billion people in 100+ countries, with 431 million at risk for cutaneous form.

Cutaneous Leishmaniasis

Parasitic disease, the most prevalent form of leishmaniasis is cutaneous leishmaniasis (CL), which is prevalent in the tropics, with approximately 1.5-2.0 million annual cases globally.

In Iran

CL presents itself in two scientific forms: anthroponotic CL (ACL), familiar as urban-type (dry-form) produced by ***Leishmania tropica***, and zoonotic CL (ZCL) as rural-type (wet-form) induced by *L. major*.

Treatment Challenges

Meglumine antimoniate is standard treatment, but 11-12% of cases show unresponsiveness.

Important

WHO highlights drug resistance as a top challenge. Providing essential knowledge about the treatment of CL cases is an important issue.

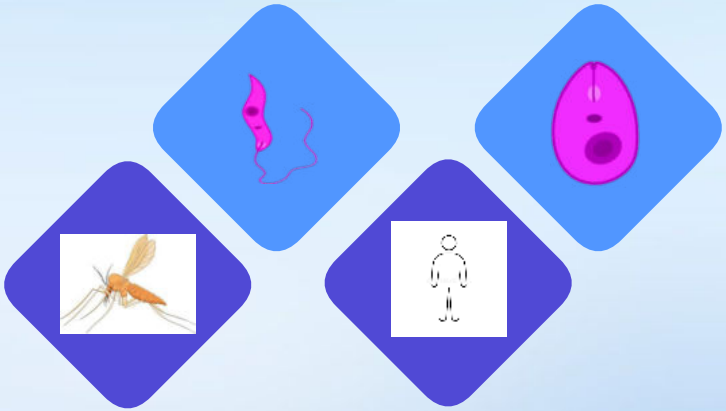
Anthroponotic transmission patterns

Human-to-human transmission

Anthroponotic cutaneous leishmaniasis spreads between humans via infected female phlebotomine sandflies, primarily in urban settings.

L. tropica as main agent

This parasite species causes anthroponotic form, transmitted by Phlebotomus sergenti in densely populated areas.



Urban cycle characteristics

Diseases display in suburbs with poor housing conditions and affect low-income populations.

Transmission Patterns

Population movement, civil unrest, climate change and inadequate housing contribute to transmission patterns.

Global concern and challenges

Global Distribution

Prevalent in Central America, South America, North Africa and Middle East.

High-Risk Countries

Afghanistan, Brazil, Colombia, Algeria, Iraq, Syria, and Iran represent 95% of new cases.

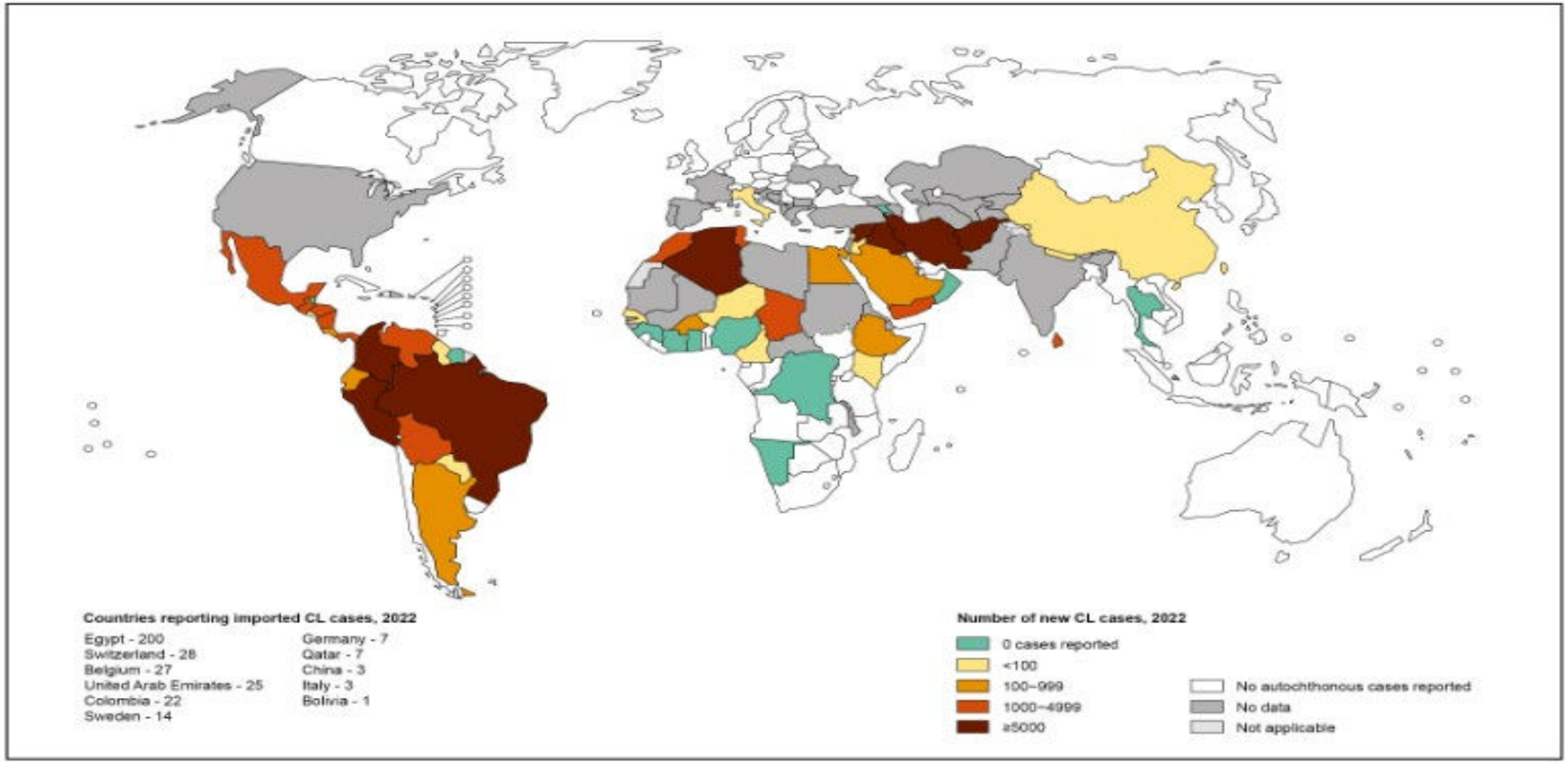
Treatment Failure

Increasing treatment failure is a global concern.

Complexity of Risk Factors

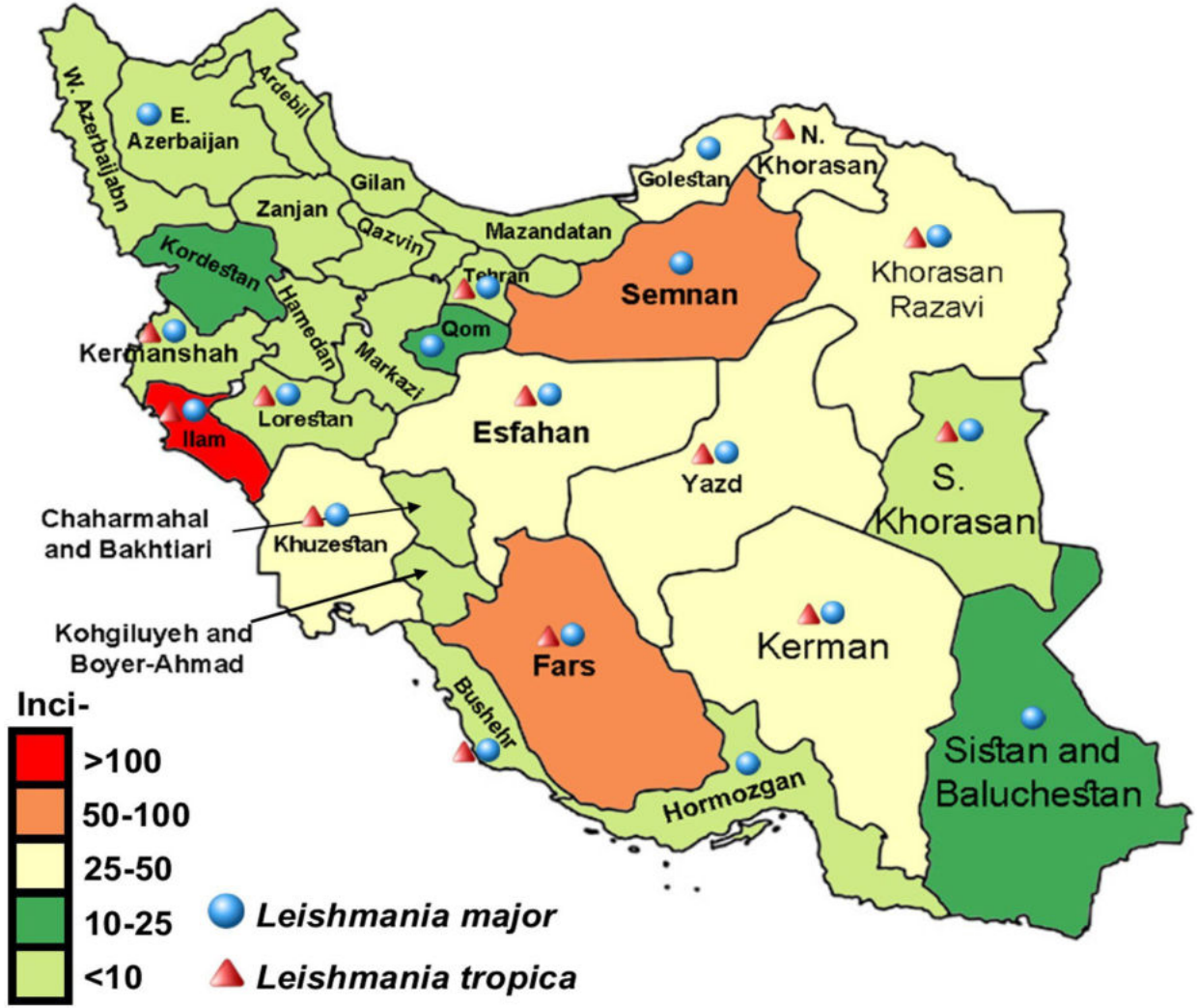
It is essential to understand the risk factors leading to unresponsiveness.

Status of endemicity of cutaneous leishmaniasis (CL) worldwide, 2022 (as reported by November 2023)



Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization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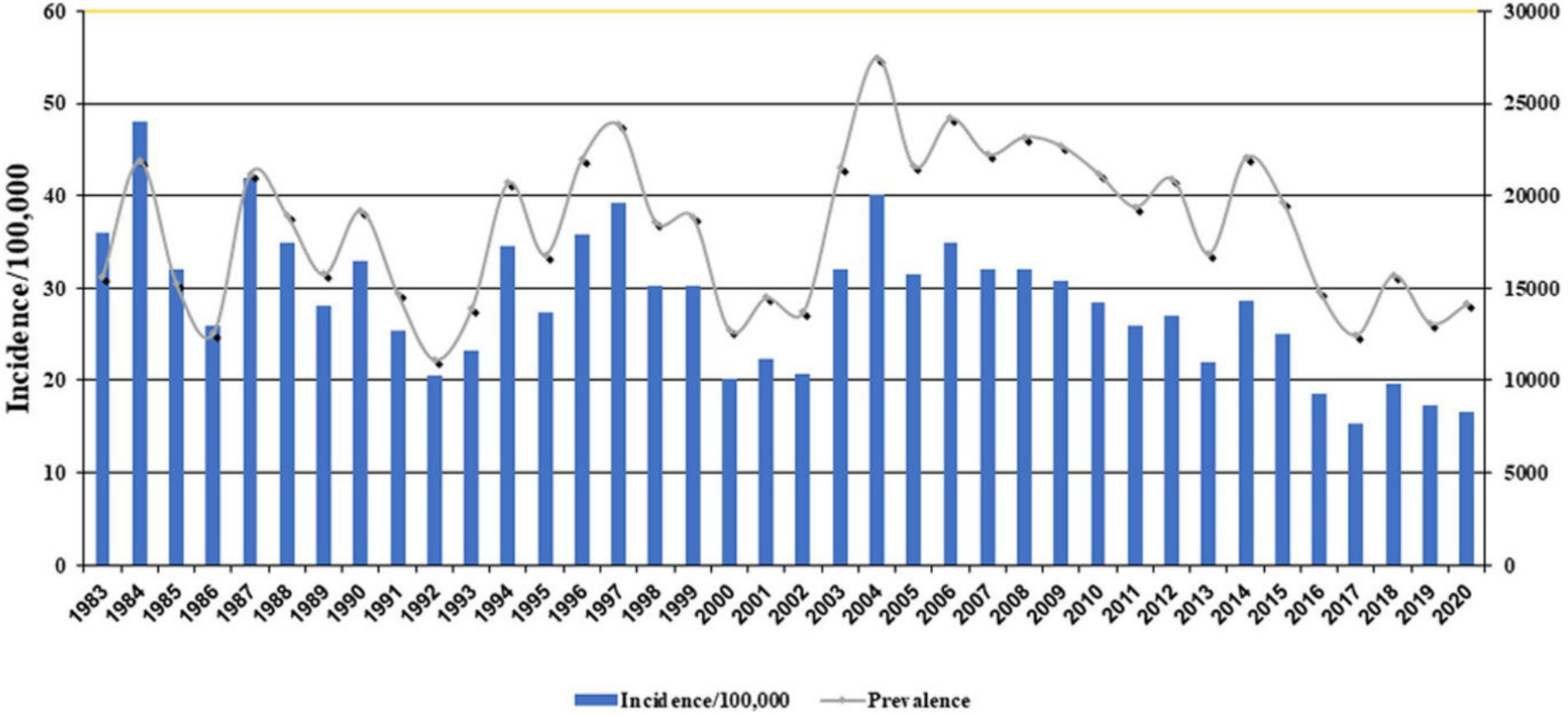
Leishmania major
Leishmania tropica

Incidence and prevalence rates of cutaneous leishmaniasis in Iran, 1983–2020.



Treatment

Pentavalent Antimonials (Gold Standard Treatment)

Two main forms exist: **meglumine antimoniate (MA)** and **sodium stibogluconate**.

- Typical treatment involves **intramuscular (IM)** injection.
- **intralesional (IL)** injections with **biweekly cryotherapy** (liquid nitrogen)

Other Treatments

- **Amphotericin B deoxycholate:** a polyene antifungal administered only in hospitals under supervision.
- **Lipid formulations of Amphotericin B:** such as *liposomal amphotericin B* and *amphotericin B lipid complex*; these have similar cure rates but much lower toxicity and are given by **IV infusion over 2 hours**.
- **Paromomycin:** an aminoglycoside antibiotic administered by **IM injection** or as a **topical cream** for cutaneous leishmaniasis.
- **Miltefosine:** an oral alkyl phospholipid initially developed as an anticancer drug, now used for leishmaniasis; should be taken **after meals** and in **divided doses**.
- **Ketoconazole, Fluconazole, and Itraconazole:** oral antifungal agents with **variable efficacy** in treating leishmaniasis.

Treatment Protocols

1. Intramuscular (IM) Administration:

Dosage: Typically, **20 mg/kg/day** of **MA** is administered **intramuscularly (IM)** for **21–28 days**.

- The standard method for more severe cases or larger lesions
- Treatment duration depending on **patient response** and **severity**

2. Intralesional (IL) Administration:

Dosage: **20 mg/kg** is typically injected into the lesions once a week for up to **12 weeks**.

- For CL, **intralesional (IL) MA** injections are sometimes used.

WHO Protocol and Regional Variations

- The **WHO protocol** provides the framework for treatment
- But countries like **Iran** have tailored the protocol slightly, …
- The administration routes or treatment durations according to **lesion size, location, and number**

Indications for IM vs IL Route

- **Intramuscular (IM) MA** is preferred for cases with **larger lesions** (≥3 cm), **multiple lesions** (>5), or those located near **vital organs**
- **Intralesional (IL) MA (with cryotherapy)** is typically used for localized, less severe cases

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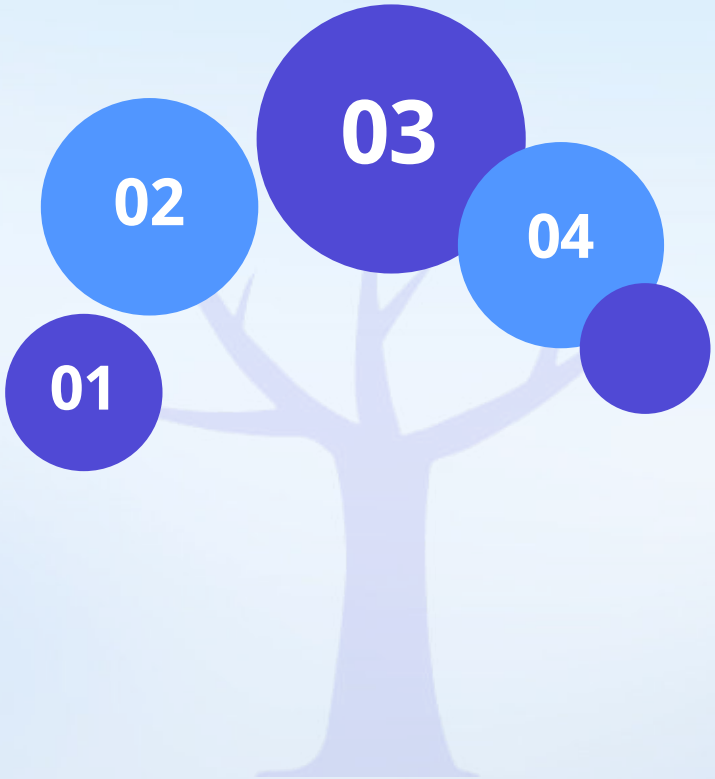
Treatment Resistance Factors

Demographic factors



Age and Gender Factors

Older patients and males show higher unresponsiveness to ACL treatment due to immune impairment and poor adherence.

Socioeconomic Influences

Lower socioeconomic level correlates with delayed treatment seeking and incomplete medication courses, increasing treatment failure risk.

Healthcare Access Condition

Long distance from treatment facilities and inadequate health infrastructure limit effective disease management in endemic regions.

Education Level Impact

A limited understanding of the importance of treatment affects adherence and outcomes in patients with leishmaniasis.

Clinical Factors

Lesion Location and Number

Facial lesions and multiple lesions significantly increase risk of treatment unresponsiveness in ACL patients.

Treatment Timing

Delayed treatment (>4 months) significantly reduces effectiveness and increases drug resistance development.

01 → 02 → 03 → 04

Chronic Disease Impact

Diabetes, opium addiction, and cardiovascular conditions impair immune response, increasing treatment failure risk.

Lesion Characteristics

Size, duration and type of lesion affect treatment outcomes and healing potential.

Poor treatment adherence

1

Patient-related factors

Forgetfulness, life stress, hopelessness, and poor family support impact treatment completion.

2

Healthcare system barriers

Inadequate education, unmanaged complex regimens, and poor provider relationships reduce adherence.

3

Patient-related factors

Long distance to clinics, adverse effects, and irregular treatment schedules decrease compliance.

4

Patient-related factors

Poverty, unstable living conditions, and cultural beliefs affect medication adherence.

Environmental Factors

Poor Housing Conditions

01

Cracks in walls and floors increase sandfly density, leading to higher infection rates.

Waste Management

02

Lack of solid waste disposal creates breeding sites for disease vectors.

Domestic Animals

03

Dogs in homes serve as reservoirs, increasing transmission risk in endemic areas.

Vegetation Proximity

04

Trees near homes provide resting sites for sandflies, increasing exposure risk.

Host immune response variations

Th1 vs Th2 Response

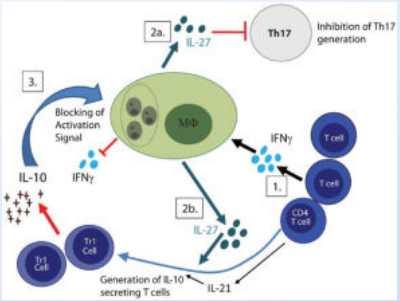
Th1 cytokines provide protection while Th2 cytokines increase susceptibility to leishmaniasis.

Key Protective Cytokines

IL-12, IFN-γ and TNF-α activate macrophages to kill parasites through nitric oxide production.

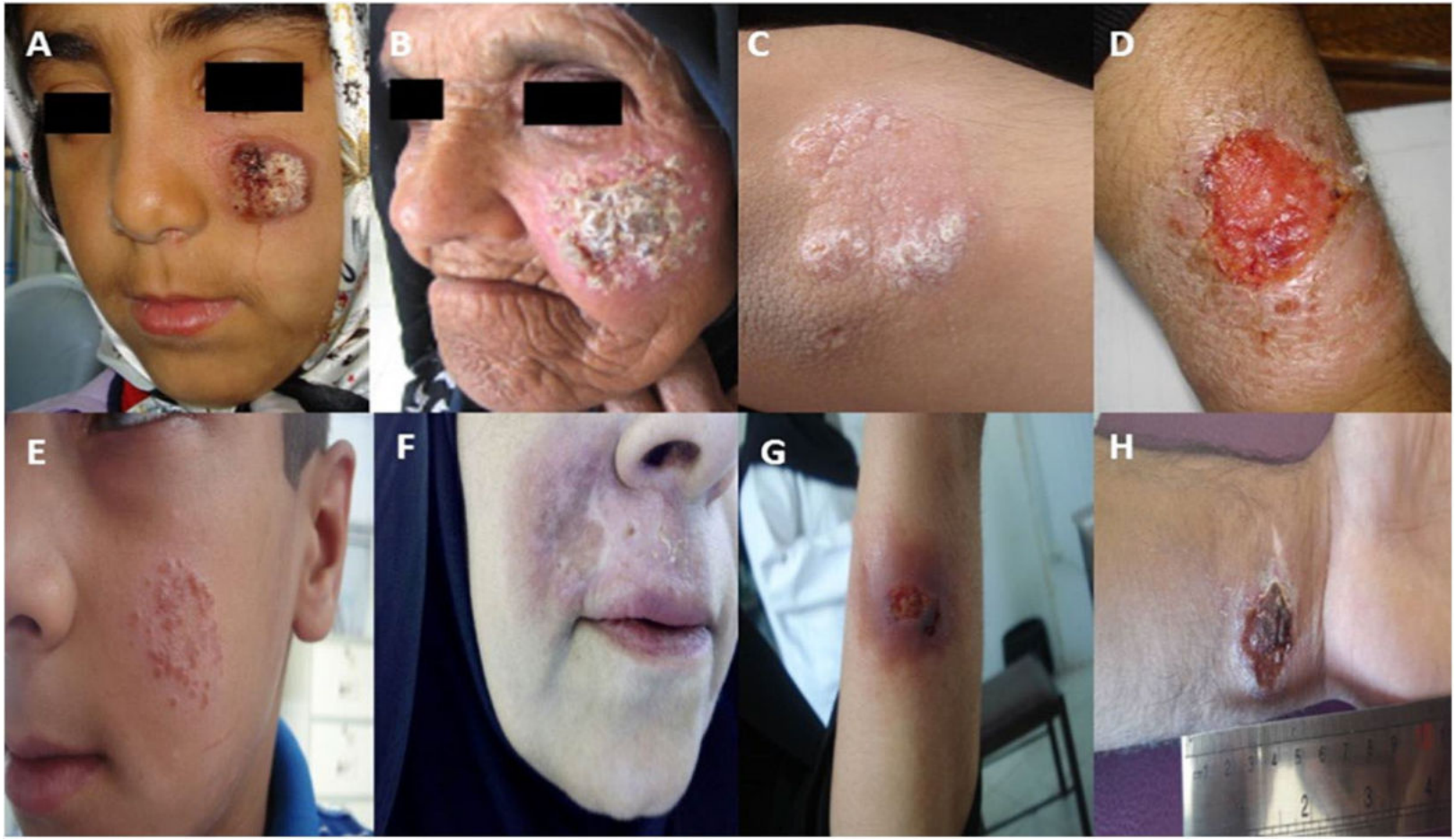
Disease-Promoting Cytokines

IL-4, IL-10 and IL-13 inhibit protective responses and allow parasite persistence.



Multifunctional T Cells

T cells producing multiple cytokines provide better protection than single-cytokine producers.


A
B
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03

Parasite-Related Resistance Mechanisms

Mutations in Parasite

Nucleotide differences

1

Genetic Variations Impact Treatment

Nucleotide differences in ITS1 region linked to unresponsive cases versus responsive patients.

2

Species-Specific Responses

L. tropica shows polymorphisms affecting drug efficacy compared to other *Leishmania* species.

3

Intraspecies Diversity Significance

Genetic heterogeneity within the same species affects clinical presentation and treatment outcomes.

Proper identification guides treatment selection and predicts potential drug resistance cases.

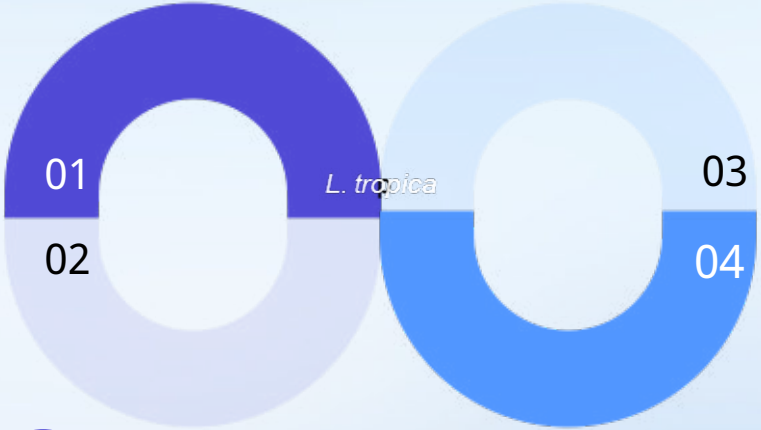
Genetic Make-Up of Parasite

Intraspecies Diversity

Intrspeceis diversity of *L. tropica* affecting treatment outcome and clinical manifestations.

ATP-binding cassette (ABC) Transporters

Membrane proteins help drug efflux, reducing intracellular drug concentration in resistant parasites.



Antimony Resistance Markers

Gene mutations in aquaglyceroporin 1 (AQP1), multidrug resistance protein A (MRPA), γ-glutamylcysteine synthetase (γ-GCS), trypanothione reductase (TR), and thioldependent reductase 1 (TDR1). contribute to drug resistance mechanisms.

Leishmania RNA Virus (LRV)

Viral presence increases inflammatory responses and may contribute to treatment failure.

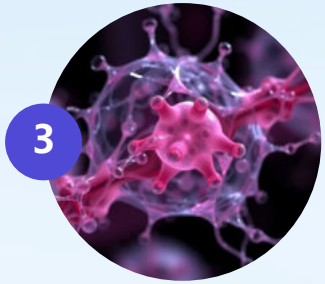
ABC transporters

Role in drug resistance

ABC transporters facilitate drug efflux, reducing intracellular drug concentration and promoting resistance.

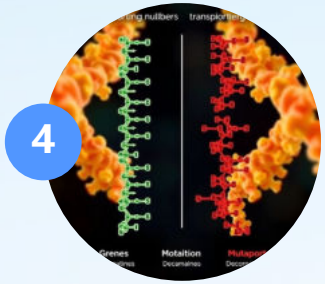
Types

ABCC7, ABCG2, ABCC3, and ABCI4 transporters are linked to antimonial drug resistance.



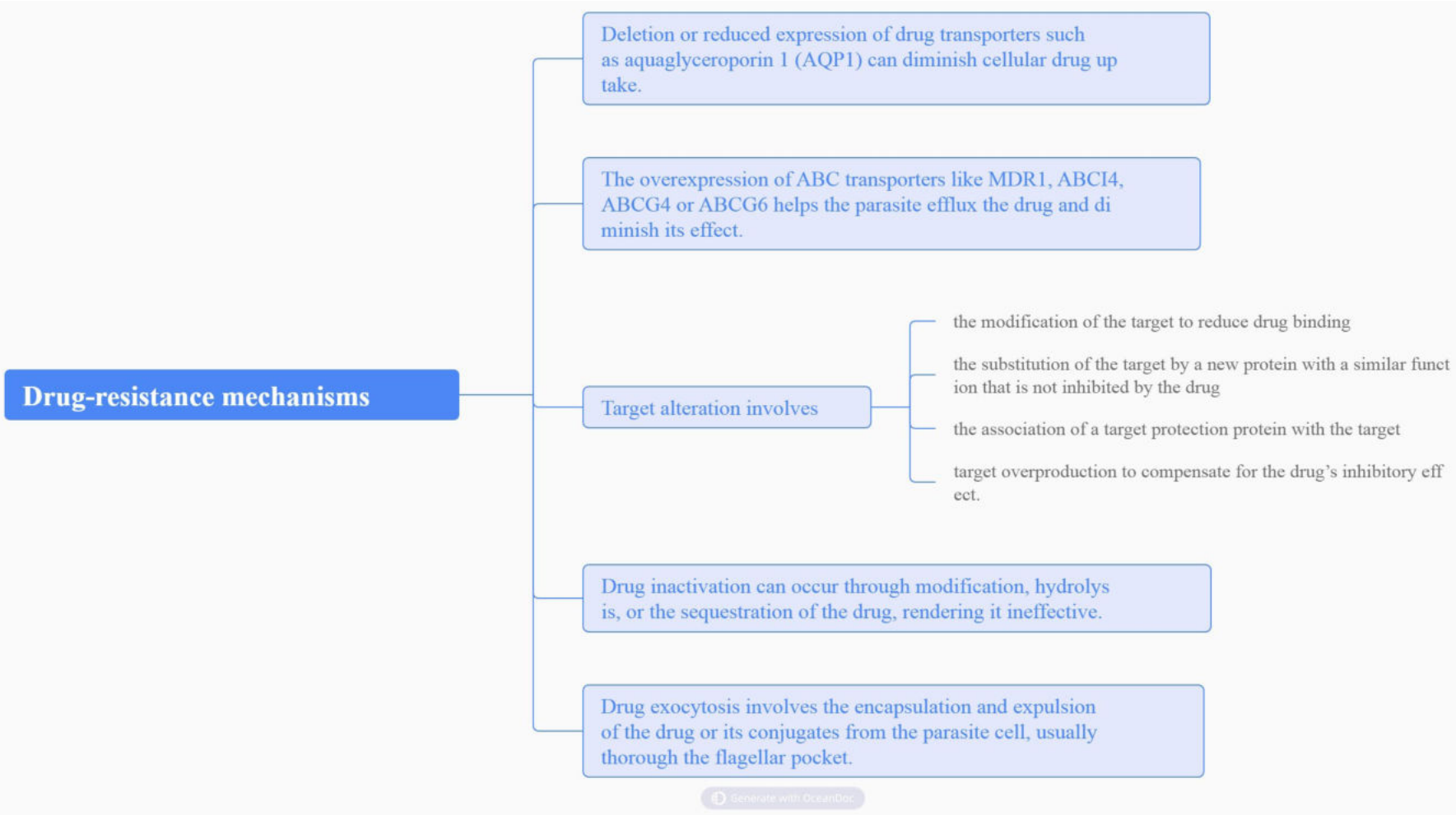
Cellular location

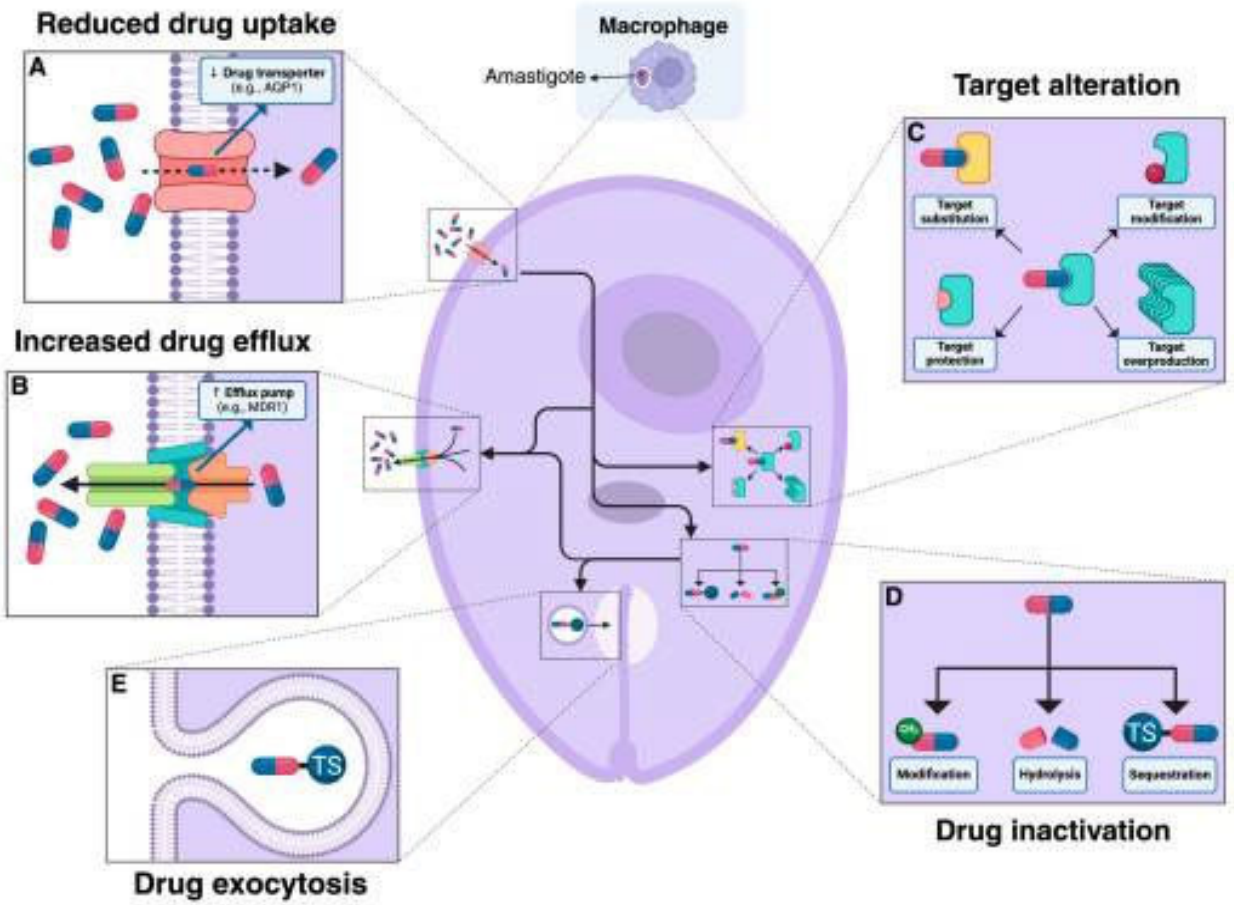
Found in plasma membranes, intracellular vesicles, and near flagellar pockets for drug transport.



Resistance mechanisms

Gene amplification increases transporter numbers, while mutations alter binding capacity and transport efficiency.





Molecular Mechanisms of Drug Resistance in *Leishmania*: Genomic Changes

4

Strategies

Patient Education and Support

Importance of Education

Educating patients about their condition is crucial.

Adherence to Treatment

Importance of adherence to treatment regimens.

Family Support and Resources

Providing support empowers patients and improves outcomes.

Drug Interactions

1 **Pharmacokinetics Alteration**

Co-administration of other medications may alter the pharmacokinetics of leishmaniasis treatments.

2 **Efficacy and Toxicity**

This can lead to reduced efficacy or increased toxicity.

3 **Clinician’s Evaluation Evaluation**

Understanding potential drug drug interactions is critical for critical for optimizing treatment regimens.

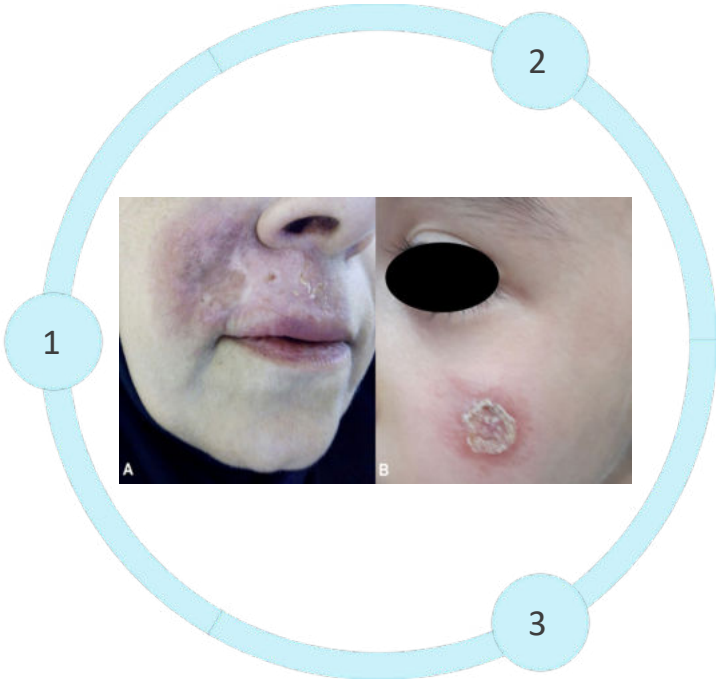
4 **Avoid Adverse Outcomes Outcomes**

Clinicians must evaluate all medications a patient is taking.

Role of Diagnostic Tools

Early Detection and Exact Diagnosis

Essential for effective and suitable treatment.



Innovative Techniques

Techniques like molecular and rapid tests detect resistance.

Timely Treatment

Key to effective management of of cutaneous leishmaniasis.

Global and Local Strategies for Drug Resistance

1

Global Health Initiatives

Manage resources and research research globally.

2

Local Programs

Focus on community-specific educational efforts.

3

Collaborative Approach

Improve the potential for successful successful interventions.

Advance Research on Treatments

- Novel Treatment Methods (Nanomedicines, Gene therapies, …)
- Combination therapy
- Comprehensive clinical trial studies

Animal Models Assist in Drug Resistance Resistance

Pathogenesis Understanding

Animal models assist in comprehending the disease mechanisms.

Preclinical Testing

Provides a platform for testing new therapies before human trials.

Clinical Applications

Guides the application of findings to improve treatment protocols.

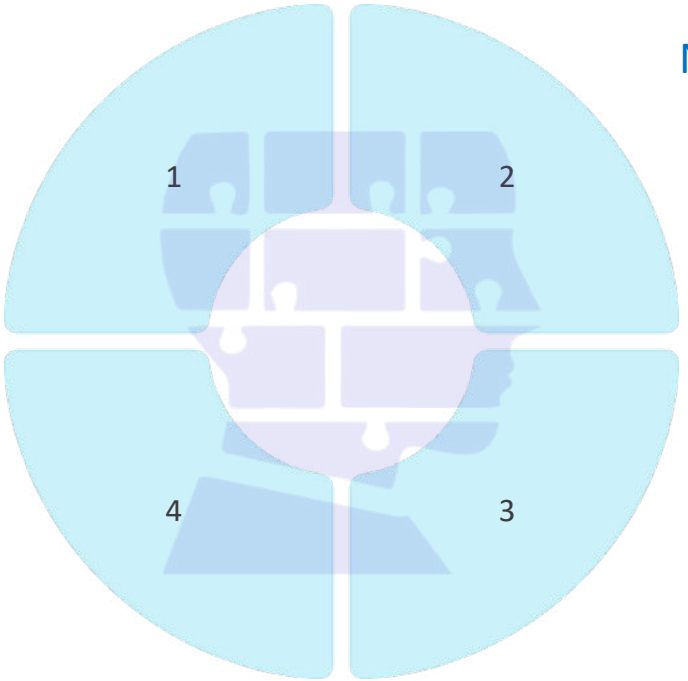
Future Research Directions

Molecular Mechanisms of Resistance

Understanding the mechanisms mechanisms that lead to resistance against therapies.

Research on other related factors

Many unknown factors can contribute to drug resistance.



New Therapeutic Agents

Developing innovative treatments to combat resistance.

Host and *Leishmania* Interactions

Investigating interactions that could reveal new intervention points.

Conclusion and Recommendations Recommendations

Multifaceted Approach

Improved diagnostic methods, patient education, new therapeutic strategies and… .

Understanding Risk Factors

Crucial for formulating effective treatment plans.

Research on Resistance Mechanisms

Identifying key resistance mechanisms is necessary.

Thank you for your attention