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Review Article: Global Clinical and Epidemiological Perspectives on Toxoplasmosis: A Systematic Review of Pathogenesis, Diagnostic Advancements, and Therapeutic Challenges

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Abstract

This systematic review seeks to compile the available knowledge of Toxoplasma gondii pathogenesis, recent diagnostic advances and therapeutic challenges in an effort to provide evidence to clinicians and researchers for their control and prevention of toxoplasmosis. A comprehensive search of the literature was performed in major electronic databases including PubMed, Scopus, and Google Scholar, for articles published from 2010 to 2024. The review emphasized systematic reviews, meta-analyses, and clinical trials relating to the clinical, diagnostic and therapeutic issues in toxoplasmosis. Worldwide toxoplasmosis remains a great challenge to public health and this is reflected in the evolution of diagnostic techniques from traditional serological assays to modern, highly sensitive molecular assays, in particular PCR and IgG avidity assays which are particularly important in the management of infection in pregnancy. However, a major treatment gap exists whereby current anti-Toxoplasma drugs effectively eradicate the acute tachyzoite stages but do not eliminate the endemic, latent bradyzoite cysts, resulting in lifelong infection and reactivation of disease in immunosuppressed hosts. There have been improvements in diagnosis, but there is an urgent need for new drugs to kill every stage of the organism and for a vaccine for humans. Public awareness campaigns and routine screening, especially in pregnant women, will decrease the toll taken each year around the world by this parasite.

Keywords: Toxoplasma gondii, Pathogenesis, Congenital Toxoplasmosis, Serodiagnosis, Antiparasitic Therapy, Zoonosis.

Introduction

Toxoplasma gondii, an obligate intracellular protozoan parasite exhibiting an exceptionally evolutionary success, infect almost all species of warm-blooded **(Al-Malki, 2021)** Originated in 1908, this is probably the most widely studied parasite of concern in the public health screen, due to its unique biology **(Weiss & Dubey, 2009).** Its lifecycle occurs in two phases, a sexual phase, occurring only in felids, and an asexual phase in intermediate hosts, including humans **(Dubey, 2014)**.

Epidemiological data would suggest while the majority of infections are subclinical, toxoplasmosis can be catastrophic clinically in certain cohorts. In pregnant women, primary infection can lead to transplacental transmission resulting in miscarriage, stillbirth, or severe neonatal infection with hydrocephalus and chorioretinopathy **(Mohammed & Hamad, 2023).** Patients with an immunocompromised state such as HIV/AIDS or transplant recipients are susceptible to the reactivation of dormant bradyzoites resulting in fatal toxoplasmic encephalitis **(Vidal, 2019).** Dormancy of tissue cysts for the rest of the host's life is a problem since our current treatments target the tachyzoite stage and not the dormant cyst **(Cerutti *et al*., 2020).** In this review we explore the many facets of toxoplasmosis. Specifically, this review aims to syn thesis current evidence on the pathogenesis, advances in diagnosis and treatment of toxoplasmosis.

Methods

A thorough review of literature was accomplished through an extensive search of major electronic databases which include PubMed, Scopus, ScienceDirect and Google Scholar. The peer-reviewed literature was mainly concentrated from 2010-2024 around the search terms "Toxoplasma gondii", "Pathogenesis", "Congenital Toxoplasmosis" and "Diagnostic strategies". The articles selected primarily gave relevance to clinical outcomes, molecular mechanisms of infection, updates in clinical guidelines. Over 80 high impact articles including meta-analysis and clinical trials, were consolidated to give the evidence based review presented here.

Etiology and Life Cycle

Toxoplasma gondii is highly morphological flexible and exists in three principal infective stages: tachyzoites, bradyzoites and oocysts. The tachyzoite stage, responsible for acute infection and rapid spread; morphologically they are crescent-shaped measuring 4–6 microns in length and 2–3 microns wide **(Al-Malki, 2021).** On Romanowsky's stain, they have pale blue cytoplasm and crimson red nucleus **(Dubey, 2014).**

Bradyzoite, the slowly dividing latent stage within tissue cysts, which are found within the brain, heart, and skeletal muscles, which shield the Toxoplasma from the host's immune response for the entire duration of the host's life **(Cerutti *et al*., 2020).** Oocysts are only produced by the sexual cycle in the cat's intestinal epithelium, which is then sporulated in the environment, resilient to weather extremes and remain infective for months **(Shapiro *et al*., 2019).** The challenge and complexity of the cycle is demonstrated in the five different tissue cyst types (A through E) varying by replication rate and number in cat small intestinal tissues **(Attias *et al*., 2020).** The biological stages of Toxoplasma and the attributes of each that are Zeppelin enjoyed in the clinical environment side, are compared in the below table **(Table 1).**

Table 1: Comparative Characteristics of Toxoplasma gondii Infectious Stages.

Feature	Tachyzoites	Bradyzoites	Oocysts
Morphology	Crescent-shaped (4-6 μ m)	Small, slow-dividing	Oval/Spherical (10-12 μ m)
Replication Rate	Rapid (Acute phase)	Slow (Chronic phase)	Sexual replication (Felids only)
Location	Pseudocysts in various cells	Tissue cysts (Brain/Muscles)	Environment (Soil/Water)
Transmission	Congenital / Blood / Organ	Undercooked meat	Fecal-oral (Cat feces)
Resistance	Low (Destroyed by gastric acid)	High (Survives gastric juices)	Very High (Climate resistant)

The intricate biological parameters of the interplay between definitive cat hosts, the environment, intermediates hosts together with the various horizontal and vertical transmission pathways is described in **Figure 1.**

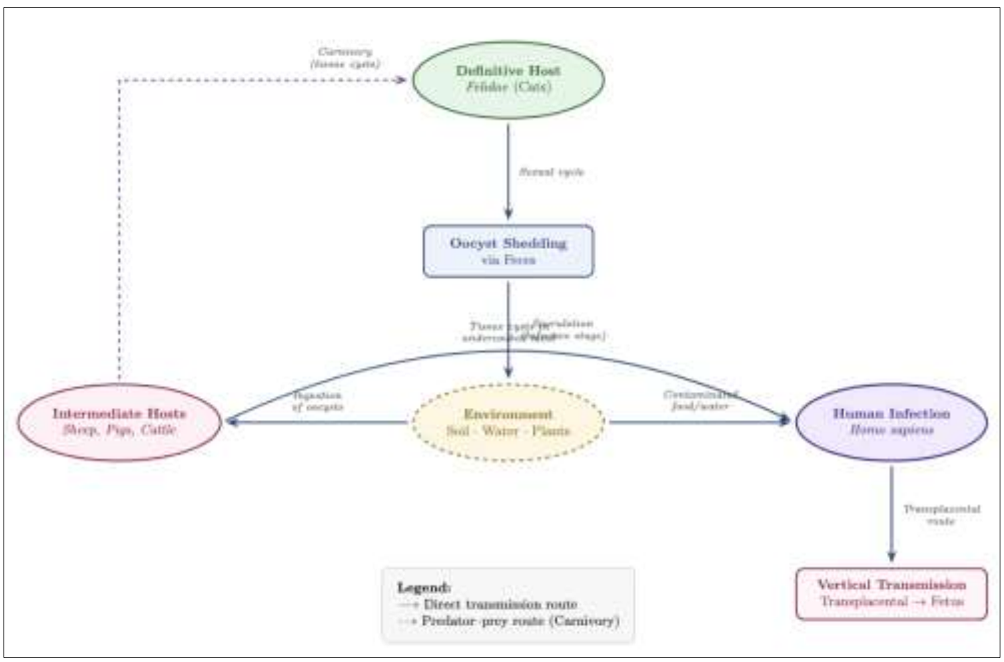

Figure 1: Life cycle and transmission dynamics of Toxoplasma gondii.

The life cycle has two phases, a sexual cycle restricted to the intestinal epithelium of felids (the definitive hosts), and an asexual cycle in warm-blooded intermediate hosts. Cat feces contain unsporulated oocysts, but the feces become infectious (the oocysts sporulated) in a few days **(1–5).** Human infections occurs as a result of: **(1)** Ingesting sporulated oocysts found in contaminated water, soil or fresh vegetation; **(2)** Eating raw or undercooked meat containing encysted tissue, referred to as bradyzoites; **(3)** By vertical (transplacental) transmission from a primarily infected mother to the foetus with the presence of tachyzoites in the placenta. This illustrates the hidden persistence of the parasite in our environment and in the food we eat, helping explain why toxoplasmosis remains a common and insidious zoonosis.

Pathogenesis and Molecular Mechanisms

An exception is T. gondii, which utilises its unique "gliding motility" (having neither cilia or flagella) via a musclar-like actin-myosin motor to penetrate membranes of host cells **(Egarter *et al*., 2014).** After attachment, secretions from apical organelles called micronemes move and enter the cell by secreted “adhesins” **(Kato, 2018).** The parasite then resides in a parasitophorous vacuole preventing it from being lysosomal.

The outcome of clinical disease is determined by the host’s immune response. In an immunocompetent host, a diffuse response including polymorphonuclear neutrophils, monocytes and dendritic cells occurs and limits proliferation of tachyzoites **(Dupont *et al*., 2012).** If the immune system is suppressed (for example in HIV/AIDS), the eventual reactivation of bradyzoites into disseminated tachyzoites leads to fatal necrotic lesions in the central nervous system **(Vidal, 2019).** The parasite also has the ability to breach biological barriers like the blood-brain barrier and the placenta, this is carried out using a mechanism called trans endothelial migration (TEM) in order to achieve systemic infection, **(Furtado *et al*., 2012).**

Transmission Dynamics

Transmission to humans and other warm-blooded animals occurs as follows: Environmental (Fecal-Oral) sporulated oocysts are ingested from soil, water, or fresh food contaminated by cat feces **(Shapiro *et al*., 2019).** Foodborne Consumption of undercooked meat containing viable tissue cysts(intracystic bradyzoites). This mode of infection remains an important source of infection in many peoples because of their meat eating habits **(Almeria & Dubey, 2021).**

- **Vertical (Congenital):** Transplacental transmission occurs if a woman contracts a primary infection during pregnancy. The infection is more likely to cross the placenta the later the pregnancy **(Khan & Khan, 2018).** Congenital infection often results in fetal defects involving the CNS and eyes.
- **Iatrogenic:** In rare cases, organ transplantation (nearly always heart) or blood transfusion has occurred from seropositive to seronegative persons **(Derouin *et al*., 2008).**

Global Epidemiology

The prevalence of T. gondii is more dependent on geography, on the location and socioeconomic and cultural architecture. About 500 million people are infected around the world, with seroprevalence ranging from 10% to more than 80% in parts of Latin America and Africa **(Pappas *et al*., 2009).** Areas of high prevalence are associated with the occurrence of warm humid climates which favour oocyst survival, and the genesis of stray cats population, caused by a vacuum cleaner of cats on site (**Khademvatan *et al*., 2014).** In women of childbearing age the prevalence it is moderate to high in the Middle East thus warranting strong screening programmes to detect the cases showing signs of the condition to avert congenital complications **(Al-Adhroey *et al*., 2019).** The important geographical variation of T. gondii seroprevalence is due to climatic and cultural factors. It is illustrated in summary in the visual synthesis shown in the **Figure. 2** illustrating comparative burden of disease caused by T. gondii pictured across the continents as defined by the major world areas where the data were collected.

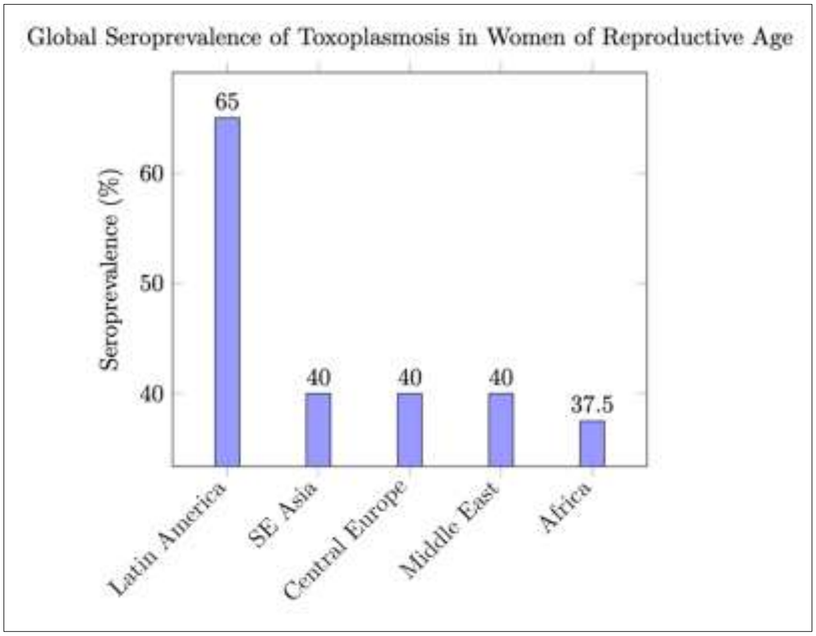

Figure 2 : Global Seroprevalence of Toxoplasmosis Among Women of Reproductive Age Across Different Geographical Regions.

This Figure exemplifies the non-homogeneous distributions of T. gondii infection around the world. For instance, seroprevalence rates in Latin America can reach around 65%, as a function of the suitable environment (for oocyst survival) and large population of stray felids. The Middle East and Central Europe (~40%), which have moderate rates, are linked with cuisine with oocyst-transmission vectors (e.g. undercooked meat) and varying levels of public health awareness. This illustrates the requirement for screening programmes wherever prevalence rates rise over 30% for congenital toxoplasmosis.

Diagnostic Modalities

Early and prompt recognition of the disease is useful in the succeeding sequelae of toxoplasmosis of risk and importance individuals. Serological testing is still the key [2020] and specifically for detection of Immunoglobulin G (IgG) and Immunoglobulin M (IgM): the IgM antibodies where they appear five days to weeks indicating acute infection; while the IgG antibody levels tends to develop later in the disease course, and frequently, remains the remaining of the life span of the host **(Sharifi *et al*., 2019).**

To distinguish between acute and chronic phases, which is important for evidencebased clinical management in pregnancy, IgG avidity testing is carried out. Notably, high avidity index test results presuppose infection at least four months prior, ruling out primary infection occurring in the first trimester **(Teimouri *et al*., 2020).** In terms of prenatal diagnosis, PCR analysis of amniotic fluid has gained ground over cordocentesis based on high sensitivity and relative safety. PCR is recommended to be carried out from 18 weeks' gestation, as earlier testing is associated with false-negative results **(de Oliveira Azevedo *et al*., 2016).** Affected fetal ultrasonography and MRI are done searching for intracranial abnormalities and signs including ventriculomegaly and intracerebral calcifications which are pathognomonic for severe congenital involvement **(LazarteRantes *et al*., 2021).** Clinical diagnosis is therefore based on a mixture of serological and molecular techniques, which has various values and shortcomings as shown in Table 2. Moreover, emerging technologies such as CRISPR-based diagnostic assays are being investigated for their potential to provide rapid and highly specific detection of T. gondii in clinical samples, although they are not yet in routine clinical use.

Table 2: Summary of Diagnostic Methodologies for Toxoplasmosis.

Method	Target	Clinical Application	Advantages	Limitations
IgM Serology	Specific Antibodies	Acute infection detection	Early detection (5-7 days)	May persist for years (false acute)
IgG Avidity	Antibody Binding Strength	Distinguishing acute vs chronic	Reliable in first trimester	Not useful after 4 months
PCR (Amniotic fluid)	Parasite DNA	Prenatal diagnosis (Fetal)	High sensitivity (>90%)	Invasive (Amniocentesis)
Ultrasonography	Fetal morphology	Detecting cerebral damage	Non-invasive	Low sensitivity for early infection
Dye Test (Sabin-Feldman)	Live Parasite	Gold standard (Reference)	High specificity	Requires live parasite/Expertise

In practice, the path from positive screening results to definitive prenatal diagnosis is often labyrinthine. We recommend a structured approach as outlined in the algorithm of **Figure. 3.**

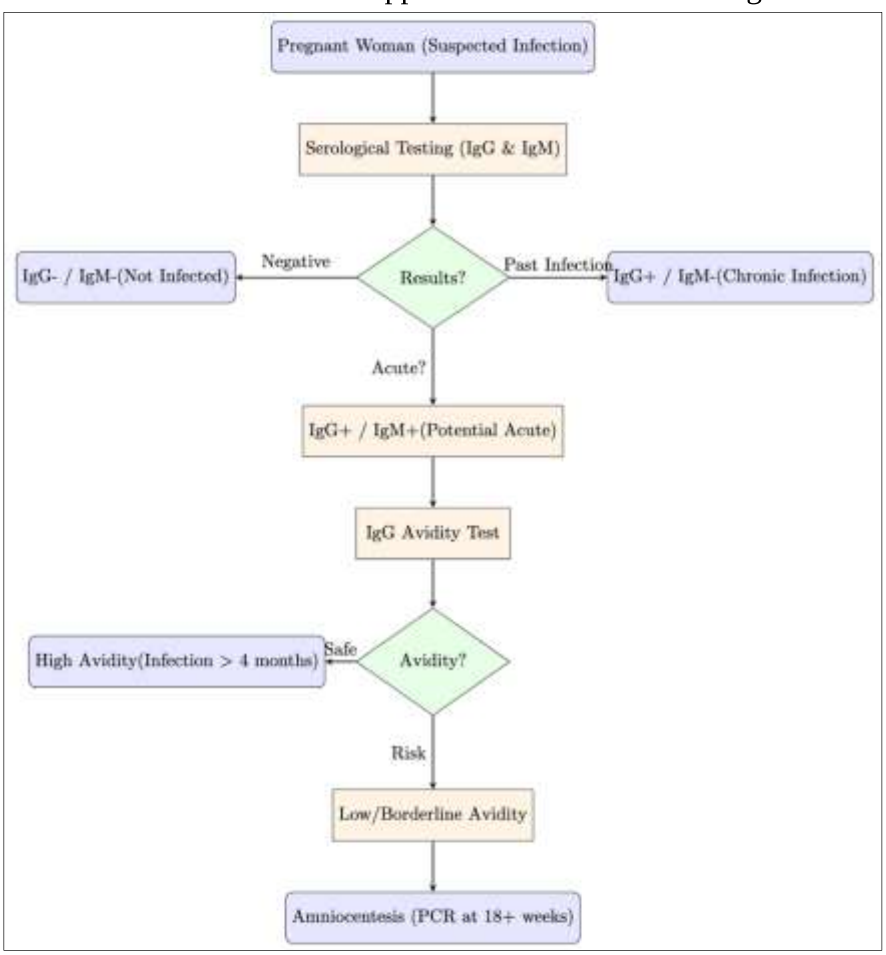

Figure 3: Clinical diagnostic algorithm for the management of suspected Toxoplasma gondii infection during pregnancy.

The Flowchart describes a pragmatic clinical management algorithm for risk stratification of pregnant patients. Initial screening tests involve IgG & IgM serology; if both are negative, there is no previous exposure to the infection and preventive advice must be ongoing. If both are positive IgG+/IgM+, then an IgG Avidity Test is carried out to ascertain the timing of the infection. Where avidity is high the test effectively excludes a primary infection in the last four months & thus reassures in the first trimester. Where avidity is low or borderline there is a potential for acute infection so Amniocentesis/PCR testing after 18 weeks should confirm fetal transmission is occurring.

Current and Emerging Therapeutic Regimens

Therapeutic targeting is focused towards 'acute' active tachyzoite stage within the free-living host. Combined treatment approaches of Pyrimethamine with Sulfadiazine alongside folic acid to reduce the risk of toxoplasmosis and thrombocytopenia by mitigating bone marrow suppression is considered the treatment of choice for acute and congenital infection **(Ben-Harari *et al*., 2017).** Treatment usually requires discontinuation due to side effects involving allergic reactions and/or blood toxicity **(Hopper *et al*., 2019).**

In cases of pregnancy where fetal infection has not yet been established, Spiramycin is administered to reduce the rate of transplacental transmission. When documentable fetal infection is established by PCR or ultrasound, the regimen is usually switched to pyrimethamine-sulfadiazine after the first trimester **(Montoya *et al*., 2021).** In spite of these options, a large clinical gap remains: current drugs do not fully eradicate latent bradyzoite cysts, and recent work into endochin-like quinolones and other dihydrofolate reductase inhibitors show sufficient action against both acute and latent forms where a clear pathway exists to clearing the parasite entirely **(Hopper *et al*., 2019).**

Lastly, investigators have begun looking into the use of nanotechnology for targeted delivery to tissue cysts, but the apparent low-hanging fruit is that of re-purposing existing FDA-approved drugs to find new anti-Toxoplasma agents.

Prevention and Vaccine Prospects

Prevention is preferable to cure in the absence of any commercial human vaccine. The primary prevention is behavioural: do not eat undercooked meat, wash hands thoroughly after playing in soil or handling cat litter, and do not feed house cats raw poultry – feed only heat-treated or processed food **(Hill & Dubey, 2018).**

While a live-attenuated vaccine (Toxovax) exists for veterinary sheep use, humans face challenges in developing a vaccine due to the complex T. gondii antigenic variability and the need for a vaccine that elicits humoral and cell-mediated mucosal immunity **(Al-Malki, 2021).** While experimental models for DNA and recombinant proteins have shown feasibility in murine studies, clinical translation appears non-existent **(Rostkowska *et al*., 2016).**

Conclusion and Future Directions

Epidemiology and consequences of toxoplasmosis worldwide. Toxoplasmosis is an important source of human morbidity worldwide. The use of molecular diagnostics, such as PCR, and the adoption of routine screening for congenital infections are improving the impact of this persistent parasite but the incomplete efficacy of pharmaceutical treatments and the absence of a human vaccine remain significant hurdles for patients. The development of new compound with a less toxic profile and a better understanding of the immunity genetics that cause individuals to be more susceptible to the parasite are vital next steps. Increased public awareness campaigns and providing routine screening for women at risk during pregnancy are imperative in the fight to reduce the global impact of this parasite.

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