Compressive review in Diagnosis and Treatment of Primary Amoebic Meningoencephalitis

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Abstract

Primary Amoebic Meningoencephalitis (PAM) is a rare but rapidly fatal brain infection caused by the thermophilic amoeba Naegleria fowleri. The disease primarily affects healthy individuals exposed to warm freshwater, where trophozoites enter via the nasal cavity and migrate along the olfactory nerve to the brain.

Once in the central nervous system, the amoeba triggers extensive tissue destruction through proteolytic enzymes, pore-forming proteins, and immune evasion strategies.

This review outlines the organism's life cycle, environmental resilience, and genomic plasticity, including the role of extracellular vesicles (EVs) in delivering virulence factors and modulating host immunity. The host's immune response, though rapid, often causes collateral damage through neutrophil infiltration, cytokine storms, and blood–brain barrier disruption.

Diagnostic advancements such as PCR, immunofluorescence, and molecular assays have improved early detection. Treatment remains challenging, relying on early administration of amphotericin B, miltefosine, and azole antifungals, supported by intensive neurocritical care.

Emerging nanomedicine-based delivery systems offer promise for targeted, less toxic therapies. Preventive strategies emphasize public education, safe water practices, and environmental monitoring.

Introduction :-

Primary Amoebic Meningoencephalitis (PAM) is a rare but highly fatal infection of the central nervous system caused by the free-living amoeba *Naegleria fowleri*. First identified in 1965, PAM typically affects healthy individuals—especially children and young adults—after exposure to warm freshwater environments such as lakes, hot springs, or inadequately chlorinated pools. The amoeba enters through the nasal passages and migrates along the olfactory nerve to the brain, where it triggers severe inflammation, tissue destruction, and cerebral edema.

Clinically, PAM resembles bacterial meningitis, presenting with fever, headache, nausea, and altered mental status. This similarity often leads to delayed or incorrect diagnosis, which contributes to its extremely high mortality rate—over 95% in reported cases. Traditional diagnostic methods like CSF microscopy and culture are slow and insensitive. In contrast, molecular techniques such as PCR, real-time PCR, and LAMP have improved detection speed and accuracy.

Treatment remains challenging. Amphotericin B is the primary drug used, but survival is rare unless therapy begins early. Recent case reports suggest that combining amphotericin B with miltefosine, azole antifungals, and supportive measures like therapeutic hypothermia may improve outcomes. However, these approaches are still under investigation and lack standardized protocols.

1. Life Cycle of Naegleria fowleri

Naegleria *fowleri* is a thermophilic, free-living amoeba that thrives in warm freshwater environments. Its life cycle includes three morphologically and functionally distinct stages: **trophozoite**, **flagellate**, and **cyst**. These stages allow the organism to adapt to environmental fluctuations and facilitate both survival and infection.

I] Trophozoite Stage (Feeding and Infective Form):-

- The **trophozoite** is the active, amoeboid form responsible for feeding, reproduction, and tissue invasion.

- It measures approximately 10–25 µm and moves via eruptive pseudopodia.
- Trophozoites reproduce asexually through **binary fission**, typically every 2–3 hours under optimal conditions (35–45°C).
- In the environment, they feed on bacteria and organic debris. In humans, they invade the nasal mucosa and migrate along the olfactory nerve to the brain, causing **Primary Amoebic Meningoencephalitis (PAM)**.
- This is the **only form found in human tissues** and is responsible for the disease's pathogenesis.

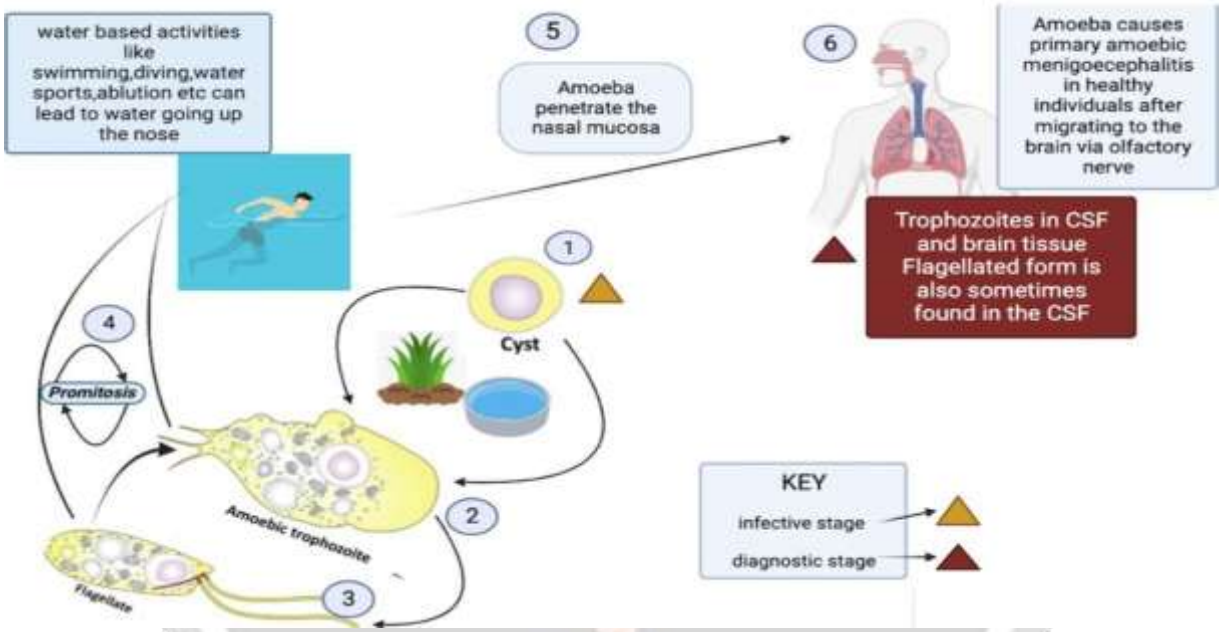

Fig.1:- Life cycle and Transmission on Naegleria Fowleri

II] Flagellate Stage (Motile Transitional Form):-

- Under **sudden ionic or nutrient stress**, trophozoites can transform into a **biflagellate form** within 1–2 hours.
- This stage is **pear-shaped**, motile, and non-feeding, allowing the organism to relocate in search of more favorable conditions.

III] Cyst Stage (Dormant and Resistant Form):-

- In response to **adverse environmental conditions** such as desiccation, cold temperatures, or nutrient depletion, trophozoites encyst.
- The **cyst** is spherical (7–15 µm), with a **double-walled structure** that provides resistance to environmental stress.
- Cysts are **non-motile and non-infective**, serving as a survival mechanism during unfavorable conditions.

2. Environmental impact on Naegleria fowleri

- Naegleria fowleri thrives in warm, shallow freshwater and biofilm-rich sediments; temperature is the main driver, with growth favoured up to ~45°C. Dense bacterial prey and biofilms supply nutrients and protective niches, increasing trophozoite numbers. Water chemistry and osmotic shifts influence stage transitions (flagellation, encystment), while stagnant or poorly circulated water concentrates heat and microbes.

- Human factors poorly maintained pools, warm domestic water systems, and use of untreated water for nasal rinsing create additional risk sites. Cysts enable persistence through unfavourable periods and resist mild disinfection.

3. Genomic characteristics and extracellular genetic elements

Naegleria fowleri has a compact, dynamic eukaryotic genome with conserved core genes and a flexible accessory genome that varies between environmental and clinical isolates. Key features include:

• **Nuclear genome**

Encodes metabolic pathways, cytoskeletal and motility proteins, expanded families of proteases, pore-forming and secreted adhesion proteins associated with tissue invasion and virulence.

• **Mitochondrial genome**

Circular, gene-rich, useful for phylogenetics and species identification; shows adaptations consistent with a thermophilic lifestyle.

• **Genome plasticity**

Presence of repetitive elements, gene duplications, and signatures of horizontal gene transfer from bacteria and other microbes, reflecting its bacterivorous ecology and contributing to an open pan-genome.

• **Research and diagnostic implications**

Genomic and EV markers inform species-specific PCR targets, candidate virulence determinants, and potential biomarkers; expanded sequencing and functional studies are needed to link variation to pathogenicity.

4. Infection and route of infection:-

Naegleria fowleri causes infection when its trophozoite form the active, feeding stage enters the human body through the nasal passages, typically during recreational or occupational exposure to warm freshwater. This includes swimming, diving, or using contaminated tap water for nasal irrigation (e.g., neti pots).

1. Initial Exposure

- The amoeba is commonly found in geothermal waters, hot springs, lakes, rivers, and poorly chlorinated pools.
- Infection does not occur through drinking water; it requires direct contact with the nasal mucosa.

2. Nasal Invasion

- Once inside the nasal cavity, *N. fowleri* adheres to the olfactory epithelium, a specialized tissue responsible for smell.
- Using proteolytic enzymes and amoeboid movement, the trophozoites penetrate the mucosal barrier.

3. CNS Invasion and Disease Onset

- Once in the brain, *N. fowleri* multiplies rapidly and releases cytolytic enzymes, causing necrosis, inflammation, and cerebral edema.

- The resulting condition, Primary Amoebic Meningoencephalitis (PAM), typically manifests within 2–5 days of exposure and progresses rapidly to coma and death if untreated.

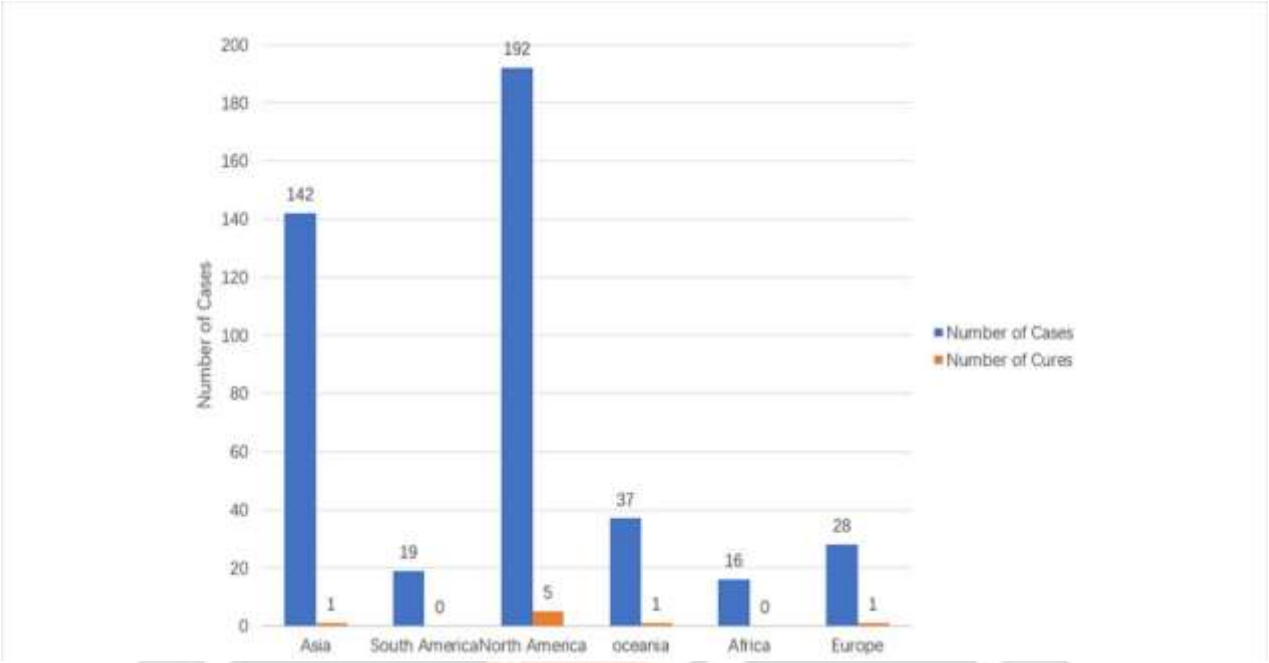

Fig.2 :- The number of N. fowleri cases and cure status in various continents from 1937 to 2024

5. Mechanism of Naegleria fowleri entry into the central nervous system

Naegleria fowleri infection begins when warm, trophozoite-containing water introduced into the nasal cavity The trophozoite is the invasive stage and the main actor in CNS entry.

- **Attachment and mucosal interaction**

  Trophozoites adhere to the olfactory epithelium using surface adhesins and lectin-like molecules. They exploit mucosal micro abrasions and attach tightly to epithelial cells, resisting mucociliary clearance.

- **Epithelial breach**

  Through directed amoeboid movement and secretion of hydrolytic enzymes (proteases, phospholipases) and pore-forming proteins, trophozoites degrade epithelial barriers and extracellular matrix components, enabling transepithelial penetration.

- **Perineural migration across the cribriform plate**

  After crossing the mucosa, trophozoites migrate along olfactory nerve bundles and perineural spaces in the lamina propria.

Mechanisms of immune evasion by Naegleria fowleri

Naegleria fowleri employs a coordinated set of strategies that allow rapid establishment in the nasal mucosa and swift transit to the CNS, often before effective host immunity is generated.

Surface adhesion and concealment Trophozoites express surface adhesins, glycoconjugates, and mucin-binding factors that promote firm attachment to the olfactory epithelium and resist mucociliary clearance. Tight adhesion

both anchors the parasite at the invasion site and reduces exposure of key pathogen-associated molecular patterns to epithelial pattern-recognition receptors, delaying innate detection.

Enzymatic disruption of barriers and immune factors the amoeba secretes a broad array of hydrolytic enzymes (serine and cysteine proteases, metalloproteases, phospholipases) that degrade extracellular matrix, epithelial junctional proteins, complement components, and immunoglobulins. Proteolytic cleavage of these host molecules impairs opsonization, complement-mediated lysis, and neutrophil/macrophage function locally.

Pore-forming toxins and direct cytolysis Pore-forming proteins and cytolysins produced by trophozoites create membrane lesions in host cells, including epithelial cells and recruited immune effectors. This direct killing or paralysis of neutrophils and macrophages reduces phagocytic clearance and local antimicrobial activity.

➢ **Pathogenic mechanism of Naegleria fowleri**

Naegleria fowleri, a free-living thermophilic amoeba, causes Primary Amoebic Meningoencephalitis (PAM), a rapidly fatal infection of the central nervous system. The disease progresses swiftly due to the organism's ability to invade neural tissue and trigger intense inflammation.

The following mechanisms explain how *N. fowleri* initiates and sustains infection:

1. Disruption of the Blood-Brain Barrier

Once in the brain, *N. fowleri* secretes proteolytic enzymes—such as phospholipases, cysteine proteases, and metalloproteinases—that degrade extracellular matrix components and compromise the blood-brain barrier. This facilitates deeper tissue invasion and exposes the brain to inflammatory mediators.

2. Cytotoxic Effects on Neural Cells

The trophozoites exert direct cytotoxicity by releasing pore-forming proteins (e.g., amoebapores) and inducing apoptosis in neurons and glial cells. These molecules disrupt cell membranes, leading to necrosis and widespread brain damage.

3. Induction of Severe Inflammation

The presence of *N. fowleri* in the CNS triggers a massive inflammatory response. Activated microglia and astrocytes release cytokines such as TNF-α, IL-1β, and IL-6, which amplify tissue damage. Neutrophils infiltrate the brain but are often ineffective due to the amoeba's resistance to phagocytosis and its ability to kill immune cells upon contact.

4. Immune Modulation and Evasion

N. fowleri modulates host immunity by suppressing protective cytokines and promoting antiinflammatory signals like IL-10. It also resists complement-mediated lysis and avoids phagocytosis through rapid motility and cytotoxic interactions with immune cells.

6. Rapid Proliferation and Spread

The amoeba replicates quickly in the brain, doubling every few hours under optimal conditions. This rapid growth overwhelms host defenses and leads to diffuse cerebral edema, hemorrhage, and death within days of symptom onset.

6. Brain tissue damage driven by the host immune response

Host immunity to Naegleria fowleri is rapid but dysregulated; much of the brain injury in primary amoebic meningoencephalitis (PAM) arises from an intense, uncontrolled innate inflammatory response rather than direct amoebal action alone.

- Early neutrophil recruitment and collateral injury Infection elicits a massive neutrophil influx into the olfactory bulbs and meninges.
- Activated neutrophils release proteases, matrix metalloproteinases, and reactive oxygen species that damage blood brain barrier (BBB) components and parenchymal cells, producing haemorrhage and necrosis.
- Blood–brain barrier disruption and edema

Proteolytic enzymes and inflammatory mediators increase BBB permeability, permitting plasma proteins and immune cells into brain parenchyma. Resulting vasogenic edema and raised intracranial pressure cause secondary ischemia and widespread neuronal injury.

- Cytokine storm and microglial activation

High local concentrations of proinflammatory cytokines (IL-1, TNF-α, IL-8 and others) activate microglia and amplify leukocyte recruitment. Microglial and macrophage activation releases neurotoxic mediators that contribute to neuronal apoptosis and synaptic dysfunction.

- Complement activation and bystander damage

Complement deposition occurs but is incompletely protective; complement fragments and membrane attack complex formation can damage host membranes and exacerbate inflammation when not tightly regulated.

- Impaired phagocytic killing and frustrated phagocytosis

Neutrophils and macrophages often fail to clear trophozoites effectively; frustrated phagocytosis releases lytic enzymes and oxidants into the tissue, increasing collateral damage without eliminating the pathogen.

- Microvascular thrombosis and ischemic injury

Inflammation and endothelial injury promote microthrombi formation, further reducing perfusion and causing focal ischemic necrosis that compounds amoebal cytolysis and edema-related harm.

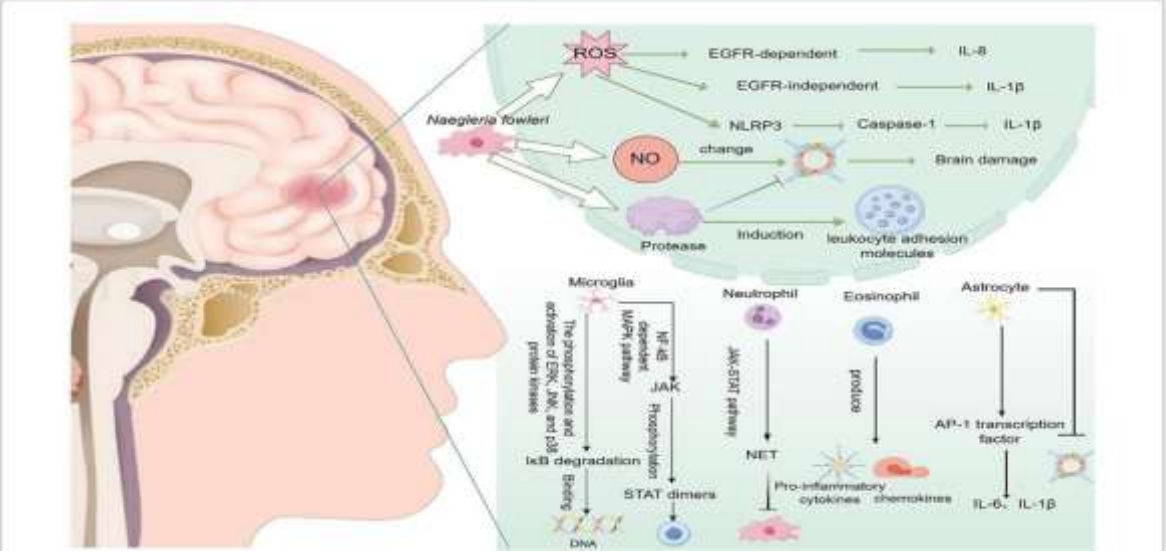

Fig.3 : - Inflammation and Brain damage caused by N. fowleri

entering Central Nervous System.

- Net effect on clinical course

The combined effect direct amoebal cytolysis plus overwhelming inflammatory collateral damage produces rapid, haemorrhagic necrotizing meningoencephalitis with high intracranial pressure and poor outcomes despite immune activation.

Immune cells and inflammatory factors mediating brain tissue injury in PAM

Host inflammatory responses to Naegleria fowleri drive much of the neuropathology in primary amoebic meningoencephalitis through rapid recruitment and activation of leukocytes, release of cytotoxic mediators, and disruption of neurovascular integrity.

- Neutrophils first responders that cause collateral damage

Massive neutrophil influx into the olfactory bulbs and meninges releases proteases, myeloperoxidase, and reactive oxygen species; these mediators degrade extracellular matrix and endothelial junctions, promoting haemorrhage and necrosis rather than effective parasite clearance.

- Cytokine and chemokine storm

High local levels of IL-1, TNF-α, IL-8 and other chemokines drive sustained leukocyte recruitment and vascular permeability, fuelling vasogenic edema and intracranial hypertension that are central to clinical deterioration.

- Complement and frustrated phagocytosis

Complement activation occurs but is often inadequate; deposited complement fragments and sub lytic membrane attack complexes can damage host cells. Phagocytes that cannot ingest trophozoites release lytic enzymes extracellularly, increasing bystander tissue damage.

- Blood–brain barrier breakdown and vascular effects

Proteolytic enzymes and inflammatory mediators disrupt the BBB, allowing plasma proteins and immune cells into the parenchyma; this vasogenic edema, combined with microvascular thrombosis from endothelial injury, produces ischemia and amplifies necrosis.

7. Potential role of extracellular genetic elements in Naegleria fowleri pathogenicity

1. Mediators of Host-Pathogen Communication

EVs released by N. fowleri may act as messengers that modulate host cell behaviour even before direct contact occurs. These vesicles can carry extracellular RNAs, small non-coding RNAs, and regulatory proteins that influence host immune responses, potentially dampening inflammation or altering cytokine signalling to favor amoebic survival.

2. Delivery of Virulence Factors

Proteomic analyses of *N. fowleri* EVs have identified cytolytic enzymes, such as cysteine proteases and phospholipases, which are known to degrade host tissues. These enzymes, when delivered via EVs, may facilitate tissue invasion, blood-brain barrier disruption**, and** neuronal damage without requiring direct amoebic contact.

3. Immune Evasion and Modulation

EVs may help *N. fowleri* evade immune detection by masking surface antigens or delivering immunomodulatory molecules that suppress host defenses. This strategy is similar to what has been observed in other protozoan pathogens like Leishmania and Trypanosoma, suggesting a conserved role for EVs in parasitic immune evasion.

4. Horizontal Gene Transfer Potential

Although not yet fully established in *N. fowleri*, extracellular vesicles in other eukaryotic microbes have been implicated in horizontal gene transfer. If *N. fowleri* EVs carry DNA or RNA capable of integrating into host or microbial genomes, they could contribute to genetic adaptation, virulence evolution, or antimicrobial resistance.

Diagnostic methods for Naegleria fowleri

1. Specimens and basic tests

Cerebrospinal fluid (CSF) is the primary specimen. Initial CSF testing includes wet-mount microscopy of fresh, unfixed CSF to look for motile trophozoites and routine CSF biochemistry (marked neutrophilic pleocytosis, high protein, low glucose) that mimics bacterial meningitis.

2. Molecular confirmation

Species-specific PCR on CSF or brain tissue is the principal confirmatory test available at specialized/reference labs; it is rapid and sensitive for detecting N. fowleri DNA.

3. Immunologic and histopathologic methods

Immunofluorescence or immunohistochemistry on tissue or CSF sediments can detect amoebal antigens and support diagnosis when available.

Diagnostic methods	Types of specimens	Advantages	Limitations
Direct microscopic examination	CSF	Preferred, most direct, and fastest	Low detection rate
Culture	CSF Blood	In hypotonic water, *N. fowleri* rapidly transforms into a flagellate	Time-consuming
Computed tomography (CT), Magnetic resonance imaging (MRI)	Intracranial structures and tissues	In late-stage PAM, it can be used to assess brain damage and guide treatment	Non-specific and no abnormalities in early infection
Immunohistochemical (IHC) staining Indirect immunofluorescence (IIF) staining	Brain tissue	High specificity, high sensitivity, localization, qualitative, and quantitative analysis	There are cross-reactions between species, and there are no specific antibodies
Enzyme-linked immunosorbent assay (ELISA)	Serum	Convenient and fast	Low sensitivity and specificity, not suitable for timely diagnosis
polymerase chain reaction (PCR)	CSF Tissue Blood	Highly specific, sensitive, and rapid	Requires clinical suspicion of PAM
Metagenomic next-generation sequencing (mNGS)	CSF Blood	Rapid, accurate, and capable of diagnosing most rare diseases	Expensive, time-consuming, and susceptible to contamination
Matrix-assisted laser desorption/ ionization-time of flight mass spectrometry (MALDI-TOF MS)	Brain tissue	No need for prior culture or subculture, convenient, rapid, and accurate	High technical and sample requirements, and expensive instrumentation

Table.1 :- Diagnostic methods for N. fowleri and their advantages and disadvantages.

8. Current status of treatment for Naegleria fowleri infection

Clinical outcome remains poor; only a very small number of well-documented survivors exist, so early recognition and immediate aggressive therapy remain critical.

- Antimicrobial strategy

Treatment is empirical and combination-based rather than single-agent. Regimens used in survivors and recommended by reference centres include intravenous amphotericin B (with intrathecal amphotericin B in some cases), miltefosine (oral/IV where available), and azole antifungals (for example fluconazole, posaconazole) often given together with other agents such as rifampin; these drugs have shown in vitro anti-amoebic activity and are used in multi-drug protocols.

- Supportive and neurocritical care

Aggressive management of intracranial pressure (osmotherapy, CSF drainage, hyperosmolar therapy, possible decompressive surgery), seizure control, airway/ventilatory support, and hemodynamic stabilization are essential adjuncts that materially affect survival chances.

- Role and access of miltefosine

Miltefosine has become a key component in modern regimens because of demonstrated activity and inclusion in multiple survivor cases; public-health agencies and reference labs can assist with rapid access and dosing guidance when suspected PAM is identified.

- Adjunctive and experimental approaches

Investigational strategies under study include novel amoebicidal compounds, combinations optimized in vitro and animal models, and adjunctive therapies aimed at limiting injurious inflammation or targeting specific virulence mechanisms; however, clinical evidence for these approaches is limited and they remain investigational.

- Practical clinical workflow

Because treatment is time sensitive, clinicians should promptly suspect PAM in compatible cases (freshwater nasal exposure with fulminant meningoencephalitis), start supportive care, perform immediate diagnostic sampling (CSF), and contact national/reference public-health.

Nanomedicine delivery systems for Naegleria fowleri

Nanomedicine offers ways to concentrate amoebicidal agents at the olfactory mucosa, perineural spaces, CSF, and brain while reducing systemic toxicity—critical for a fast-progressing CNS infection like PAM.

Rationale and strategic goals

- Enhance rapid local drug levels at the nose-to-brain route and in CSF to outpace trophozoite replication.
- Improve penetration across nasal epithelium, perineural pathways, and the blood–brain barrier (BBB).
- Deliver combination cargos (small molecules, lipophilic drugs, siRNA/antisense, protease inhibitors) and enable controlled release to sustain amoebicidal concentrations.
- Reduce systemic toxicity (e.g., amphotericin B nephrotoxicity) and allow lower effective doses through targeted delivery.

Candidate nanocarriers and payloads

- Lipid nanoparticles and liposomes — encapsulate amphotericin B, miltefosine, or azoles to improve solubility and CNS uptake; ionizable LNPs also suit nucleic-acid cargos (siRNA/ASO targeting virulence genes).
- Polymeric nanoparticles (PLGA, PEGylated) — for sustained intranasal or intrathecal release of antiparasitic or protease inhibitors.
- Solid lipid nanoparticles and nano emulsions — suitable for terpene or hydrophobic natural product payloads that have shown anti-amoebic activity in vitro.
- Inorganic nanoparticles (iron oxide, gold) — dual therapeutic and imaging

  (theragnostic) roles; potential for photothermal adjuncts in preclinical settings.

Routes of administration and targeting tactics

- Intranasal (nose-to-brain) delivery — primary strategy to reach olfactory mucosa and perineural spaces quickly; formulations should Favor mucopenetration, mucoadhesion control, and neuronal uptake.
- Intrathecal or intraventricular instillation — direct CSF delivery for severe/advanced disease when rapid, high CSF concentrations are required; nanocarriers can prolong residence time and lower dosing frequency.
- Intravenous with BBB-targeting ligands — receptor-mediated targeting (transferrin, insulin, or peptide ligands) to enhance crossing into affected brain regions if systemic delivery is chosen.

Preclinical evidence and examples

- Nanoparticle–terpene fusion systems have shown in vitro and initial in vivo promise against N. fowleri, demonstrating improved amoebicidal potency over free compounds in experimental models.
- Recent reviews and experimental reports outline using nanoparticles and artificial peptides to target N. fowleri virulence mechanisms and improve delivery of known antiparasitic, emphasizing intranasal platforms and EV-based strategies as promising avenues.

Safe nasal hygiene

- For nasal rinsing (neti pots, sinus irrigation), use only distilled, sterile, or previously boiled (then cooled) water; tap water should be boiled for 1 minute (3 minutes at higher elevations) then cooled before use.
- If distilled/sterile water is not available, disinfect tap water by boiling or using appropriate filter devices labelled to remove parasites before using for nasal irrigation.

Pools, spas and domestic water systems

- Use properly maintained and chlorinated pools/spas; poorly maintained or untreated pools and spas are higher risk.
- Avoid inhaling or forcefully aspirating water from home plumbing (for example during swimming pool filling, water slides, or manual nasal rinsing with untreated tap water) in areas with warm freshwater sources follow local public-health guidance if unusual cases occur.

Public-health and situational awareness

- Heed local advisories about water quality and avoid freshwater recreation in sites with warnings or known algal/bacterial blooms; report unusual illnesses after freshwater exposure to health authorities promptly.

- Educate high-risk groups (children, frequent freshwater swimmers, waterpark users) about simple preventive actions: nose clips, avoiding submersion, and safe nasal rinsing practices.

Future perspectives for Naegleria fowleri research and control

Research and clinical responses are shifting from reactive case management toward proactive, multidisciplinary programs that combine faster diagnostics, targeted therapeutics, delivery innovation, and public-health preparedness to improve the dismal outcomes of PAM.

9. Diagnostics and surveillance

- Prioritise rapid, point-of-care molecular tests and standardized CSF/mucosal EV-RNA panels to shorten time to definitive diagnosis; scalable metagenomic and targeted PCR workflows should be integrated into regional reference networks for rapid routing and reporting.
- Expand environmental surveillance (high-risk recreational waters) using sensitive molecular assays and EV/DNA markers to enable preventive advisories and focused remediation in hotspots.

Therapeutics and rational drug development

- Move from empiric multi-drug regimens to structure-guided, target-based compounds that inhibit validated amoebal targets (proteases, pore-forming proteins, unique metabolic enzymes) with demonstrated CNS safety profiles.

Delivery innovations and adjunctive strategies

- Develop intranasal and intrathecal nano delivery platforms (LNPs, polymeric nanoparticles, EV-mimetics) to achieve rapid, high local drug concentrations in the olfactory mucosa/CSF and reduce systemic toxicity of agents like amphotericin B.
- Combine amoebicidal therapy with adjuncts that limit injurious inflammation (targeted cytokine modulators, protease inhibitors) guided by translational neuroimmunology studies to preserve host tissue while enabling clearance.

Public-health, operational readiness and clinical networks

- Establish prearranged pathways for emergency access to critical drugs (e.g., miltefosine) and rapid consultation with national/reference centres; create regional stockpiles and protocols for intrathecal or intranasal administration in suspected PAM cases.
- Integrate clinician education, rapid-response diagnostic routing, and environmental monitoring into local health systems so exposure histories trigger immediate specialist involvement and specimen transfer.

Research priorities and enablers

- Expand genomic, proteomic, and structural datasets for N. fowleri to reveal parasite-unique pockets and virulence regulators suitable for drug design; build validated in vivo nose-to-brain models and PK/PD correlates to bridge preclinical to clinical translation.
- Foster multidisciplinary consortia (infectious disease, neurocritical care, nanotechnology, regulatory science, public health) and adaptive trial frameworks for rare, high-mortality infections so promising interventions can be evaluated ethically and rapidly.

10. Conclusion

Naegleria fowleri infection (PAM) is a rare but rapidly fatal CNS disease driven by a combination of aggressive amoebal virulence and a dysregulated host inflammatory response.
Early recognition, immediate specimen collection, and rapid initiation of combination antiparasitic therapy together with aggressive neurocritical care offer the only realistic chance of survival.

Priority translational goals are faster point-of-care diagnostics, structure-guided and repurposed drug candidates with verified CNS exposure, and delivery platforms (intranasal/intrathecal nano delivery) that achieve rapid, high local drug concentrations while limiting systemic toxicity.

Parallel public-health measures education to avoid nasal exposure to warm untreated freshwater and established emergency pathways for access to key drugs remain essential to reduce risk and improve outcomes. Continued multidisciplinary research linking genomics, structural biology, nanomedicine, and neuroimmunology offers the best path to convert incremental advances into meaningful clinical impact.

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