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Primary Amoebic Meningoencephalitis: A Comprehensive Review

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ABSTRACT: Primary amoebic meningoencephalitis (PAM) is a rapidly progressive, and highly fatal infection of the central nervous system caused by the free-living amoeba *Naegleria fowleri*. The infection is commonly acquired through exposure to contaminated warm freshwater during swimming or other water-related activities, where the amoeba enters the body through the nasal cavity and reaches the brain via the olfactory nerve. PAM mainly affects healthy children and young adults and presents with symptoms similar to bacterial meningitis, including fever, severe headache, vomiting, neck stiffness, seizures, and altered mental status. The disease progresses rapidly and often results in death within a few days due to delayed diagnosis and limited treatment options. Early detection through laboratory and molecular diagnostic methods, along with prompt treatment using combination therapies such as amphotericin B and miltefosine, may improve survival outcomes. This review focuses on the epidemiology, pathogenesis, clinical features, diagnosis, treatment, and prevention of PAM, emphasizing the importance of awareness and rapid medical intervention to reduce mortality associated with this emerging infectious disease.

KEYWORDS: Primary amoebic meningoencephalitis, *Naegleria fowleri*, brain-eating amoeba, central nervous system infection, amphotericin B, nanomedicine.

I. INTRODUCTION:

Primary Amoebic Meningoencephalitis (PAM) is a rare, acute, and almost always fatal infection of the central nervous system caused by the free-living thermophilic amoeba Primary amoebic meningoencephalitis and the organism *Naegleria fowleri*, commonly known as the "brain-eating amoeba." It mainly affects healthy children and young adults after exposure to warm contaminated freshwater such as lakes, rivers, stagnant water, and poorly chlorinated swimming pools, especially during summer. Infection occurs when contaminated water enters the nose, allowing

trophozoites, the infective form of the amoeba, to migrate through the olfactory nerves, cross the cribriform plate, and invade the brain, causing severe, cerebral oedema, and brain tissue destruction.

Symptoms usually appear within 1–12 days and initially resemble bacterial meningitis, including fever, headache, nausea, vomiting, neck stiffness, and photophobia, but rapidly progress to seizures, coma, and death, often within two weeks, with a mortality rate above 90% despite treatment. Diagnosis remains challenging due to its similarity to bacterial or viral meningitis, making early clinical suspicion, freshwater exposure history, and rapid laboratory diagnosis essential for survival. Preventive measures include avoiding diving or swimming in warm freshwater, using nose plugs, keeping the head above water, and ensuring proper chlorination and decontamination of water sources.

PAM mainly affects healthy children and young adults and progresses rapidly within days of exposure. Early symptoms resemble bacterial meningitis and include headache, fever, nausea, vomiting, and neck stiffness. As the disease advances, neurological manifestations such as

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seizures, hallucinations, altered mental status, coma, and death occur due to cerebral oedema and increased intracranialpressure.

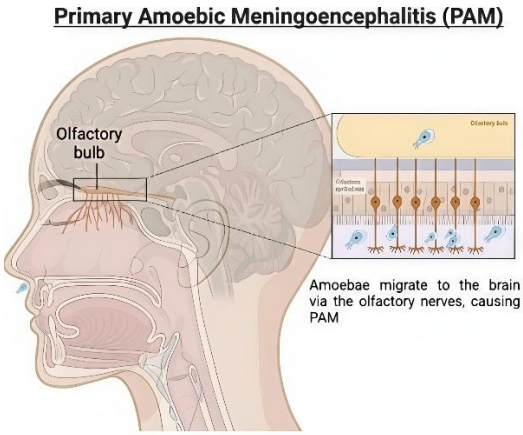

Fig 1. Overview of PAM

EPIDEMIOLOGY: N. fowleri causes a fulminant meningoencephalitis (PAM) that is rare but almost universally fatal. Fewer than a few hundred cases have been reported globally. The highest burden is in warm regions, with ~41 % of cases reported from the United States, 11 % from Pakistan, and 9 % from Mexico. More recent analyses confirm the largest case counts in the United States, Pakistan, and Australia. All inhabited continents have reported PAM, but most cases cluster in warm freshwater settings such as lakes, rivers, and inadequately treated water systems. Nevertheless, absolute numbers remain very low, typically in the dozens per year worldwide. In the United States, for example, PAM averages fewer than 30 cases annually, predominantly in summer. Improved PCR-based diagnostics have contributed to an increase in antemortem detection in recent years.

This infection occurs most frequently during the summer months when the water temperature is adapted to the thermal needs of the amoeba and people engage in recreational water activities. The cause of death was attributed to an amoeba invading their meninges, which unleashed severe damage and inflammation in the brain. Countries may be more prone to theseinfections because of their year-round warm climates and access to contaminated watersources. It is worth mentioning that most USA cases happen in southern regions of the country, where the weather is warmer.

TYPES OF PATHOGENIC FREE-LIVING AMOEBA:

1.Naegleria fowleri: Naegleria fowleri is a thermophilic amoeba with three life stages: trophozoite (10–35 mm, infectious), transient flagellate (10–15 mm), and cyst (7–15 mm, environmental). The organism causes Primary Amoebic Meningoencephalitis (PAM), a rapidly progressive and often fatal central nervous system infection developing within days of exposure. Sporadic animal cases, including in cattle and tapirs, have also been documented.

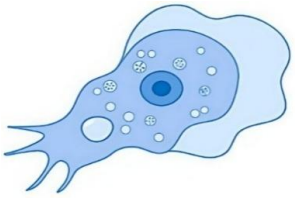

Fig 2. Naegleria fowleri

2.Acanthamoeba species: Acanthamoeba species are free-living amoebae with two life stages: double-walled cysts (10–25 mm), consisting of a fibrous exocyst and a hexagonal, star-shaped, or polygonal endocyst, and trophozoites (15–45 mm) bearing spine-like acanthopodia.

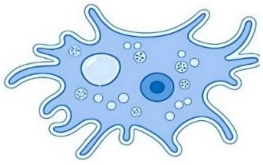

Fig 3. Acanthamoeba species

3.Balamuthia mandrillaris: B. mandrillaris is a free-living amoeba first identified in the brain of a mandrill monkey. It exists in two stages, trophozoite (15–60 mm, pleomorphic with broad lobose pseudopodia) and cyst (10–25 mm, double-walled, smooth, without pores), with both forms considered infectious. Unlike Naegleria, no flagellate stage occurs.

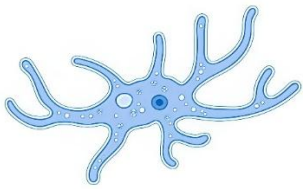

Fig 4. Balamuthia mandrillaris

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4. Rare emerging species: The morphological and biological features of pathogenic free-living amoebae. Other free-living amoebae are only rarely associated with human disease. Sappinia species are binucleate soil amoebae, with both cysts and trophozoites containing two nuclei; S. pedata has been linked to a single reported case of human encephalitis. Vermamoeba vermiformis (formerly Hartmannella vermiformis) is widespread in water and dust, with occasional reports of keratitis and PAM-like central nervous system infections, though evidence remains limited. Paravahlkampfia species, including P. francinae, have been isolated from cerebrospinal fluid in meningoencephalitis, but their role in human pathogenesis is still uncertain.

LIFE CYCLE OF NAEGLERIA FOWLERI: Naegleria fowleri is a eukaryotic, free-living, thermophilic microorganism that can live freely in water, soil, or hosts, persisting in warm and humid environments. Naegleria is a genus of FLA that belongs to the family Vahlkampfiidae, order Schizopyrenida, and class Heterolobosea. The genus consists of 47 species, which can be identified. It typically resides in micro freshwater. It comprises of three distinct phases:

- **Trophozoites(active stage):**Active, infective, feeding, reproductive stages (10-25 mm) with one nucleus that multiplies by mitosis in optimum environmental conditions.
- **Flagellate(temporary movement):**Pear-shaped, mobile, non-reproductive and non-feeding stages of 10-16 mm.
- **Cyst (dormant survival):** Non-reproductive and non-feeding stages of 8-20 mm.

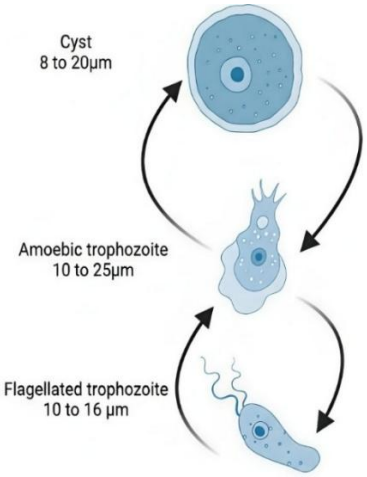

Fig 5. Life cycle of naegleria fowleri

CAUSES: Primary Amoebic Meningoencephalitis is caused by Naegleria fowleri, a thermophilic, free-living amoeba that lives in temperatures above 30 °C and can tolerate temperatures up to 45 °C. This protozoan parasite is found in the soil and freshwaters, such as ponds, lakes, rivers, streams, hot springs, and unchlorinated swimming pools. The use of tap water for nasal irrigation has also been reported as a risk factor for the disease. The free-living amoeba enters through nasal cavity, travels along the olfactory nerve to the brain.

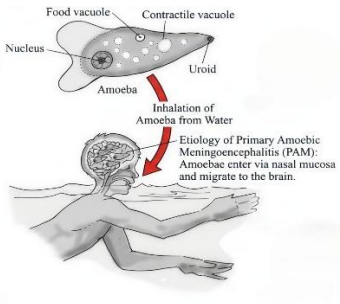

Fig.6 Causes of PAM

N. fowleri is a heat-loving amoeba found globally, particularly in warm freshwater like lakes, rivers, and hot springs. It thrives in water temperatures up to 115°F, especially during the summer months of July to September when prolonged heat raises water temperatures and lowers levels. Although rare, infections typically occur when swimming or diving in warm freshwater. In some cases, infections have also been linked to using contaminated tap water for nasal irrigation. However, Naegleria fowleri cannot infect individuals by drinking contaminated water, swimming in properly maintained pools, or through person-person contact.

PATHOPHYSIOLOGY: The migration of N. fowleri to the brain is facilitated by its production of various proteolytic enzymes, including phospholipases, cysteine proteases, and serine proteases, which degrade the extracellular matrix and disrupt cellular junctions, allowing the amoeba to traverse neural tissues. Once in the brain, the trophozoites induce a robust inflammatory response, characterized by the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumour necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6).This inflammatory response, although initially aimed at controlling the infection, leads to significant tissue damage, oedema, and necrosis, exacerbating the disease progression.

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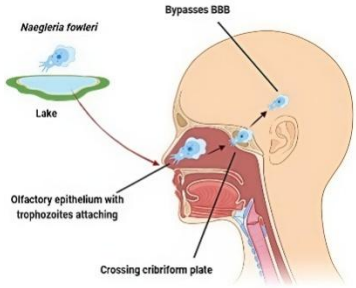

Fig 7. Pathophysiology of PAM

In addition, a highly pathogenic mouse-passaged strain of N. fowleri destroyed B103 nerve cells by contact dependent lysis. Conversely, the cytopathologic effect of axenically cultivated N. fowleri in B103 nerve cells is a result of piecemeal ingestion (trogocytosis) of target cells using a 'food-cup' structure on their surface. Those observations support the idea that adhesion, direct contact with target cells and the release of cytolytic molecules are very important factors during the process of cytopathogenicity of Naegleria.

The damage inflicted by N. fowleri involves several mechanisms: N. fowleri amoebae secrete proteins that can form pores or holes in host cell membranes. This disrupts the integrity of host cells and allows the entry of ions and molecules, leading to cell dysfunction and death. Within host cells, proteases can degrade proteins, disintegrating cellular components and eventual cell death.

SIGNS AND SYMPTOMS:

ONSET	SIGNS AND SYMPTOMS
Early	Fever Headache Nausea Vomiting Changes in smell and taste
Late	Stiff neck Fatigue Haemorrhage Confusion Changes in personality Hallucinations Seizures Coma

Table1. Signs and symptoms

PAM mainly affects children and young adults. Therefore, it can be considered a dangerous childhood disease. Patients are usually male (75%) have an average age of 14 years. PAM is considered extremely fatal. N. fowleri is classified as a neglected (tropical) disease. These NTDs include infectious diseases that are fatal and/or very dangerous, but not as focused on as other infectious diseases (neglected). The reason for this neglect can be manifold.

Alterations in taste and smell may occur initially because of involvement of the olfactory nerve. Photophobia may occur late in the clinical course, followed by neurological abnormalities, including lethargy, seizures, confusion, coma, diplopia or bizarre behaviour, leading to death within a week. Cranial nerve palsies (third, fourth, and sixth cranial nerves) may indicate brain oedema and herniation. Cardiac rhythm abnormalities and myocardial Necrosis have been found in some cases. The acute haemorrhagic necrotizing meningoencephalitis that follows invasion of the CNS generally results in death 7–10 days post infection. Naegleria fowleri symptoms begins first with a bifrontal headache, fever, nausea, restlessness, irritability and vomiting. The neurological changes such as lethargy, seizures, confusion, coma, diplopia or bizarre behaviour, leading to death within a week. Brain oedema may cause a cranial nerve palsies in the third, fourth, and sixth cranial nerves, myocardial necrosis and abnormalities of the Cardiac rhythm have been occurring.

RISK FACTORS: Evidently, deaths due to N. fowleri are on the rise. Prolonged hot and dry periods due to global warming are causing higher freshwater temperatures that are coinciding with augmented amoeba densities in water supplies, as well as an increase in recreational activities that are likely attributing to a rise in PAM cases. There is a need to revisit risk factors that can contribute to PAM and debate possible preventative strategies. Some of the risk factors are;

- Diving or jumping into the warm, usually stagnant, fresh during periods of highwater temperature and low water levels.
- Submerging the head under water during religious practices.
- Putting head under the water in hot springs and other untreated thermal waters.
- Digging in, or stirring up, the sediment while taking part in water-related activities in shallow, warm freshwater areas.

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- Irrigating sinuses (nose) using contaminated tap water.

DIAGNOSIS: PAM is a severe infection caused by Naegleria fowleri and is typically diagnosed in advanced stages due to over clinical symptoms. Diagnostic procedures include brain imaging through CT scans or MRIs to detect signs of brain swelling or inflammation. The definitive diagnosis is confirmed via a brain biopsy, which can detect the amoeba directly. CSF analysis through lumbar puncture also plays a role in the diagnostic process.

Table2. Diagnostic methods

Diagnostic method	Description
Direct visualization	The motile amoeba can be observed under a microscope in a fresh sample of cerebrospinal fluid (CSF).
Environmental diagnosis	Water samples can be collected, concentrated, and put into culture to grow and select for N. fowleri.

Diagnosing is challenging due to its rare occurrence and non-specific clinical presentation. Traditional diagnostic methods include microscopic examination of cerebrospinal fluid (CSF) for the presence of motile trophozoites, which can be observed using wet mount preparations. However, this method requires immediate sample processing and expertise in identifying the amoeba, which is not always feasible in clinical settings.

TREATMENT: Treatment options for PAM remain limited due to the lack of controlled trials or clinical studies. Current therapeutic approaches are based on in-vitro studies The recommended treatment regimen typically involves a combination of 5 or 6 antimicrobial or antifungal agents that either demonstrate in-vitro activity against N. fowleri or have been associated with survival in patients. Miltefosine is the most recent addition to this regimen, which commonly includes amphotericin B, azithromycin, fluconazole, rifampicin, and dexamethasone. However, the efficacy of these drugs remains inconsistent, and their use is often linked to significant toxicity.

→AMPHOTERICIN B: Amphotericin B is considered the primary medication for treating N. fowleri infections. The recommended intravenous and intrathecal (administered directly to the spinal canal) dosage of amphotericin B for adults with N. fowleri infection is 1.5 mg/kg/d[2]. Amphotericin B acts against N fowleri by altering membrane permeability, resulting in death of the amoeba.

→ **MILTEFOSINE:** Miltefosine is an anticancer agent used to treat breast cancer. Miltefosine also has microbicidal properties against amoebas, including Leishmania, Acanthamoeba, Balamuthia, and N. fowleri. The recommended dosage of miltefosine is 50 mg orally 2 or 3 times a day, depending on weight. Due to in vitro studies showing microbicidal properties, miltefosine is now a standard of care against N. fowleri infections.[46]

→MEDICALLY INDUCED HYPOTHERMIA: N. fowleri results in damage to neuronal cells and release of cytotoxic proteins. This cell debris and protein release leads to the secretion of proinflammatory cytokines, which results in hyperinflammation and further brain injury. [47]Medically induced hypothermia has been used previously to reduce swelling in patients with traumatic brain injury; however, the data have been inconclusive as to its benefit. [48,49] Despite this, medically induced hypothermia was used successfully with the survivor from 2013 and the survivor from 2016 to reduce brain inflammation during treatment. The other patient from 2013 who survived with significant brain damage did not undergo hypothermia treatment; however, his brain damage has been attributed to delayed diagnosis and start of treatment.

→ **FLUCONAZOLE:** Fluconazole is an azole antifungal medication that is routinely used to treat yeast infections. The efficacy of fluconazole against N. fowleri has been attributed to its penetration into the CNS.Additionally, fluconazole and amphotericin B have displayed synergistic effects in combination through the recruitment of neutrophils. Fluconazole was used in the 2003 case and both 2013 cases of N. fowleri infection. Miconazole, a discontinued azole antifungal agent, was used in the 1978 surviving case of N. fowleri infection.

→AZITHROMYCIN: Azithromycin is an antibacterial macrolide medication that inhibits bacterial protein synthesis. Azithromycin can treat both Gram-positive and Gram-negative bacteria. Azithromycin has been shown to suppress more than 90% of N. fowleri growth in vitro and is recommended to be used in conjunction with the other medications described here for treatment of N. fowleri infection.

→RIFAMPICIN: Rifampicin is an antimycobacterial medication used to treat tuberculosis. Rifampicin targets bacterial RNA

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polymerase and has shown some efficacy against N. fowleri in vitro. The efficacy in vivo has been contested, however. There is concern that rifampicin does not sufficiently penetrate the CNS in vivo, as the concentrations detectable do not reach the required minimal inhibitory concentration necessary for N fowleri infection (but may be sufficient for bacterial infections). The second concern is that rifampicin is known to interact with and inhibit azole fungistatic, including fluconazole. Despite this, the CDC recommends using rifampicin in combination with the above-mentioned medications for patients with N fowleri infection.

CURRENT STATUS OF THERAPY: Currently, the clinical treatment mainly relies on "old drugs with new uses" such as antifungal or antibiotic drugs like amphotericin B and miltefosine. Although these drugs have achieved therapeutic effects in individual cases, their therapeutic window is extremely narrow. Advanced technologies are increasingly being explored to improve the diagnosis and treatment of Primary Amoebic Meningoencephalitis (PAM) caused by Naegleriafowleri. Because the disease progresses extremely rapidly and conventional treatment options are limited, modern research focuses on rapid molecular diagnosis, targeted drug delivery systems, discovery of novel anti-amoebic compounds, and advanced neurocritical care technologies to enhance survival rates.

→NANOMEDICINE DELIVERY SYSTEM: For instance, drug–nanoparticle conjugates, including flavonoids like hesperidin and naringin bound to silver or gold nanoparticles, have demonstrated potent amoebicidal activity, achieving up to 99% reduction in N. fowleri viability while maintaining low cytotoxicity to human cells. The conjugation of repurposed CNS drugs such as zonisamide and perampanel with silver nanoparticles, which improves their anti-amoebic efficacy and potentially overcomes BBB limitations.

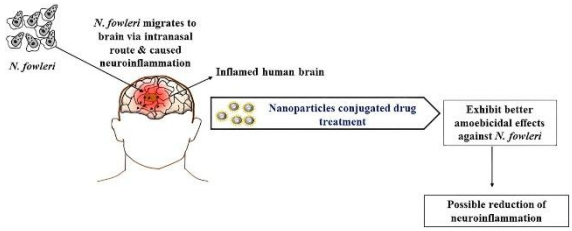

Fig 8. Nanomedicine delivery system

Nanoparticles also facilitate controlled drug release, increased surface interaction with amoebae, and enhanced cellular uptake, thereby improving therapeutic outcomes compared to free drugs. Furthermore, nanotechnology enables the co-delivery of multiple agents and may reduce systemic toxicity, which is crucial given the aggressive combination therapy currently required for PAM. [58]

Overall, although still largely in preclinical and experimental stages, nanomedicine-based delivery systems represent a highly promising strategy to overcome pharmacokinetic barriers and improve survival outcomes in PAM, warranting further in vivo studies and clinical translation.

→TARGETED RATIONAL DRUG DESIGN: It is worth nothing that the anti-amoebic drugs currently used in the clinic (such as amphotericin B and miltefosine) are mostly "old drugs with new uses," and their discovery processes mostly rely on empirical screening, lacking a deep understanding of the biological characteristics of the pathogen. With the development of genomics, structural biology, and computational chemistry, target-based rational drug design is becoming the mainstream approach in new drug development. Comparative Genomics and Subtractive Genomics have become powerful tools for systematically mining novel drug and vaccine targets. For example, liposomal formulations of Amphotericin B have been investigated to improve drug penetration into the brain while reducing systemic toxicity. These nano-carrier systems may significantly enhance the therapeutic efficacy of anti-amoebic treatments in the future.

→MOLECULAR DIAGNOSTIC TECHNOLOGY: This technology particularly based on the Polymerase Chain Reaction (PCR) and real-timePCR assays. These methods enable the detection of *Naegleria fowleri* DNA in cerebrospinal fluid (CSF) within a few hours, which is significantly faster and more sensitive than traditional microscopic examination. Early diagnosis is critical because PAM symptoms progress quickly and early treatment can be life-saving. More recently, technologies such as Next-Generation Sequencing (NGS) and Metagenomic Sequencing allow identification of pathogens directly from clinical samples without prior knowledge of the causative organism. These high-throughput sequencing methods are especially useful in detecting rare infections like PAM when routine tests fail to identify the pathogen.

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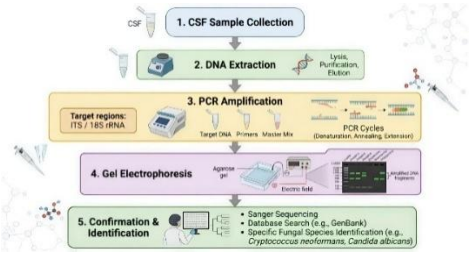

Fig 9. Molecular diagnostic technology

→HIGH-THROUGHPUT DRUG SCREENING AND DRUG REPURPOSING TECHNOLOGIES: High-throughput screening (HTS) and drug repurposing are emerging as key strategies for improving treatment of Primary Amoebic Meningoencephalitis (PAM) caused by Naegleria fowleri. Large-scale phenotypic screening of FDA-approved drugs and compound libraries, including the Reframe library, has identified several promising repurposed agents such as camptothecin, pyrimethamine, terbinafine, and nitroxoline with potent anti-amoebic activity and potential CNS penetration. These technologies accelerate drug discovery by rapidly identifying "old drugs with new uses," reducing time and cost compared with traditional de novo drug development, and offer practical pathways for discovering safer, more effective PAM therapies.

→NEUROCRITICAL CARE TECHNOLOGY: These are improving the supportive management of PAM patients. Since the infection causes severe brain inflammation and oedema, technologies such as intracranial pressure monitoring, therapeutic hypothermia, and advanced neuroimaging methods like Magnetic Resonance Imaging (MRI) help clinicians monitor disease progression and control cerebral swelling. These supportive technologies, combined with aggressive antimicrobial therapy, may increase the chances of survival. This technology integrates into a management of PAM, followed by a simplified conceptual breakdown.

1. Multimodal Monitoring

- External Ventricular Drains (EVD): This is the gold standard for PAM. It serves a dual purpose: measuring ICP and allowing for the drainage of Cerebrospinal Fluid (CSF) to reduce pressure.
- Intraparenchymal Monitors: Fiber-optic catheters placed directly into the brain tissue to monitor pressure and oxygenation levels ($PbtO_2$).
- Continuous EEG (cEEG): Used to detect subclinical seizures caused by severe neuroinflammation, which can further exacerbate brain damage.

2. Advanced Imaging & Targeted Delivery

- MRI/MRS (Spectroscopy): Used to monitor the extent of necrosis and metabolic changes in the brain tissue.
- Intrathecal/Intraventricular Drug Delivery: Because the Blood-Brain Barrier (BBB) is often difficult to penetrate, clinicians use specialized ports to deliver amoebicidal drugs directly into the CSF, mirroring the "targeted" logic of the nanoparticles in your diagram.

3. Neuroprotective Temperature Management

- Targeted Temperature Management (TTM): Sophisticated cooling blankets or intravascular cooling catheters are used to induce therapeutic hypothermia (32\text{°C}–34\text{°C}), which can slow the metabolic rate of both the amoeba and the brain, potentially limiting inflammation. [66,67,68]

PREVENTION STRATEGIES: Prevention strategies for Primary Amoebic Meningoencephalitis (PAM), caused by the *Naegleria fowleri* amoeba, focus on avoiding nasal exposure to warm freshwater where the organism thrives. Because the infection is rapid and almost always fatal, prevention is the primary strategy to reduce the incidence of the disease.

Key Prevention Strategies:

✓ **Avoid Nasal Exposure in Warm Water:**

- Avoid Swimming/Diving: Do not jump or dive into, or submerge your head in, warm fresh water, hot springs, or thermally polluted water, especially during summer months.
- Use Nose Clips: Wear nose clips or keep your head above water when participating in water sports or activities in warm, shallow, stagnant, or unchlorinated fresh water.
- Avoid Stirring Sediment:Avoid digging or stirring up the sediment (mud/soil) in shallow warm water, as this is where *N. fowleri* is most likely to reside.

✓ **Safe Nasal Irrigation and Ablution:**

- Treat Tap Water:Do not use tap or faucet water directly for nasal or sinus rinsing

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(e.g., using a neti pot) or for ritual ablution, as the amoeba can inhabit plumbing.

- Use Sterile or Boiled Water: Only use water that has been boiled for at least 1 minute (3 minutes at high altitude) and cooled, or use distilled, sterile, or filtered water (1-micron pore size).

✓ **Water Management and Public Education:**

- Maintain Proper Chlorination: Ensure swimming pools, hot tubs, and spas are properly cleaned and chlorinated (at least 0.5 mg/L or 0.5 ppm residual chlorine) to kill the amoebae.
- Public Awareness Campaigns: Promote education in high-risk areas about the danger of warm, untreated water, particularly during heatwaves or high-risk times.

✓ **Residential Water Safety:**

- Flush Pipes: Let bath and shower taps run for a few minutes to flush out pipes before use, especially if water has been stagnant.
- Cool Water Pipes:Run garden hoses or sprinklers for a few minutes to ensure cool water runs through before allowing children to play with them.

✓ **Future Prevention Strategies (In Research/Development):**

- Naegle RiopelDevice:Non-invasive nasal plug designed to block *N. fowleri* at the entry point of the nostril.
- Enhanced Surveillance: Integrating molecular techniques (like qPCR) for environmental monitoring of water sources.

FUTURE PERSPECTION: The future perspective of Primary Amoebic Meningoencephalitis (PAM) management is shifting toward earlier diagnosis, precision therapeutics, and advanced CNS-targeted interventions. Emerging molecular diagnostic technologies such as real-time PCR, genomic profiling, non-invasive biomarkers, and advanced neuroimaging may enable earlier detection before irreversible CNS damage occurs. High-throughput drug screening and drug repurposing platforms are accelerating identification of novel anti-Naegleria fowleri agents, while rational drug design is focusing on pathogen-specific molecular targets. Nanomedicine and nanoparticle-based drug delivery systems represent a promising frontier by enhancing blood–brain barrier penetration, improving targeted amoebicidal delivery, and reducing systemic toxicity.

Future strategies may also incorporate immunotherapy, monoclonal antibodies, and personalized neurocritical care protocols combining aggressive intracranial pressure control with precision pharmacology. Together, these innovations may transform PAM from a nearly universally fatal disease into a more rapidly diagnosable and potentially treatable CNS infection.

At present, although mNGS has accelerated diagnostic speed, nano delivery technology has shown potential for crossing the blood–brain barrier, and physical–chemical combined prevention and control strategies are being advanced, each link still faces the core challenges of “difficult translation, high cost, and unclear mechanisms”. The focus of future research should be on “translational medicine” and “precision prevention and control.

DISCUSSION: Primary amoebic meningoencephalitis (PAM) is an emerging and highly fatal central nervous system infection caused by the thermophilic amoeba Primary Amoebic Meningoencephalitis and is increasingly recognized as a public health concern due to rising global temperatures, increased recreational water exposure, and improved diagnostic awareness. Recent reports have shown sporadic outbreaks and isolated cases in regions previously considered non-endemic, suggesting that climate change and environmental alterations may support the wider distribution of the causative organism, Naegleria fowleri. The disease primarily affects healthy children and young adults following exposure to warm freshwater contaminated with the amoeba, which enters the body through the nasal cavity and rapidly migrates to the brain, causing severe inflammation, cerebral edema, and rapid neurological deterioration. Despite advances in molecular diagnostic techniques and intensive care management, PAM continues to have a mortality rate exceeding 95% because of delayed diagnosis and the rapid progression of symptoms that resemble bacterial meningitis. Recent therapeutic approaches involving combinations of amphotericin B, miltefosine, azithromycin, rifampicin, and supportive neurocritical care have

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shown limited but promising survival outcomes when initiated early. Therefore, increased awareness, rapid diagnosis, public education regarding safe water practices, and continued research into targeted therapies remain essential for controlling this rare but devastating emerging disease.

CONCLUSION: In conclusion, primary amoebic meningoencephalitis (PAM) remains one of the most devastating infectious diseases of the central nervous system, beginning as a rapidly progressive Naegleria fowleri infection acquired through nasal exposure to contaminated warm freshwater and often advancing swiftly from nonspecific meningoencephalitis symptoms to severe cerebral oedema, neurological collapse, and death.As understanding of disease progression improves, future treatment strategies are increasingly focused on earlier molecular detection, rapid point-of-care diagnostics, targeted combination pharmacotherapy, nanotechnology-enabled drug delivery, blood–brain barrier–penetrating therapeutics, immunomodulatory approaches, and high-throughput drug repurposing platforms to identify more effective anti-Naegleria compounds. In parallel, future prevention strategies are expected to play an equally critical role through strengthened public health education, safer recreational water practices, improved chlorination and monitoring of freshwater systems, promotion of sterile water uses for nasal irrigation, environmental surveillance of N. fowleri, and climate-responsive risk assessment as rising global temperatures expand amoebic habitats. Together, the progression from current emergency-based management toward integrated prevention, precision diagnostics, and innovative therapeutics offers the most promising pathway to reducing the historically overwhelming mortality of PAM.

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