Parasitic disease in the pediatric intensive care unit - A review of severe manifestations of pediatric parasitic disease

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Abstract. Parasitic diseases, previously thought to be the domain of developing nations only, are being increasingly recognized as a significant source of morbidity/mortality in developed and developing nations alike. While many parasites cause long-term low-level disease, some parasitic diseases can have severe manifestations necessitating intensive care unit admission. In this review, we focus on severe malaria (including cerebral malaria), neurocysticercosis, *Strongyloides* hyperinfection syndrome, American trypanosomiasis (Chagas disease), baylisascariasis and amoebic meningoencephalitis.

Keywords: American trypanosomiasis, amoebic meningoencephalitis, baylisascariasis, Chagas disease, hyperinfection syndrome, neurocysticercosis, pediatric parasitic disease, parasitic disease, severe malaria, strongyloidiasis

1. Introduction

Parasitic diseases have long been viewed as a problem limited to developing countries and consequently may not be routinely considered by intensive care providers. However, with widespread global migration and travel, these illnesses increasingly affect developed countries [1]. Several parasitic infections may result in death or severe illness resulting in intensive care unit admission, and timely diagnosis may lead to improved survival.

During the past decade, there has been an increased recognition of the impact of parasitic diseases on child health. The World Health Organization (WHO) has targeted multiple parasitic diseases in their neglected tropical diseases initiative. More recently the Centers for Disease Control and Prevention (CDC) has focused research and educational efforts on neglected parasitic infections, and new journals are dedicated exclusively to this topic (e.g., PLOS Neglected Tropical Diseases) [2, 3]. This review will cover selected parasitic infections with the potential to cause severe disease requiring pediatric intensive care unit admission: malaria, neurocysticercosis, *Strongyloides* hyperinfection syndrome, American trypanosomiasis (Chagas disease), baylisascariasis and amoebic meningoencephalitis. A summary of these diseases is presented in Table 1.

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Table 1
Summary of clinical and diagnostic features of parasitic diseases causing severe disease

	Severe malaria	Neurocysticercosis	<i>Strongyloides</i> hyperinfection syndrome	Chagas' disease (American trypanosomiasis)	Baylisascariasis (neural larva migrans)	Amebic meningoencephalitis
Organism	<i>P. falciparum</i> , <i>P. vivax</i> , <i>P. knowlesi</i>	<i>T. solium</i>	<i>S. stercoralis</i>	<i>T. cruzi</i>	<i>B. procyonis</i>	<i>N. fowleri</i> , <i>Acanthamoeba</i> spp., <i>B. mandrillaris</i> , <i>Balamuthia</i>
Time to illness	1–4 wk	Years to decades	Months to decades and immune system alteration	1–2 wk	2–4 wk	<7 days (<i>Naegleria</i>), wk to mo. (<i>Acanthamoeba</i> , <i>Balamuthia</i>)
Route of infection	<i>Anopheles</i> mosquito	Ingestion of eggs from individual with taeniasis by fecal-oral route	Walking barefoot in endemic areas, carried chronically in auto-infectious cycle	Triatomine ("kissing bug"); contaminated blood products; congenital infection; ingestion	Ingestion of eggs in raccoon feces in contaminated soil	Swimming/playing in warm freshwater; nasal irrigation with non-sterile water
Presentation	Cerebral malaria (seizures/coma); severe anemia; metabolic acidosis and hypoglycemia; algid malaria	New-onset seizures; intracranial hypertension; encephalitis	Gastrointestinal symptoms; pneumonitis; sepsis and/or meningitis (often polymicrobial) with enteric flora	Acute myocarditis; pericardial effusion; meningoencephalitis	Eosinophilic meningitis in young children with irritability, lethargy, seizures, ataxia, coma and death	Fulminant hemorrhagic meningoencephalitis with cerebral edema, elevated intracranial pressure, herniation
Diagnostics	Microscopic identification of parasite forms in red blood cells; rapid diagnostic testing; polymerase chain reaction	Neuroimaging to identify cysts (computed tomography/magnetic resonance imaging); enzyme-linked immunoelectro-transfer blot serologic and cerebrospinal fluid testing	Microscopic examination of stool and other body fluids; serologic testing	Microscopy of blood/ cerebrospinal fluid specimens for trypanomastigotes; polymerase chain reaction	Neuroimaging with deep focal lesions; serologic testing (enzyme immunoassay, immunofluorescent antibody assay and Western blot); morphologic identification on biopsy	Wet-mount microscopy of cerebrospinal fluid to identify amebic forms; immunofluorescent stains of biopsy material and polymerase chain reaction

2. Malaria

2.1. Etiology/epidemiology

Malaria remains the most important human parasitic infection worldwide. Infection is caused by five *Plasmodium* species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. In 2013, there were an estimated 584,000 malaria deaths worldwide; 78% occurred in children younger than 5 yr of age [4]. *P. falciparum* malaria has long been recognized as the most deadly form of the disease and predominates

in sub-Saharan Africa. *P. vivax* is increasingly recognized as a cause of severe malaria, particularly in the Indian subcontinent and Southeast Asia where prevalence of this species is high. The mortality rate of *P. vivax* appears to be significantly less than *P. falciparum* malaria in infants but similar in patients aged 5–15 yrs [5]. *P. knowlesi* is present in Malaysia and may be confused with *P. malariae* on microscopic examination; it has a shorter replication time (24 hr) and can also cause severe disease.

Female *Anopheles* mosquitoes transmit *Plasmodium* species while feeding on human hosts. Sporozoites

from the mosquito infect hepatocytes and multiply, forming up to 30,000 merozoites within a hepatocyte before being released into the bloodstream. *P. vivax* and *P. ovale* produce dormant liver stage hypnozoites that can lead to recurrent disease. Merozoites infect erythrocytes, where they develop into ring forms that divide and consume the cell's hemoglobin, replicating before the cell ruptures. Erythrocyte rupture releases more merozoites, which continue the cycle of infection. A subset of ring forms (trophozoites) develops into gametocytes that can infect mosquitoes.

2.2. Clinical manifestations

Malaria is a leading cause of febrile illness in endemic areas and an important etiology of illness in travelers returning from the tropics [6]. Early symptoms include fatigue, muscle aches, headache and abdominal pain accompanied by irregular fever; the classic cyclical pattern of fever is not invariably present, especially in children. The presentation of severe malaria depends on age: pediatric patients often present with severe anemia, convulsions or coma (cerebral malaria), acidosis, hypoglycemia and shock. Older patients have increased incidence of acute kidney injury, acute lung injury and/or acute respiratory distress syndrome, and jaundice [7]. Cerebral malaria (CM) is thought to be due to microvascular obstruction and impaired perfusion due to parasitized erythrocytes. There may be a metabolic component contributing to encephalopathy as well. Delirium can be seen with the high fevers of malaria, and declining mental status may progress rapidly to posturing, seizures and coma. Imaging often shows cerebral edema in children, a finding usually not present in adults [8]. Cerebrospinal fluid (CSF) analysis may reveal a mild lymphocytic pleocytosis and mildly elevated protein levels, and opening pressure is elevated in an estimated 43–80% of patients [9, 10]. Bacterial and viral meningoencephalitis should be considered in the differential diagnosis of CM.

Severe acidosis and hypoglycemia are associated with hyperparasitemia (>5% of erythrocytes infected) and increased mortality [11]. Hyperpnea or tachypnea in the absence of localizing chest signs should suggest acidosis and prompt blood gas monitoring. Concurrent invasive bacterial infection and shock (most often with enteric Gram-negative bacilli, a syndrome known as “algid” malaria) occurs in a small subset (<5%) of African children with falciparum malaria [12].

Acute renal injury in non-immune adults with *P. falciparum* malaria, particularly with hyperparasitemia, significantly contributes to overall mortality. However, its role in pediatric malaria is less well described and often overshadowed by cerebral manifestations; 25% of patients with cerebral malaria and 4–17% of patients with uncomplicated malaria have evidence of renal impairment [13–15].

2.3. Diagnosis

Early consideration of malaria in the differential diagnosis is essential in patients from endemic areas and recently returned travelers. Many malaria-related deaths in returning travelers are reportedly due to delayed diagnosis [16]. Microscopy remains the gold standard for diagnosis; thick and thin blood smears should be performed to detect and speciate malaria parasites. Because returning travelers and other non-immune patients can be symptomatic despite low levels of parasitemia, three thick and thin blood smears separated by 12 to 24 hr should be obtained (though the first smear is usually diagnostic in reputable centers). Rapid diagnostic testing (RDT) is increasingly available and provides results in <15 min; however, sensitivity of RDT is generally lower (especially in low-level parasitemia), and negative RDTs should be followed by microscopy. Polymerase chain reaction (PCR) is the most sensitive modality for diagnosis, can also provide speciation and is available at selected public health reference laboratories, but results are usually not timely enough to guide initial treatment decisions.

Other laboratory studies supporting the diagnosis of malaria in children include normocytic anemia (not invariably present), thrombocytopenia, mild to moderate transaminase elevation (rarely leading to hepatic failure), metabolic acidosis and hypoglycemia. Urinalysis may show hemoglobinuria in patients with significant hemolysis.

2.4. Treatment

Treatment of malaria is determined by the *Plasmodium* species identified, with special consideration of resistance patterns in the location infection was acquired and severity of illness. Treatment recommendations should be sought in consultation with an infectious diseases specialist. First-line therapy for severe malaria in the United States of America (USA) is quinidine gluconate along with doxycycline,

tetracycline, or clindamycin [17]. Artesunate is available from CDC as an alternative; it should be strongly considered for hospitalized patients needing intravenous (IV) therapy for severe disease and high parasitemia (>5%), poor response or intolerance of IV quinidine, or inability to take oral therapy. Artesunate should be followed by atovaquone-proguanil, doxycycline (or clindamycin for pregnant women), or mefloquine. WHO guidelines for treatment of severe malaria advocate for artemisin-based combination therapy or quinine dihydrochloride plus doxycycline or clindamycin [18]. For severe *P. vivax*, chloroquine plus primaquine are recommended. Primaquine eradicates hypnozoites but should only be administered after testing for glucose-6-phosphate dehydrogenase deficiency. Options for uncomplicated falciparum malaria treatment include atovaquone-proguanil, artemether-lumefantrine or quinine plus another agent (per CDC guidelines), and for uncomplicated malaria due to other species, chloroquine $\pm$ primaquine.

In addition to early diagnosis and therapy, hematologic and metabolic abnormalities (including blood glucose) should be aggressively controlled. Blood transfusions should be given for severe anemia (hemoglobin ≤ 7 g/dL in non-endemic countries) [19]. Quinidine may lower blood glucose and cause arrhythmias, and electrocardiogram monitoring is indicated. Non-hypoglycemic seizures should be treated with antiepileptics. Corticosteroids and mannitol do not increase survival in patients with CM and have been reported to prolong coma in studies in Thailand and India, respectively [20–22]. In addition to antimalarial treatment, broad-spectrum antibiotics should be considered for children with suspected severe malaria (at least until cultures are negative) due to potential concurrent bacterial infection.

Patients with severe dehydration should receive IV rehydration with crystalloid or albumin, with some evidence that the latter leads to better outcomes [23]. Persistent low urine output after careful rehydration may suggest acute renal injury. Renal injury in malaria is due to acute tubular necrosis and is often reversible but may require dialysis.

2.5. Sequelae

Gross neurologic deficits are described in almost 5% of children with CM, and a greater proportion has cognitive deficits [24–26]. Mortality in pediatric patients with severe malaria ranges from approximately 3–8%

in developing countries and depends on early diagnosis and availability of appropriate care, as well as parasite and patient factors [27, 28].

2.6. Prevention/vaccination

Malaria control programs, including insecticide-treated mosquito nets and intermittent preventive treatment in pregnant women and young infants, have greatly decreased the global incidence of malaria in high transmission areas during the past decade. The latest WHO malaria report found worldwide mortality rates dropped 47% in all age groups and 53% in children aged <5 yr from 2000 to 2013 [4]. For travelers to endemic regions, the mainstays of prevention are chemoprophylaxis and personal protective measures. Specific recommendations should be made in consultation with a travel medicine expert and depend upon destination, length of stay and patient factors. There is currently no approved malaria vaccine, but several vaccine candidates are undergoing clinical trials in Africa and elsewhere [29].

3. Neurocysticercosis

3.1. Etiology/epidemiology

Neurocysticercosis is the most common parasitic CNS infection and is caused by larvae of the cestode flatworm *Taenia solium*; humans are the definitive host and pigs the intermediate host. It is the leading cause of acquired epilepsy in endemic countries. WHO has estimated that neurocysticercosis causes >50,000 deaths annually [30, 31]. Neurocysticercosis is increasingly diagnosed in the USA, primarily due to the influx of immigrants from Latin America where the disease is highly endemic [32]. An estimated 2.1% of USA emergency room visits for seizures may be attributable to neurocysticercosis; even higher rates approaching 10% have been reported in the Southwest, where most of the 221 reported cysticercosis-related deaths were identified from 1990–2002 [33, 34].

Infection occurs through ingestion of *T. solium* eggs excreted in the feces of persons with taeniasis (intestinal infection with adult tapeworms). Cysticercosis is not acquired by consumption of undercooked or “measly” pork (pork with mature cysts in the tissue), but autoinfection may occur in persons with taeniasis who ingest tapeworm eggs. Once ingested, the eggs liberate

oncospheres that cross the intestinal wall and enter the bloodstream. They then spread hematogenously to various tissues and develop into cysticerci (larval cysts). Cysts are rapidly cleared by the host immune response in many tissues but may persist in immunologically privileged sites such as the eye and CNS [35].

3.2. Clinical manifestations

As it often takes more than a decade for cysts to degenerate and initiate an immune reaction leading to seizures, the peak incidence of neurocysticercosis is in adolescents and adults; somewhat younger patients may be diagnosed in highly endemic areas [36, 37]. The cardinal presentation of neurocysticercosis is epileptic seizures, the sole manifestation in almost 70% of patients [38]. However, significant variability in symptoms exists, related to the number and location of the CNS lesions. Seizures are more common in parenchymal disease, whereas intracranial hypertension is associated with lesions in the subarachnoid space or ventricular system. In patients with fourth ventricle cysts, intracranial hypertension can result in sudden loss of consciousness related to head movements (Bruns' syndrome). Focal signs occur when large subarachnoid cysts compress brain parenchyma.

A rare but severe manifestation of neurocysticercosis is encephalitis characterized by clinical and radiologic evidence of diffuse cerebral edema. Published cases show a female predominance in adolescent patients (average age in one series, 15.5-yr-old) [39, 40]. Two mechanisms have been proposed for this syndrome: an appropriate but severe local and systemic host response to live parasites, and a pronounced inflammatory reaction to antigens released during parasite death [41].

3.3. Diagnosis

Neuroimaging is diagnostic if cystic lesions show a scolex (head). Computed tomography (CT) has good diagnostic sensitivity to identify calcified cysts and remains the primary imaging study. Magnetic resonance imaging (MRI) is superior to CT for small lesions, those adjacent to bone, or lesions located within the posterior fossa, brainstem, ventricles, or basal cisterns [42]. Neuroimaging may help determine whether cysts are viable or degenerating. Viable cysts appear as hypodense, rounded lesions, and the scolex may appear as a hyperintense dot in the interior. Fluid

attenuation inversion recovery or diffusion-weighted MRI sequences may improve visualization of the scolex in degenerating lesions.

In cases where imaging is suggestive but not clearly diagnostic, serologic testing for *T. solium* aids in confirming the diagnosis. The enzyme-linked immunoelectrotransfer blot performed on CSF or serum is the best serologic test, with a sensitivity of 94–100% and specificity of nearly 100% [43, 44]. However, sensitivity drops to approximately 50% in patients with a single cyst and 75% with calcified cysts [44, 45]. Laboratory findings of neurocysticercosis include moderate peripheral eosinophilia in approximately 1/3 of cases; CSF studies can be unremarkable or reveal a mononuclear pleocytosis rarely >300 cells/mm³. Protein levels may be elevated (50–300 mg/dL), but glucose is usually normal. Additional diagnostic criteria have been proposed for cases which are difficult to diagnose [46].

3.4. Treatment

The mainstay of neurocysticercosis treatment is control of epileptic seizures and intracranial hypertension. Controversy exists over the need therapy for all patients with neurocysticercosis. Recommendations for antiparasitic therapy depend on the location and number of lesions, and on the likelihood of viable cysts. Treatment-associated parasite death can lead to an acute inflammatory reaction surrounding the cyst. A recent study of antihelminthics in neurocysticercosis found that in adults with viable lesions, albendazole may reduce the number of lesions at follow up, but it does not lower recurrent seizure risk. Limited data are published for viable lesions in children; for non-viable lesions, albendazole reduces seizure recurrence but has little impact on number of lesions at follow up [47]. Praziquantel has also been used successfully, but both phenytoin and corticosteroids decrease praziquantel serum levels.

For patients with multiple cystic parenchymal lesions, albendazole (15 mg/kg/day orally twice daily for 1 to 4 wk) is used in conjunction with corticosteroids and anticonvulsants during the treatment period. Albendazole may also be used in selected patients with solitary parenchymal cysts, with corticosteroids only co-administered with treatment-related side effects (severe headache, seizures). In cysticercotic encephalitis, antiparasitics are generally contraindicated due to the risk of worsening intracranial hypertension, and high dose corticosteroids should be administered.

The surgical treatment of extraparenchymal cysts varies significantly based on location. Neurosurgical intervention may be required for obstructive hydrocephalus or mass effect. In subarachnoid and sylvian cystic disease or ventricular cysts causing ependymitis, ventricular shunt placement should be considered prior to initiation of cysticidal therapy to avoid further increases in intracranial pressure. Neuroendoscopic excision is increasingly used for intraventricular lesions, but not all lesions are amenable to this approach.

3.5. Prevention

Major public health efforts have been undertaken in endemic countries to reduce the burden of cysticercosis. Because of the fecal-oral route of infection, clean water for hand washing and hygienic latrines are essential. It is advisable to assess for household contacts with subclinical taeniasis, who may have been the source of infection [48].

4. *Strongyloides* hyperinfection syndrome

4.1. Etiology/epidemiology

Strongyloidiasis is caused by the roundworm *Strongyloides stercoralis* and affects an estimated 100 million people worldwide [49]. The parasite replicates in the soil in tropical and subtropical areas. Infection is acquired transcutaneously, often by walking barefoot. After penetrating the skin, filarial larvae migrate to the lungs where they then are expectorated and swallowed. In the small intestine, larvae mature and produce eggs, which develop into rhabditiform larvae in the intestinal lumen. These can either pass in the stool or become infective filarial larvae. Autoinfection in human hosts occurs when filarial larvae invade the intestinal wall and complete the life cycle without need to develop in the soil.

4.2. Clinical manifestations

Acute infection may cause irritation at the site of skin penetration and mild pneumonitis during larval migration. Once infection is established, chronic strongyloidiasis is usually asymptomatic and can persist for decades. The hyperinfection syndrome (HS) occurs when an infected person suffers an alteration of the immune system due to immunomodulating

medications or diseases. In HS, vastly increased numbers of larvae may be present in only the lungs and intestine (as in the normal life cycle), or they can be disseminated throughout the body.

The most common symptoms of HS are gastrointestinal. Abdominal pain, nausea, vomiting, watery diarrhea, constipation, anorexia and weight loss, and bloody stools have all been reported [50]. Pulmonary symptoms also occur frequently and range from cough to hemoptysis to respiratory collapse [51]. In severe pulmonary disease, filarial and/or rhabditiform larvae and occasionally eggs can be seen in sputum samples. Larva currens (literally “racing larva”) may appear with or without HS as an itchy linear rash on the abdomen, thighs and buttocks, reflecting intradermal larval migration.

In HS, bacteremia with enteric flora is frequent (30–53%) and is due to the increased number of parasites penetrating the intestinal wall [52]. Bacteremia is often polymicrobial with Gram-positive and Gram-negative enteric species, and less frequently yeast. Infection of the CNS also occurs, and polymicrobial sepsis and/or meningitis should prompt evaluation for strongyloidiasis.

Corticosteroids are the most well documented medication associated with HS [50, 53]. Vincristine and other immunosuppressive medications have also been implicated, but causality is often difficult to establish due to concomitant administration of corticosteroids [50]. Diseases associated with HS include human T-cell lymphotropic virus type 1, human immunodeficiency virus, hematologic and other malignancies, and solid organ and hematopoietic stem cell transplants.

4.3. Diagnosis

Diagnosis of strongyloidiasis is sometimes made by microscopic examination of stool for parasitic ova and larvae. In HS, larvae may be identified in sputum and other body fluid specimens as well. Alternative methods of diagnosis include the blood agar plate culture method, in which serpiginous tracks of bacterial growth along the path of motile larvae from a stool sample plated on blood agar are observed, and serologic testing. Peripheral eosinophilia is often present but may be absent in HS [50]. Chest radiographs are variable but may show pulmonary infiltrates, or less frequently, cavitation or abscess formation [54].

4.4. Treatment

Uncomplicated strongyloidiasis is treated with a 1-2 day course of oral ivermectin (200 µg/kg once daily). Albendazole may also be adequate if longer courses (at least three to five days) are used. For HS, ivermectin should be continued until clinical improvement occurs and larvae and eggs are no longer detectable in stool; some experts recommend treating until negative stool exams persist for 2 wk [50, 55]. Efforts should be made to reduce immunosuppressive therapy and treat concurrent bacterial infections as these may contribute to poor outcomes. Even with treatment, reported mortality rates in hyperinfection syndrome range from 31% to 82% [52, 56]. Intrarectal veterinary formulations of ivermectin have been reported to improve outcomes in HS [57, 58].

4.5. Prevention

Prevention of strongyloidiasis should include attention to hygiene and avoidance of walking barefoot in endemic areas with potentially contaminated soil. Prevention of HS is focused on identifying patients receiving immunomodulatory therapy (including even moderate doses of corticosteroids) who have lived in endemic areas and may be asymptotically carrying *S. stercoralis*. In asymptomatic patients, stool studies are often negative due to the low-level of parasite shedding. In patients at risk for HS, serologic testing should be performed; if positive, ivermectin treatment for two days is recommended.

5. Chagas disease (American trypanosomiasis)

5.1. Etiology/epidemiology

Chagas disease is caused by *Trypanosoma cruzi*, a protozoan parasite spread primarily by reduviid bugs of the subfamily Triatominae (“assassin bugs” or “kissing bugs”). The parasite is carried in the triatomine’s gut and passed in the feces which contaminate the wound created during a blood meal. Other less frequent modes of transmission include blood transfusions, congenital infection (almost 5% of pregnancies in chronically infected women), organ transplantation, and contaminated food or liquid [59, 60].

T. cruzi is encountered primarily in areas of Central and South America corresponding to the ecologic range of triatomine species. Although vector species are present in the Southern USA, infestation of human dwellings and vector-borne transmission are very low [61]. The Pan American health organization estimated in 2005 that nearly 7.7 million individuals were infected in the Americas (1.4% of the population) [62]. With an increasing immigrant population from endemic countries over recent decades, the USA disease burden has grown significantly to >300,000 infected individuals [63].

5.2. Clinical manifestations

Chagas disease presents in distinct acute and chronic phases. The acute phase occurs after a 1 to 2 wk incubation period and commonly lasts 6 to 8 wk. Ninety-five percent of acute infections are asymptomatic [64]. Of symptomatic infections, most are mild, self-limited febrile illnesses. Other symptoms may include malaise, hepatosplenomegaly, and lymphadenopathy. Patients can develop inflammation and swelling at the site of inoculation (chagoma). Unilateral swelling of the periorbital tissues (Romaña’s sign) occurs after conjunctival inoculation.

Severe acute-phase disease occurs in about 1% of all vector-borne infections but with higher frequency in children, particularly those under 2 yr. Orally acquired infection is more likely to have a severe acute clinical presentation due to the high number of parasites ingested. Severe disease manifestations include acute myocarditis, pericardial effusion, and meningoencephalitis. The myocarditis of acute Chagas disease is diffuse, with interstitial edema, hypertrophy of myocardial fibers and dilation of cardiac cavities. In addition to diffuse myocardial involvement, damage to the cardiac conduction system can be seen even in early disease [65]. The most common conduction system abnormalities include right-bundle branch block or left anterior fascicular block; additional cardiac findings include segmental left ventricular wall motion abnormalities and diastolic dysfunction [66]. Central nervous system (CNS) manifestations include confusion, headache, hypertonia, seizures and meningismus. Nearly 60% of patients with CNS disease only have neurologic manifestations [67]. After resolution of the acute phase, 20–30% of patients have chronic infection over years to decades, a phenomenon likely linked to human immunogenetic susceptibility [68].

An estimated 66–138 cases of congenital Chagas disease occur annually in the USA, and >14,000 are estimated throughout the Americas. Although most infected newborns are asymptomatic or have mild disease (during which hepatosplenomegaly is a common finding), a small number present with life-threatening pneumonitis/respiratory distress, meningoencephalitis, myocarditis and/or anasarca [69, 70]. Co-infection with human immunodeficiency virus has been associated with severe meningoencephalitis in congenital Chagas [71].

5.3. Diagnosis

Acute disease can be diagnosed by microscopic detection of trypomastigotes in fresh blood specimens, stained blood smears, buffy coat preparation (microhematocrit technique) or serum precipitate (Strout technique), and by PCR. For patients with evidence of CNS disease, direct detection of trypomastigotes can be performed on CSF; centrifugation and repeated testing may increase diagnostic sensitivity of CSF testing. Patients with meningoencephalitis often have a mild CSF pleocytosis with a lymphocytic predominance and increased protein levels. Electrocardiogram and echocardiography should be performed to identify potential conduction system abnormalities and evaluate cardiac function as described above.

Microscopic assessment for congenital disease should be performed using microhematocrit, Strout technique or PCR of cord or peripheral blood within the first month of life. PCR testing for *T. cruzi* DNA is available in some medical centers and at CDC; PCR is especially helpful in diagnosing acute and congenital infection, particularly in the setting of low-level parasitemia. If testing is negative during the first month of life, serologic evaluation for anti-*T. cruzi* IgM and IgG should be performed at 9–12 mo of age when maternal antibodies have waned [72].

Diagnosis during the chronic phase of disease relies on serologic testing, as parasitemia is rarely detectable. Available serologic tests include enzyme-linked immunosorbent assay (ELISA), immunofluorescent antibody assay and indirect hemagglutination. Because no single assay for *T. cruzi* has sufficient sensitivity and specificity, diagnosis should be confirmed using two different laboratory techniques.

5.4. Treatment

Anti-trypanosomal treatment is recommended for all cases of acute and congenital disease, and for patients up to 18 yr of age with chronic disease [73]. Some experts also recommend treatment of selected chronically infected adults. Contraindications to anti-trypanosomal treatment include pregnancy and severe renal or hepatic insufficiency. Currently, only two drugs have proven efficacy against *T. cruzi*, nifurtimox and benznidazole. In the USA, neither drug is approved by the Food and Drug Administration (FDA), but both can be obtained from CDC under investigational protocols [74]. Benznidazole (5–7.5 mg/kg/day in children <12 yr, 5–7 mg/kg/day in children ≥12 years) is given in two divided doses for 60 days. Nifurtimox (15–20 mg/kg/day in children ≤10 yr, 12.5–15 mg/kg/day in children 11–16 yr, and 8–10 mg/kg/day in children ≥17 yr) is given in three to four divided doses for 90 days. Both drugs reduce symptom severity and duration of detectable parasitemia in acute and congenital disease. Parasitological cure is achieved in 60–85% of acute phase infections and in >90% of congenitally infected infants treated in the first year of life [73]. The value of anti-trypanosomal therapy for mild to moderate Chagas-induced cardiac disease is less well established; the multicenter BENEFIT (BENZnidazole Evaluation For Interrupting Trypanosomiasis) trial is currently testing benznidazole versus placebo in 3000 adult patients [75].

5.5. Sequelae

Mortality in children with severe acute disease approaches 5–10%, mainly due to myocarditis and meningoencephalitis. Oral infection tends to have higher mortality rates, ranging from 8–35% [64].

5.6. Prevention

Because of increasing immigrant populations from endemic areas and contaminated blood transfusions, the FDA recommends screening all first-time blood donors [61]. Serologic testing should also be performed for pregnant women (and if positive, their newborns) from endemic areas and for persons who have received blood products in endemic areas.

6. *Baylisascaris* encephalitis (neural larva migrans)

6.1. Etiology/epidemiology

Ingestion of raccoon roundworm (*Baylisascaris procyonis*) eggs causes baylisascariasis. Infection often leads to neural larva migrans (NLM) which usually results in death or neurologic devastation. The definitive host of *B. procyonis* is the North American raccoon (*Procyon lotor*) whose range extends from Canada to Panama. Prevalence of *B. procyonis* in raccoons in the USA is high, ranging from 72–82% [76].

Raccoons defecate in communal latrines located on raised flat surfaces such as stumps and logs, and in urban settings, decks or patios. Infected raccoons shed an average of 20,000–26,000 *B. procyonis* eggs per gram of feces [77]. Eggs can contaminate soil for years, even after fecal matter has disintegrated. Children aged <4 yr (especially males) have the highest incidence of *Baylisascaris* infection due to behaviors such as geophagia. Infection in older children and adults has been reported, often in persons with developmental delay [76].

6.2. Clinical manifestations

After ingestion, *B. procyonis* eggs hatch and larvae penetrate the intestinal wall and spread hematogenously. Clinical presentation depends upon the number of eggs ingested and their subsequent distribution. Visceral larva migrans may present with macular rash, pneumonitis and hepatomegaly. Ocular larva migrans (OLM) with visual impairment or blindness may present in isolation or concurrently with NLM. Subclinical infection may be more widespread than previously believed; one study from Chicago reported that 8% of children aged 1 to 4 yr are seropositive for *B. procyonis* [78].

Central nervous system disease is thought to occur more frequently with ingestion of a large number of eggs. Although larvae are not specifically neurotropic and only 5–7% enter the CNS in a mouse model, when larvae do reach the CNS their large size (1.5–1.9 mm), widespread migration and stimulation of eosinophilic inflammation usually cause extensive neurologic damage [79]. Clinical signs of *B. procyonis* NLM can develop as early as 2 to 4 wk after infection and often progress rapidly. Initial signs and symptoms of encephalitis may include low-grade fever, irritability, lethargy, and visual difficulties, but may proceed

quickly to seizures, ataxia, extensor posturing, coma and death.

6.3. Diagnosis

Baylisascaris encephalitis should be strongly considered in young children with rapidly progressive neurologic disease and peripheral and/or CSF eosinophilia. CSF usually shows mild to moderate pleocytosis with 4–68% eosinophils (absolute eosinophil counts in published case reports range from 1 to 125 cells/mm³ with a median of 16.5 cells/mm³). Glucose levels are often normal and protein levels are usually normal to mildly elevated [80]. Complete blood counts may show a mild leukocytosis, often with marked peripheral eosinophilia. In addition to *Baylisascaris*, the differential diagnosis of eosinophilic meningitis includes angiostrongyliasis, gnathostomiasis, paragonimiasis, schistosomiasis, toxocariasis, trichinosis, selected fungal infections (e.g., coccidioidomycosis), and non-infectious etiologies [81, 82].

Neuroimaging may be useful for diagnosing NLM, but imaging may lag behind clinical disease. Findings include nonspecific white matter disease and focal lesions, especially in periventricular and deep cerebellar distributions [83]. There may also be evidence of hydrocephalus, cortical edema and loss of gray-white differentiation, often with minimal meningeal or parenchymal enhancement. In addition to neuroimaging, ophthalmologic examination to rule out OLM should be performed on all patients with neurologic manifestations.

Diagnostic confirmation of baylisascariasis previously consisted of morphologic identification of larvae in tissue sections, often post-mortem. However, serologic tests (ELISA, immunofluorescent antibody assay) and Western blot are now available; these can obviate need for an invasive biopsy. ELISA-based serologies use larval excretory-secretory antigens to detect serum and CSF antibodies (contact CDC's Division of Parasitic Diseases for testing information). Serologic cross-reactivity between *Baylisascaris* and *Toxocara* can occur; confirmatory Western blot using antigens specific for *Baylisascaris* is recommended [84].

6.4. Treatment

Even with treatment, outcomes of reported *Baylisascaris* encephalitis are poor. Albendazole is the primary

antihelminthic therapy (50 mg/kg/day twice daily). Treatment is usually given for at least 1 to 4 wk. Corticosteroids have frequently been used as adjunctive therapy to reduce the inflammatory response accompanying both infection and therapy. OLM has been treated successfully using the combination of laser photocoagulation and systemic corticosteroids; systemic antihelminthic therapy has a less proven role for treatment of isolated OLM.

6.5. Sequelae

Until recently, all reported human cases of *B. procyonis* encephalitis have resulted in death or significant neurologic sequelae. However, isolated patients with *Baylisascaris* encephalitis have been reported to recover completely after treatment with albendazole and corticosteroids [85].

6.6. Prevention/vaccination

Prevention centers on reducing exposure to soil contaminated with raccoon feces. Parents should encourage hand washing after children play outside or have contact with animals, and should eliminate raccoon latrines near homes. In cases of possible ingestion of contaminated soil, prophylactic albendazole (25–50 mg/kg per day for 10–20 days) is sometimes administered.

7. Amoebic meningoencephalitis

7.1. Etiology/epidemiology

Naegleria fowleri is a thermophilic, free-living amoeba found in freshwater environments worldwide. It causes nearly uniformly fatal primary amoebic meningoencephalitis (PAM). Infection occurs when water is deeply inhaled into the nasal passages during swimming, playing or other recreational activities in warm freshwater. A less common mode of infection is the use of non-sterile water for sinus irrigation for sinusitis or allergic rhinitis [86, 87]. Amoebae pass through the cribriform plate, penetrate into the subarachnoid space and invade the brain parenchyma.

PAM primarily affects immunocompetent children who swim in freshwater during warm summer months. From 1962–2008, 111 cases of PAM were reported in the USA. The median patient age was 12 yr (range,

8 mo–66 yr) with a male predominance (nearly 4/5 of patients). Over half of the cases reported in the USA occurred in Florida and Texas [88]. Because there are no reliable clinical features to distinguish PAM from acute bacterial meningitis and other CNS infections, it is imperative to obtain a history of warm freshwater exposure within the preceding week.

7.2. Clinical manifestations

Symptoms of PAM typically present within five to seven days of exposure to freshwater but can occur as soon as 24 hr. Early symptoms include bitemporal or bifrontal headaches (often acute in onset), high fever, nuchal rigidity, nausea and vomiting, and irritability and restlessness. Symptoms quickly progress to confusion, altered levels of consciousness and seizures as fulminant hemorrhagic CNS necrosis progresses. Cranial nerve palsies (third, fourth and sixth) indicate brain edema and raise concern for impending herniation. Death occurs due to elevated intracranial pressure and brainstem herniation, typically within 10 days of exposure (range 6–17 days) [88].

Two other free-living amoebae, *Acanthamoeba* (several species) and *Balamuthia mandrillaris*, cause granulomatous amoebic encephalitis (GAE). *Acanthamoeba* encephalitis often occurs in the immunocompromised, but *Balamuthia* generally affects immunocompetent patients. Signs of GAE are similar to PAM, but GAE has a more insidious onset over weeks to months.

7.3. Diagnosis

Definitive diagnosis of PAM and GAE can be made using a wet-mount of CSF immediately after collection to look for actively moving amoebic forms. The microbiologist or pathologist should be alerted to the clinician's suspicion for amoebic disease, as trophozoite forms may resemble leukocytes. Gram stain is of very limited utility. Other diagnostic studies for confirmation of suspected cases include immunofluorescent stains of biopsy material, or PCR (available at CDC).

CSF findings include a variable pleocytosis with polymorphonuclear predominance (from 300 to 26,000 cells per mm³), elevated protein and decreased glucose. CSF pressures are often elevated to 30–60 cm H₂O. In late disease, the number of erythrocytes in CSF increases significantly due to hemorrhagic meningoencephalitis.

Imaging findings in PAM and GAE consist of isolated case reports. CT and MRI may be normal in early disease but soon show brain edema and basilar meningeal enhancement. Hydrocephalus and infarctions have also been described [89].

7.4. Treatment

In four successfully treated cases of PAM, diagnosis and aggressive treatment occurred within one to two days of presentation [90–92]. Reported therapeutic regimens include combinations of amphotericin, azithromycin, fluconazole, rifampin, miltefosine and dexamethasone [93]. Amphotericin B remains the cornerstone of therapy for PAM, administered by both intravenous and intrathecal routes. High-dose azithromycin has been shown *in vitro* and in a mouse model to be effective against *Naegleria*, but other macrolide antibiotics are not as effective [94]. Rifampin and fluconazole were added to amphotericin to treat one surviving child [95]. Miltefosine (available from CDC under an investigational new drug protocol in association with the FDA) has shown activity against free-living amoeba *in vitro* and was used in two recent successful treatment regimens [96, 97]. Management also included therapeutic hypothermia for at least one surviving patient.

7.5. Sequelae

Even with treatment, outcome in PAM and GAE is generally poor, with nearly all reported cases in the USA resulting in death. However, several surviving patients have recovered without neurologic sequelae [90–92].

7.6. Prevention

N. fowleri proliferates in water when ambient temperatures rise above 30 °C (86 °F), and can tolerate temperatures up to 45 °C (113 °F). *Acanthamoeba* species are ubiquitous and have been isolated from soil, freshwater/brackish water, humidifiers, and contact lens solution among others; *B. mandrillaris* is primarily found in soil [98]. Free-living amoebae are killed by chlorination (one part per million); routine chlorination of public swimming pools should be performed, particularly during summer months. Because amoebae are ubiquitous in freshwater, there is no practical way to completely prevent potential exposure while

swimming. However, in some high-risk areas, public health authorities routinely test popular swimming locations and post warning signs. Lastly, in patients who use sinus irrigation or “neti pots”, the importance of using sterile water should be emphasized.

References

- [1] Hotez P. Neglected diseases amid wealth in the United States and Europe. *Health Aff (Millwood)* 2009;28(6):1720-5.
- [2] Parise ME, Hotez PJ, Slutsker L. Neglected parasitic infections in the United States: Needs and opportunities. *Am J Trop Med Hyg* 2014;90(5):783-5.
- [3] Savioli L, Daumerie D. World Health Organization. Department of Control of Neglected Tropical Diseases. Sustaining the drive to overcome the global impact of neglected tropical diseases: Second WHO report on neglected tropical diseases. Geneva, Switzerland: World Health Organization; 2013.
- [4] World Health Organization. World Malaria Report 2014. Geneva, Switzerland: World Health Organization; 2014. Available at: http://www.who.int/entity/malaria/publications/world_malaria_report_2014/en/index.html. Accessed December 19, 2014.
- [5] Naing C, Whittaker MA, Nyunt Wai V, Mak JW. Is *Plasmodium vivax* malaria a severe malaria?: A systematic review and meta-analysis. *PLoS Negl Trop Dis* 2014;8(8):e3071.
- [6] Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA, et al. Surveillance for travel-related disease. GeoSentinel Surveillance System, United States, 1997-2011. Morbidity and mortality weekly report Surveillance summaries 2013;62:1-23.
- [7] Dondorp AM, Lee SJ, Faiz MA, Mishra S, Price R, Tjitra E, et al. The relationship between age and the manifestations of and mortality associated with severe malaria. *Clin Infect Dis* 2008;47(2):151-7.
- [8] Potchen MJ, Kampondeni SD, Seydel KB, Birbeck GL, Hammond CA, Bradley WG, et al. Acute brain MRI findings in 120 Malawian children with cerebral malaria: New insights into an ancient disease. *AJNR Am J Neuroradiol* 2012;33(9):1740-6.
- [9] Newton CR, Kirkham FJ, Winstanley PA, Pasvol G, Peshu N, Warrell DA, et al. Intracranial pressure in African children with cerebral malaria. *Lancet* 1991;337(8741):573-6.
- [10] Waller D, Crawley J, Nosten F, Chapman D, Krishna S, Craddock C, et al. Intracranial pressure in childhood cerebral malaria. *Trans R Soc Trop Med Hyg* 1991;85(3):362-4.
- [11] Hanson J, Lee SJ, Mohanty S, Faiz MA, Anstey NM, Charunwatthana P, et al. A simple score to predict the outcome of severe malaria in adults. *Clin Infect Dis* 2010;50(5):679-85.
- [12] Bronzan RN, Taylor TE, Mwenechanya J, Tembo M, Kayira K, Bwanaisa L, et al. Bacteremia in Malawian children with severe malaria: Prevalence, etiology, HIV coinfection, and outcome. *J Infect Dis* 2007;195(6):895-904.
- [13] Burchard GD, Ehrhardt S, Mockenhaupt FP, Mathieu A, Agana-Nsiire P, Anemana SD, et al. Renal dysfunction in children with uncomplicated, *Plasmodium falciparum* malaria in Tamale, Ghana. *Ann Trop Med Parasitol* 2003;97(4):345-50.

- [14] Ehrlich JH, Eke FU. Malaria-induced renal damage: Facts and myths. *Pediatr Nephrol* 2007;22(5):626-37.
- [15] Weber MW, Zimmermann U, van Hensbroek MB, Frenkel J, Palmer A, Ehrlich JH, et al. Renal involvement in Gambian children with cerebral or mild malaria. *Trop Med Int Health* 1999;4(5):390-4.
- [16] Newman RD, Parise ME, Barber AM, Steketee RW. Malaria-related deaths among U.S. travelers, 1963-2001. *Ann Intern Med* 2004;141(7):547-55.
- [17] Centers for Disease Control and Prevention. Malaria Diagnosis & Treatment in the United States; [updated 25 November 2014]. Available at: <http://www.cdc.gov/malaria>. Accessed December 18, 2014.
- [18] Severe malaria. *Trop Med Int Health*. 2014;19 Suppl 1: 7-131.
- [19] World Health Organization. Management of severe malaria: A practical handbook. Geneva, Switzerland: WHO Press. 3rd ed. 2012. Available at: http://apps.who.int/iris/bitstream/10665/79317/1/9789241548526_eng.pdf. Accessed December 19, 2014.
- [20] Hawkes M, Elphinstone RE, Conroy AL, Kain KC. Contrasting pediatric and adult cerebral malaria: The role of the endothelial barrier. *Virulence* 2013;4(6):543-55.
- [21] Mohanty S, Mishra SK, Patnaik R, Dutt AK, Pradhan S, Das B, et al. Brain swelling and mannitol therapy in adult cerebral malaria: A randomized trial. *Clin Infect Dis* 2011;53(4):349-55.
- [22] Warrell DA, Looareesuwan S, Warrell MJ, Kasemsarn P, Intaraprasert R, Bunnag D, et al. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. *N Engl J Med* 1982;306(6):313-9.
- [23] Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, et al. Randomized trial of volume expansion with albumin or saline in children with severe malaria: Preliminary evidence of albumin benefit. *Clin Infect Dis* 2005;40(4):538-45.
- [24] Bangirana P, Opoka RO, Boivin MJ, Idro R, Hodges JS, Romero RA, et al. Severe malarial anemia is associated with long-term neurocognitive impairment. *Clin Infect Dis* 2014;59(3):336-44.
- [25] Boivin MJ, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, et al. Cognitive impairment after cerebral malaria in children: A prospective study. *Pediatrics* 2007;119(2):e360-6.
- [26] van Hensbroek MB, Palmer A, Jaffar S, Schneider G, Kwiatkowski D. Residual neurologic sequelae after childhood cerebral malaria. *J Pediatr* 1997;131(1Pt 1):125-9.
- [27] Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, et al. AQUAMAT group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): An open-label, randomised trial. *Lancet* 2010;376(9753):1647-57.
- [28] Idro R, Ndiritu M, Ogutu B, Mithwani S, Maitland K, Berkley J, et al. Burden, features, and outcome of neurological involvement in acute falciparum malaria in Kenyan children. *JAMA* 2007;297(20):2232-40.
- [29] Arama C, Troye-Blomberg M. The path of malaria vaccine development: Challenges and perspectives. *J Intern Med* 2014;275(5):456-66.
- [30] Ndimubanzi PC, Carabin H, Budke CM, Nguyen H, Qian YJ, Rainwater E, et al. A systematic review of the frequency of neurocyticercosis with a focus on people with epilepsy. *PLoS Negl Trop Dis* 2010;4(11):e870.
- [31] Román G, Sotelo J, Del Brutto O, Flisser A, Dumas M, Wadia N, et al. A proposal to declare neurocysticercosis an international reportable disease. *Bull World Health Organ* 2000;78(3):399-406.
- [32] Cantey PT, Coyle CM, Sorvillo FJ, Wilkins PP, Starr MC, Nash TE. Neglected parasitic infections in the United States: Cysticercosis. *Am J Trop Med Hyg* 2014;90(5):805-9.
- [33] Ong S, Talan DA, Moran GJ, Mower W, Newdow M, Tsang VC, et al; Emergency ID NET Study Group. Neurocysticercosis in radiographically imaged seizure patients in U.S. emergency departments. *Emerg Infect Dis* 2002;8(6):608-13.
- [34] Sorvillo FJ, DeGiorgio C, Waterman SH. Deaths from cysticercosis, United States. *Emerg Infect Dis* 2007;13(2):230-5.
- [35] García HH, Rodríguez S, Friedland JS; Cysticercosis Working Group in Peru. Immunology of *Taenia solium* taeniasis and human cysticercosis. *Parasite Immunol* 2014;36(8):388-96.
- [36] Bhattacharjee S, Biswas P, Mondal T. Clinical profile and follow-up of 51 pediatric neurocysticercosis cases: A study from Eastern India. *Ann Indian Acad Neurol* 2013;16(4): 549-55.
- [37] Sahu PS, Seepana J, Padela S, Sahu AK, Subbarayudu S, Barua A. Neurocysticercosis in children presenting with afebrile seizure: Clinical profile, imaging and serodiagnosis. *Rev Inst Med Trop Sao Paulo* 2014;56(3):253-8.
- [38] Del Brutto OH, Santibañez R, Noboa CA, Aguirre R, Díaz E, Alarcón TA. Epilepsy due to neurocysticercosis: Analysis of 203 patients. *Neurology* 1992;42(2):389-92.
- [39] Jain RS, Handa R, Vyas A, Prakash S, Nagpal K, Bhana I, et al. Cysticercotic encephalitis: A life threatening form of neurocysticercosis. *Am J Emerg Med* 2014;32(11):1444.e1-2.
- [40] Rangel R, Torres B, Del Brutto O, Sotelo J. Cysticercotic encephalitis: A severe form in young females. *Am J Trop Med Hyg* 1987;36(2):387-92.
- [41] Ignacio Madrazo N, Olhagaray B, Becerra M, Sandoval MA, Raúl Soto L. Acute cysticercosis encephalitis: Description of a histologically confirmed case. *Neurosurgery* 1983;13(5): 593-5.
- [42] García HH, Del Brutto OH. Imaging findings in neurocysticercosis. *Acta Trop* 2003;87(1):71-8.
- [43] Feldman M, Plancarte A, Sandoval M, Wilson M, Flisser A. Comparison of two assays (EIA and EITB) and two samples (saliva and serum) for the diagnosis of neurocysticercosis. *Trans R Soc Trop Med Hyg* 1990;84(4):559-62.
- [44] Wilson M, Bryan RT, Fried JA, Ware DA, Schantz PM, Pilcher JB, et al. Clinical evaluation of the cysticercosis enzyme-linked immunoelectrotransfer blot in patients with neurocysticercosis. *J Infect Dis* 1991;164(5):1007-9.
- [45] Rodríguez S, Wilkins P, Dorny P. Immunological and molecular diagnosis of cysticercosis. *Pathog Glob Health* 2012;106(5):286-98.
- [46] Del Brutto OH, Rajshekhar V, White AC Jr, Tsang VC, Nash TE, Takayanagui OM, et al. Proposed diagnostic criteria for neurocysticercosis. *Neurology* 2001;57(2):177-83.
- [47] Abba K, Ramaratnam S, Ranganathan LN. Anthelmintics for people with neurocysticercosis. *Cochrane Database Syst Rev* 2010;(1):CD000215.
- [48] Sorvillo FJ, Waterman SH, Richards FO, Schantz PM. Cysticercosis surveillance: Locally acquired and travel-related infections and detection of intestinal tapeworm carriers in Los Angeles County. *Am J Trop Med Hyg* 1992;47(3):365-71.
- [49] Olsen A, van Lieshout L, Marti H, Polderman T, Polman K, Steinmann P, et al. Strongyloidiasis-the most neglected of

- the neglected tropical diseases? *Trans R Soc Trop Med Hyg* 2009;103(10):967-72.
- [50] Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev* 2004;17(1):208-17.
- [51] Mokheles B, Shulzhenko O, Garimella PS, Kuma L, Monti C. Pulmonary Strongyloidiasis: The Varied Clinical Presentations. *Clin Pulm Med* 2004;11(1):6-13.
- [52] Al-Hasan MN, McCormick M, Ribes JA. Invasive enteric infections in hospitalized patients with underlying strongyloidiasis. *Am J Clin Pathol* 2007;128(4):622-7.
- [53] Ghosh K, Ghosh K. *Strongyloides stercoralis* septicaemia following steroid therapy for eosinophilia: Report of three cases. *Trans R Soc Trop Med Hyg* 2007;101(11):1163-5.
- [54] Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis* 2001;33(7):1040-7.
- [55] Mejia R, Nutman TB. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by *Strongyloides stercoralis*. *Curr Opin Infect Dis* 2012;25(4):458-63.
- [56] Link K, Orenstein R. Bacterial complications of strongyloidiasis: *Streptococcus bovis* meningitis. *South Med J* 1999;92(7):728-31.
- [57] Fusco DN, Downs JA, Satlin MJ, Pahuja M, Ramos L, Barie PS, et al. Non-oral treatment with ivermectin for disseminated strongyloidiasis. *Am J Trop Med Hyg* 2010;83(4):879-83.
- [58] Tarr PE, Miele PS, Perego KS, Smith MA, Neva FA, Lucey DR. Case report: Rectal administration of ivermectin to a patient with *Strongyloides* hyperinfection syndrome. *Am J Trop Med Hyg* 2003;68(4):453-5.
- [59] Howard EJ, Xiong X, Carlier Y, Sosa-Estani S, Buekens P. Frequency of the congenital transmission of *Trypanosoma cruzi*: A systematic review and meta-analysis. *BJOG* 2014;121(1):22-33.
- [60] Pereira KS, Schmidt FL, Guaraldo AM, Franco RM, Dias VL, Passos LA. Chagas' disease as a foodborne illness. *J Food Prot* 2009;72(2):441-6.
- [61] Bern C, Kjos S, Yabsley MJ, Montgomery SP. *Trypanosoma cruzi* and Chagas' Disease in the United States. *Clin Microbiol Rev* 2011;24(4):655-81.
- [62] Jannin JS, Roberto. Estimación cuantitativa de la enfermedad de Chagas en las Américas. Montevideo: Organización Panamericana de la Salud. 2006 (in Spanish).
- [63] Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. *Clin Infect Dis* 2009;49(5):e52-4.
- [64] Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. *Lancet*. 2010;375(9723):1388-402.
- [65] Coura JR. Chagas disease: What is known and what is needed—a background article. *Mem Inst Oswaldo Cruz* 2007;102 Suppl 1:113-22.
- [66] Nunes MC, Dones W, Morillo CA, Encina JJ, Ribeiro AL; Council on Chagas Disease of the Interamerican Society of Cardiology. Chagas disease: An overview of clinical and epidemiological aspects. *J Am Coll Cardiol* 2013;62(9):767-76.
- [67] Sica R. Nervous system compromise. In: Storino R, Milei J, editors. Chagas' disease. 1st ed. Buenos Aires: Mosby/Doyma; 1994; pp. 209-34.
- [68] Vasconcelos RH, Montenegro SM, Azevedo EA, Gomes YM, Morais CN. Genetic susceptibility to chronic Chagas disease: An overview of single nucleotide polymorphisms of cytokine genes. *Cytokine* 2012;59(2):203-8.
- [69] Freilij H, Altcheh J. Congenital Chagas' disease: Diagnostic and clinical aspects. *Clin Infect Dis* 1995;21(3):551-5.
- [70] Torrico F, Alonso-Vega C, Suarez E, Rodriguez P, Torrico MC, Dramaix M, et al. Maternal *Trypanosoma cruzi* infection, pregnancy outcome, morbidity, and mortality of congenitally infected and non-infected newborns in Bolivia. *Am J Trop Med Hyg* 2004;70(2):201-9.
- [71] Freilij H, Altcheh J, Muchnik G. Perinatal human immunodeficiency virus infection and congenital Chagas' disease. *Pediatr Infect Dis J* 1995;14(2):161-2.
- [72] Oliveira I, Torrico F, Muñoz J, Gascon J. Congenital transmission of Chagas disease: A clinical approach. *Expert Rev Anti Infect Ther* 2010;8(8):945-56.
- [73] Bern C, Montgomery SP, Herwaldt BL, Rassi A Jr, Marin-Neto JA, Dantas RO, et al. Evaluation and treatment of chagas disease in the United States: A systematic review. *JAMA* 2007;298(18):2171-81.
- [74] Centers for Disease Control and Prevention. CDC Drug Service [updated 12 July 2013]. Available at: <http://www.cdc.gov/laboratory/drugservice/>. Accessed December 18, 2014.
- [75] Marin-Neto JA, Rassi A Jr, Morillo CA, Avezum A, Connolly SJ, Sosa-Estani S, et al.; BENEFIT Investigators. Rationale and design of a randomized placebo-controlled trial assessing the effects of etiologic treatment in Chagas' cardiomyopathy: the BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT). *Am Heart J* 2008;156(1):37-43.
- [76] Murray WJ, Kazacos KR. Raccoon roundworm encephalitis. *Clin Infect Dis* 2004;39(10):1484-92.
- [77] Kazacos KR. *Baylisascaris procyonis* and related species. In: Samuel WM, Pybus MJ, Kocan AA, editors. Parasitic diseases of wild mammals. 2nd ed. Ames (IA): Iowa State University Press; 2001; pp. 301-41.
- [78] Brinkman WB, Kazacos KR, Gavin PJ, Binns HJ, Robichaud JD, O'Gorman M. Seroprevalence of *Baylisascaris procyonis* (raccoon roundworm) in Chicago area children. In: Program and abstracts of the 2003 Annual Meeting of the Pediatric Academic Societies, Seattle, Washington; 2003 May 3-6 (abstract).
- [79] Kazacos KR. Raccoon ascarids as a cause of larva migrans. *Parasitol Today* 1986;2(9):253-5.
- [80] Gavin PJ, Kazacos KR, Shulman ST. Baylisascariasis. *Clin Microbiol Rev* 2005;18(4):703-18.
- [81] Graeff-Teixeira C, da Silva AC, Yoshimura K. Update on eosinophilic meningoencephalitis and its clinical relevance. *Clin Microbiol Rev* 2009;22(2):322-48.
- [82] Lo Re V 3rd, Gluckman SJ. Eosinophilic meningitis. *Am J Med* 2003;114(3):217-23.
- [83] Rowley HA, Uht RM, Kazacos KR, Sakanari J, Wheaton WV, Barkovich AJ, et al. Radiologic-pathologic findings in raccoon roundworm (*Baylisascaris procyonis*) encephalitis. *AJNR Am J Neuroradiol* 2000;21(2):415-20.
- [84] Dangoudoubyam S, Kazacos KR. Differentiation of larva migrans caused by *Baylisascaris procyonis* and *Toxocara* species by Western blotting. *Clin Vaccine Immunol* 2009;16(11):1563-8.
- [85] Pai PJ, Blackburn BG, Kazacos KR, Warrier RP, Bégue RE. Full recovery from *Baylisascaris procyonis* eosinophilic meningitis. *Emerg Infect Dis* 2007;13(6):928-30.
- [86] Sowerby LJ, Wright ED. Tap water or "sterile" water for sinus irrigations: What are our patients using? *Int Forum Allergy Rhinol* 2012;2(4):300-2.
- [87] Yoder JS, Straif-Bourgeois S, Roy SL, Moore TA, Visvesvara GS, Ratard RC. Primary amebic meningoencephalitis deaths associated with sinus irrigation using contaminated tap water. *Clin Infect Dis* 2012;55(9):e79-85.

- [88] Yoder JS, Eddy BA, Visvesvara GS, Capewell L, Beach MJ. The epidemiology of primary amoebic meningoencephalitis in the USA, 1962-2008. *Epidemiol Infect* 2010;138(7): 968-75.
- [89] Singh P, Kochhar R, Vashishta RK, Khandelwal N, Prabhakar S, Mohindra S, et al. Amebic meningoencephalitis: Spectrum of imaging findings. *AJNR Am J Neuroradiol* 2006;27(6):1217-21.
- [90] Brown RL. Successful treatment of primary amebic meningoencephalitis. *Arch Intern Med* 1991;151(6): 1201-2.
- [91] Centers for Disease C. *Naegleria fowleri* - Primary Amebic Meningoencephalitis: Information for Public Health and Medical Professionals: Centers for Disease Control and Prevention; 2014 [updated 14 April 2014,]. Available at: http://www.cdc.gov/parasites/naegleria/health_professionals.html. Accessed September 21, 2014.
- [92] Seidel JS, Harmatz P, Visvesvara GS, Cohen A, Edwards J, Turner J. Successful treatment of primary amebic meningoencephalitis. *N Engl J Med* 1982;306(6):346-8.
- [93] Centers for Disease Control and Prevention, CDC. *Naegleria fowleri* - Primary amebic meningoencephalitis (PAM): Treatment. 2014 [updated 28 May 2014,]. Available at: <http://www.cdc.gov/parasites/naegleria/treatment-hcp.html>. Accessed September 21, 2014.
- [94] Goswick SM, Brenner GM. Activities of therapeutic agents against *Naegleria fowleri* *in vitro* and in a mouse model of primary amebic meningoencephalitis. *J Parasitol* 2003;89(4):837-42.
- [95] Vargas-Zepeda J, Gómez-Alcalá AV, Vázquez-Morales JA, Licea-Amaya L, De Jonckheere JF, Lares-Villa F. Successful treatment of *Naegleria fowleri* meningoencephalitis by using intravenous amphotericin B, fluconazole and rifampicin. *Arch Med Res* 2005;36(1):83-6.
- [96] Centers for Disease Control and Prevention (CDC). Investigational drug available directly from CDC for the treatment of infections with free-living amebae. *MMWR Morb Mortal Wkly Rep* 2013;62(33):666.
- [97] Schuster FL, Guglielmo BJ, Visvesvara GS. In-vitro activity of miltefosine and voriconazole on clinical isolates of free-living amebas: *Balamuthia mandrillaris*, *Acanthamoeba* spp., and *Naegleria fowleri*. *J Eukaryot Microbiol* 2006;53(2):121-6.
- [98] Visvesvara GS, Moura H, Schuster FL. Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*. *FEMS Immunol Med Microbiol* 2007;50(1):1-26.