

Review Article

Recently Reemerging Helminthic Infections Causing Eosinophilic Meningoencephalitis: Neuroangiostrongyliasis, Baylisascariasis, and Gnathostomiasis

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Abstract Today most emerging infectious diseases, such as sudden acute respiratory syndrome (SARS) and novel influenza A H1N1 (swine flu), arise in the natural environment as zoonoses and are distributed by international commerce and travel. The helminthic infections that can cause eosinophilic meningoencephalitis (EM), such as neuroangiostrongyliasis, baylisascariasis, and gnathostomiasis, share these characteristics of emerging infectious diseases. Neuroangiostrongyliasis, a rodent zoonosis, is now endemic in the United States (US) following the introduction of giant African land snails as biological controls and exotic pets. Baylisascariasis, a raccoon zoonosis, has extended its US distribution range from the northern US to the southeast and west coast since the 1980s and was exported to Japan in the exotic pet trade. Gnathostomiasis, a zoonosis of wild carnivores, has been recently recognized as an emerging cause of EM in returning travelers to the United Kingdom (UK). This review analyzes scientific articles selected by PubMed and Medline search engines, 1966–2009, in order to assess the evolving epidemiology of these three examples of recently reemerging helminthic infections causing EM worldwide in order to compare their epidemiology, clinical manifestations, diagnoses, and management outcomes and to alert clinicians to populations at increased risk of helminthic EM as a result of age, ethnicity, lifestyle, food choices, location of permanent residence, or recent international travel.

Keywords meningitis, meningoencephalitis, eosinophilic; encephalitis, eosinophilic; larva migrans, visceral, cerebral; angiostrongyliasis, neuroangiostrongyliasis; baylisascariasis; gnathostomiasis, cerebral gnathostomiasis

1 Introduction

The helminthic infections that can cause eosinophilic meningoencephalitis (EM), such as neuroangiostrongyliasis

(NAS), baylisascariasis (BAS), and gnathostomiasis (GNS), share many of the characteristics of emerging infectious diseases. NAS is endemic throughout the Indo-Pacific Basin and many Atlantic and Gulf of Mexico port cities following the worldwide importation of its causative parasite, the rat lungworm, *Angiostrongylus cantonensis*, in stowaway rats on container ships [33,42,45,67,69,72]. Today, introduced giant African land snails, *Achatina fulica*, and most indigenous snail and slug species serve as competent intermediate hosts of *A. cantonensis*, now capable of completing its complex life cycle almost anywhere. BAS, a raccoon zoonosis, extended its United States (US) distribution range from the northern US to the southeast and west coast in the 1980s; it was shortly thereafter exported to Japan in the exotic pet trade and is now enzootic in raccoons throughout the US. GNS, a tropical zoonosis of wild carnivores, is an endemic cause of EM throughout Southeast Asia and Latin America and has been recently recognized as an emerging etiology of EM among travelers returning to the United Kingdom (UK).

This review analyzes scientific articles selected by PubMed and Medline search engines, 1966–2009, in order to assess the evolving ecology and epidemiology of EM worldwide; to define the case diagnosis of EM based on cerebrospinal fluid (CSF) microscopy; to stratify the causes of EM as infectious versus noninfectious; to compare the clinical presentations and management of 3 recently reemerging causes of helminthic EM, disseminated by international commerce; to alert clinicians to populations at increased risks of helminthic EM as a result of age, ethnicity, lifestyle, food choices, location of permanent residence, or recent travel.

2 Materials and methods

A National Library of Medicine PubMed and Medline search, 1966–2009, was conducted in order to (1) assess

the evolving global epidemiology of eosinophilic meningoencephalitis (EM); (2) define the case diagnosis of EM based on CSF microscopy; (3) compare the epidemiology and outcomes of the most common causes of helminthic EM worldwide; (4) compare the clinical manifestations and management of three reemerging causes of helminthic EM; (5) identify populations at increased risk of helminthic EM as a result of age, ethnicity, lifestyle, food choices, location of permanent residence, or recent travel; (6) recommend simple strategies to prevent and to control helminthic EM. Data sources that were extracted included case reports, case series, descriptive epidemiological studies, meta-analyses, case-control outbreak investigations, and treatment trials of helminthic EM. This investigation had no external funding sources.

3 Results

3.1 The epidemiology of eosinophils in the cerebrospinal fluid

The earliest description of eosinophils in the cerebrospinal fluid (CSF) was made in 1907 in association with neurosyphilis [23]. In 1913, the first confirmed description of CNS eosinophilia in a helminthic infection was made in association with neurocysticercosis [36]. In 1979, Kuberski noted that CNS invasion by helminths was the most frequent cause of eosinophils in the CSF, an uncommon finding with a very limited differential diagnosis [36]. Nevertheless, eosinophilic meningitis (EM) remained rarely reported until Rosen and co-investigators first described the pathophysiology of neuroangiostrongyliasis (NAS) in association with neural larval migrans caused by the infective third-stage larva of the rat lungworm, *A. cantonensis*, in human dead-end hosts [57]. Today, *A. cantonensis* is the most common infectious cause of EM in humans in the US and worldwide [24, 26, 29, 37, 64].

Traditionally, EM has been defined by a microscopic complete blood count on a CSF sample as 10 or more eosinophils/mm³ or 10% or greater eosinophils in the total cell count [37, 57]. Although parasitic infections are the most common infectious causes of EM, bacterial, viral, and fungal infections may also cause EM [37, 57, 64]. The most common noninfectious causes of eosinophils in the CSF are intracranial appliances or hardware, especially ventriculoperitoneal (VP) shunts for hydrocephalus [37, 57, 64].

During November 2004–January 2005, 5 cases of EM attributable to *A. cantonensis* infection were reported to the Hawaii State Department of Health in Honolulu, Hawaii [26]. In order to determine if this temporal cluster of EM cases reflected a true increased incidence of NAS over background cases in Hawaii, Hochberg and co-investigators reviewed statewide laboratory and medical records for

all EM cases in Hawaii during the period January 2001–February 2005 with over 90% of state hospitals reporting to the state and federal public health investigators [26]. The authors identified 83 cases of EM for the 50-month total study period with 70 (84%) cases occurring during the 46-month baseline study period before the outbreak and 13 (16%) cases occurring during the 4-month cluster outbreak period [26]. The authors attributed 24 (29%) of the 83 EM cases to *A. cantonensis* infections by microscopic ($n = 1$) or serologic ($n = 23$) confirmation (13) [26]. Of the remaining 59 cases, 35 (42% of 83) were in persons with intracranial hardware, often VP shunts; 5 (6%) were in patients with bacterial meningitis; 4 (5%) were in patients with viral meningoencephalitis and in the remaining 13 (16%) patients, no infectious agents were identified in 10 (12%) [26]. Of the remaining 3 noninfectious cases of EM, 1 patient had meningeal infiltrating cancer, 1 had a suspected vertebral artery dissection, and 1 case was unclassified [26].

3.2 The differential diagnosis of helminthic eosinophilic meningoencephalitis

Although the first helminthic infection to be associated with EM was larval pork tapeworm infection or neurocysticercosis, several other parasites have been noted to cause EM, with and without concomitant peripheral eosinophilia, including *A. cantonensis*, *Baylisascaris procyonis*, *Gnathostoma spinigerum*, *Trichinella spiralis*, and the *Toxocara* species roundworms of cats (*T. cati*) and dogs (*T. canis*) (Table 1) [17, 23, 29, 41]. *B. procyonis* is more likely to cause both EM and peripheral eosinophilia, and *A. cantonensis* and *G. spinigerum* may cause EM without an associated peripheral eosinophilia (Table 1) [24, 26, 29, 36, 37, 57, 64]. *T. solium* cysticerci may or may not cause CSF or peripheral eosinophilia, depending on the magnitude of the parasite burden. Many other parasites have uncommonly caused a nonintense eosinophilic pleocytosis in the CSF with less than 10 eosinophils/mm³, including *Dirofilaria immitis*, *Echinococcus granulosa*, *Fasciola hepatica*, *Paragonimus westermani*, *Onchocerca volvulus*, and *Schistosoma* species (Table 1) [24, 26, 29, 37, 64].

Although *B. procyonis*, *G. spinigerum*, *T. cati*, *T. canis*, and *T. solium* cysticerci can cause both EM and ocular larva migrans, *B. procyonis* is more often associated with a unique unilateral form of ocular larva migrans known as diffuse unilateral subacute neuroretinitis (DUSN) [17, 18, 21, 24, 25, 30, 47, 48, 52]. *B. procyonis* EM or baylisascariasis (BAS) has consistently demonstrated the highest mortality rate from helminthic EM and greatest morbidity in survivors [52]. Unlike *B. procyonis* EM, *A. cantonensis* EM may resolve spontaneously and without specific treatment [26, 29, 37, 57, 64]. *A. cantonensis* and *B. procyonis* infections are significantly more likely to cause

<u>Helminthic disease</u>	<u>Neuroangiostrongyliasis</u>	<u>Baylisascariasis</u>	<u>Gnathostomiasis</u>
<u>Helminthic parasite</u>	<i>Angiostrongylus cantonensis</i>	<i>Baylisascaris procyonis</i>	<i>Gnathostoma spinigerum</i>
<u>Common name</u>	Rat lungworm	Raccoon roundworm	Yangtze edema, Shanghai rheumatism, nodular eosinophilic migratory panniculitis (US)
<u>Zoonotic reservoir</u>	Rodents	Raccoons, rarely dogs	Domestic & wild cats & dogs
<u>Intermediate hosts</u>	Snails & slugs, especially the African giant land snail (<i>Achatina fulica</i>)	Rodents, small mammals, birds	Copepods, crustaceans (freshwater shrimp), amphibians (frogs), small fish
<u>Infective stage</u>	3rd-stage larvae in snail/slug intermediate hosts	Embryonated eggs in raccoon feces	3rd-stage muscle encysted larvae in intermediate hosts
<u>Incubation period</u>	2 weeks	Unknown, 1–3 weeks?	3 weeks – 5 years (mean: 1 year)
<u>Typical patient age range</u>	All ages	Infants with pica	Adults who consume raw/marinated amphibians, crustaceans, fish
<u>Travel history</u>	SE Asia, Caribbean, Southern US port cities	Anywhere in the US: mostly NW, MW, NE, SE, Mid- Atlantic states	SE Asia, Japan, Mexico, Ecuador
<u>CSF eosinophilia</u>	Significant, +++ ($\geq 10\%$)	Significant, +++ ($\geq 10\%$)	Significant, +++ ($\geq 10\%$)
<u>Peripheral eosinophilia</u>	Scant, +, to moderate, ++, may be absent	Moderate, ++ ($\leq 10\%$)	Significant, +++ ($\geq 10\%$)

MW: Midwest, NE, NW: Northeast, Northwest; SE, SW: Southeast, Southwest; US: United States.

Table 1: The differential diagnosis of three reemerging helminthic causes of eosinophilic meningoencephalitis (EM).

EM than *G. spinigerum* and neurocysticercosis, which are more often associated with migratory panniculitis and seizure disorder, respectively (Table 1) [24, 29, 37, 47, 52].

G. spinigerum-induced gnathostomiasis (GNS) has now been recognized as an emerging imported disease in the UK [47]. Since *G. spinigerum* is now endemic in Central and South America, most notably in Mexico, Ecuador, and Peru, GNS may soon become another emerging potential cause of EM in the US as well as in the UK, given the adventurous and exotic eating habits of travelers abroad [47].

The ubiquitous ascarid parasites of dogs and cats, *T. canis* and *T. cati*, are endemic worldwide, especially in the developing areas of the Caribbean and Latin America without preventive veterinary care [21, 25]. Although common causes of visceral (hepatic) larva migrans, *T. canis*, and *T. cati* do not usually cause neural larva migrans with EM and can be easily prevented by veterinary disease control programs, discouraging pica (geophagia) in children, and excluding pets from beaches, sandboxes, and playgrounds [21, 25].

The endemic versus the hyperendemic distribution ranges of the 3 recently reemerging causes of helminthic EM (NAS, BAS, and GNS) are compared in Table 2 [22].

3.3 The ecology and pathobiology of neuroangiostrongyliasis

A. cantonensis, the rat lungworm, was first described in China in 1935, living in the pulmonary arteries of rats [8]. The first human infection or neuroangiostrongyliasis (NAS) was reported from Taiwan in 1945 [3]. The life cycle is complex and requires a rodent definitive host and an

appropriate mollusk intermediate host, usually land snails or slugs (Figure 1). Adult worms mature in rat brains, enter the central circulation, and mate in the pulmonary arteries producing eggs. The eggs become first-stage larvae that penetrate pulmonary vessels to access the respiratory tree, where they are coughed up, swallowed, and excreted in feces. These second-stage larvae must be consumed by land snails or slugs in order to mature into infective third-stage larvae that are eaten by rodents and maintain the parasite's life cycle. Man becomes a dead-end host by consuming raw intermediate mollusk hosts or food items, such as unwashed fruits and vegetables, contaminated with larval snails or slugs; or by consuming raw fish, crustacean, or amphibian (shrimp, crabs, frogs) transport, or paratenic, hosts that consumed infected mollusks. In man and paratenic hosts, the neurotropic larvae migrate to the CNS (neural larva migrans) seeking to mature into young adults as in rat brains, but eventually die causing EM [68, 70].

3.4 The epidemiology of neuroangiostrongyliasis

A. cantonensis is enzootic throughout Southeast Asia, most Indian and Pacific Ocean islands, including the Hawaiian Islands, most Caribbean islands, and has even been reported in New Orleans, Louisiana [6, 37, 39, 50]. The geographic distribution of the parasite frequently places travelers to tropical islands and coastal cities in parasite-endemic regions. Outbreaks of NAS have been reported in travelers to and local residents from the Hawaiian Islands, and in US tourists returning from Jamaica [24, 26, 29, 37, 39, 64].

The rapid global spread of the parasite resulted from infected rat stowaways disembarking from container ships

<i>Parasites</i>	<i>Angiostrongylus cantonensis</i>	<i>Baylisascaris procyonis</i>	<i>Gnathostoma spinigerum</i>
<u>Hyperendemic ranges of distribution</u>	Caribbean Islands Hawaiian Islands Latin America Polynesian & Micronesian Islands Southeast Asia, including China	Canada US	Australia Caribbean Islands Central America (Mexico) Japan Korea South America (Ecuador, Peru) Southeast Asia, including China
<u>Endemic ranges of distribution</u>	Southern United States (US)	Japan	Southern South America

Table 2: The geographic ranges of distribution of three helminthic causes of eosinophilic meningoencephalitis (EM)²⁵.

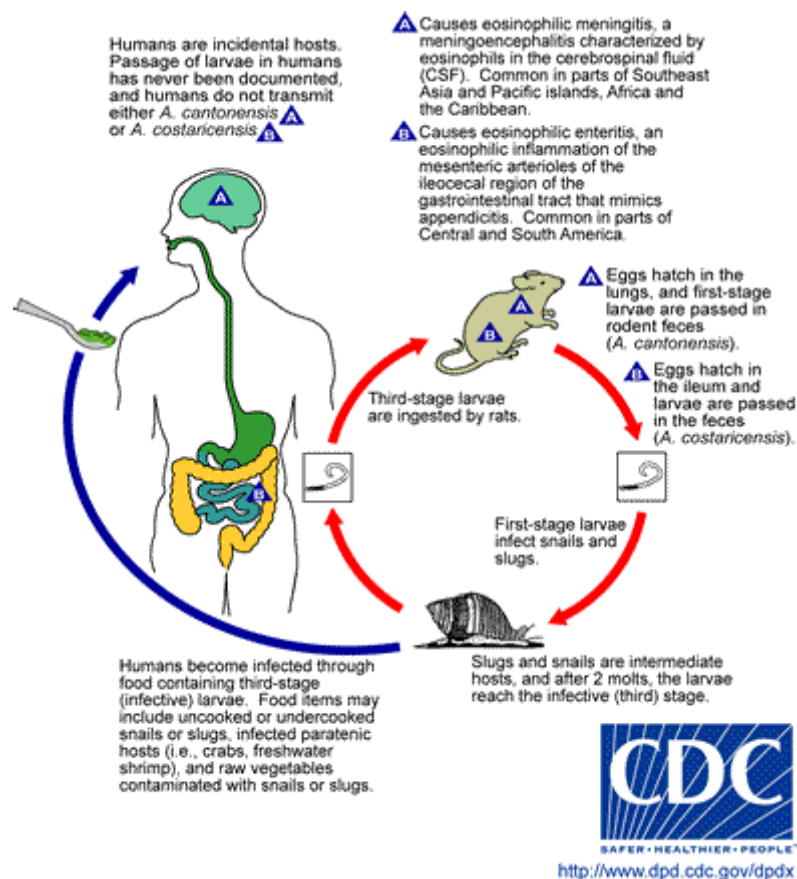


Figure 1: The life cycle of the rat lungworm, *Angiostrongylus cantonensis*, which causes eosinophilic meningitis (A), is compared to the life cycle of *Angiostrongylus costaricensis*, which causes eosinophilic enteritis. Source: CDC Image, available at <http://www.dpd.cdc.gov/dpdx>. No copyright permission required.

docked at port cities and the intentional introduction of giant African land snails, competent intermediate hosts for the parasite, as biological controls for commercial agricultural operations and as exotic pets for home terrariums [33,42, 69,72]. In 1979, Kuberski and Wallace reported the clinical outcomes in 34 patients with *A. cantonensis*-induced EM in Hawaii between 1959 and 1976 [39]. The diagnosis was based on clinical and epidemiological findings in most cases ($n = 32$), rather than the presence of the parasite in the

CNS ($n = 2$), and 14 patients reported consuming either raw land snails or slugs ($n = 8$) or undercooked crustaceans ($n = 6$) [39]. The patients usually presented with severe headache, stiff neck, paresthesias (in most adults), and mild or no fever [39]. Although 2 deaths occurred, the authors noted that the illness was usually self-limited and resolved completely without specific antihelminthic treatment [39].

A. cantonensis was responsible for an outbreak of NAS in 12 US travelers returning from Jamaica to Chicago in

2000, who had consumed romaine lettuce [64]. The lettuce food vector was actually imported to Jamaica from the US and presumably contaminated somewhere with snails or slugs or their secretions containing infective *A. cantonensis* larvae [64].

In their comparison of cluster cases to background prevalence cases of *A. cantonensis* infections in Hawaii during 2001–2005, Hochberg et al. identified 83 cases of EM for the 50-month total study period [26]. The authors attributed 24 (29%) of the 83 EM cases to *A. cantonensis* infections by microscopic ($n = 1$) or serologic ($n = 23$) confirmation with the remaining cases due to noninfectious causes, mostly the presence of intracranial appliances, usually VP shunts [26].

There is now substantial clinical, epidemiological, parasitological, and immunological evidence that an emerging *A. cantonensis* zoonosis has been established in the continental US and throughout the Caribbean in rats, mollusks, and paratenic frog hosts as a direct result of international commerce and travel. In addition, an increasing number of human cases of *A. cantonensis*-induced EM have been reported in the US since 1959. Clinicians should include NAS in the differential diagnosis of EM, especially if there is a history of raw mollusk, crustacean, or amphibian consumption, or recent travel to highly endemic areas, including Southeast Asia and all Polynesian, Hawaiian, and Caribbean Islands. Although cases of NAS are rarely confirmed by the expert identification of *A. cantonensis* larvae or adults in the CNS, most cases can now be presumed epidemiologically and confirmed immunologically. The reported mortality in US cases is relatively low ($\leq 5.0\%$) and most patients recover completely, even without specific antihelminthic treatment [6, 10, 29, 33, 37–39, 43, 50, 55, 64, 71].

3.5 The clinical manifestations and management of neuroangiostrongyliasis

Following an incubation period of approximately 2 weeks, patients with NAS will typically present as aseptic meningitis with combinations of severe headache, stiff neck, nausea, vomiting, low-grade to no fever (especially in adults), and asymmetrical hyperesthesias or paresthesias in the extremities that are frequently overlooked [39]. In their descriptive analysis of NAS in 12 travelers returning to the US from Jamaica, Slom et al. reported the most commonly presenting symptoms as headache (100%), visual disturbances including photophobia (92%), neck stiffness or pain (83%), fatigue (83%), hyperesthesias (75%), vomiting (67%), and paresthesias (50%) [64]. Low-grade fever occurred in 5 (42%) of the 12 patients with NAS, and only two of the nine patients who were hospitalized for treatment of severe headaches by CSF drainage had temperatures above 37.8°C. [64].

Papilledema and transient cranial nerve palsies, most commonly facial nerve palsies, may occur in NAS; but

permanent neurologic sequelae and death are rare, and most patients recover completely within two weeks [39]. Nevertheless, case fatalities from NAS have been reported from encephalitis or massive larval migration into critical centers of the brain [39, 62, 72]. In a 2009 retrospective analysis of 94 patients with seropositive NAS in Thailand, Sawanyawisuth et al. used a linear regression model to identify clinical factors predictive of encephalitic NAS [62]. Their model identified advanced age, prolonged duration of headache, and fever $> 38^\circ\text{C}$. as statistically significant predictive factors for encephalitic NAS, with a higher case fatality rate than meningitic NAS [62].

Occasionally, identifiable larvae may be recovered from the CSF or even observed in the retina [38, 43, 54, 55, 71]. Pirisi et al. have reported finding a mature adult worm in the lungs of a fatal case of NAS [54]. However, since man is a dead-end host and not a definitive host for *A. cantonensis*, larvae do not usually mature to adulthood in the lungs, but die in the brain resulting in transient inflammatory reactions manifesting as EM [10, 38, 71].

An episode of NAS does not confer lasting immunity, and recurrent infections following consumption of raw mollusks or other paratenic hosts are not uncommon, especially in Thailand and Hawaii [26, 29, 55].

EM is the hallmark of NAS, and finding more than 10% eosinophils in the CSF differential cell count suggests a differential diagnosis of helminthic EM that includes NAS, BAS, GNS, and extraparenchymal neurocysticercosis (Table 1) [37]. Microscopic cell counts of the CSF will typically show 100 to 5,000 leukocytes/mL, 0.1 to 0.9 (10 to 90%) of which will be eosinophils [37, 39]. CSF protein is usually elevated; glucose is normal or lowered; peripheral eosinophilia is inconsistent [37, 39].

A specific diagnosis of NAS can only be made by expert identification of *A. cantonensis* larvae in CSF or brain (or adult worms in the lungs), which happens infrequently [6, 38, 50, 55, 71]. Slom et al. could not identify *A. cantonensis* larvae in the CSF from 9 patients hospitalized in their reported case series of 12 patients with presumed NAS [64]. In most cases, only a presumptive serodiagnosis using immunological methods may be made by identifying antibodies against one or more antigenic polypeptides of *A. cantonensis* on enzyme-linked immunosorbent assays (ELISAs) or Western (or dot) immunoblot analyses of acute and/or convalescent phase serum samples [2, 5, 9, 13, 14, 19, 40, 51, 64]. The currently recommended immunological methods with the highest sensitivities and specificities for the laboratory differential diagnosis of 3 recently reemerging causes of EM (NAS, BAS, and GNA) are compared in Table 3 [5, 9, 13, 14, 19, 22, 40, 51, 64].

CT and MRI will often demonstrate nonspecific leptomeningeal enhancement in NAS [34, 35]. Contrast MRI may demonstrate both leptomeningeal enhancement

Parasites	Target antigens	Immunodiagnostic methods	Sensitivity (%)	Specificity (%)	Reference (footnote #)
<i>Angiostrongylus cantonensis</i>	204-kDa	ELISA-PCR	98	100	[9]
	31-kDa	Dot blot	100	100	[14]
	32-kDa	ELISA	“High”	100	[40]
<i>Baylisascaris procyonis</i>	L3 larva	ELISA, WB, immuno-fluorescent antibodies	NR	NR	[19]
	33-kDa	ELISA	NR	NR	[5]
	45-kDa	WB	NR	NR	[5]
<i>Gnathostoma spinigerum</i>	24-kDa	WB	100	100	[51]
	21-kDa	ELISA	100	100	[2]
	100-to-3-kDa	Dot blot	100	100	[13]

ELISA: enzyme-linked immunosorbent assay; NR: not reported; PCR: polymerase chain reaction; WB: Western blot.

Table 3: Immunological methods for the differential diagnosis of three reemerging helminthic causes of eosinophilic meningoencephalitis (EM)^{40–47}.

and multiple punctuate areas of enhancement scattered throughout the brain reflecting dying larvae and host inflammatory reactions [27, 34, 35]. The absence of scattered focal cystic lesions on CT and the combination of meningeal and punctuate parenchymal enhancement on MRI may help to differentiate NAS from neurocysticercosis and cerebral GNA [27, 34, 35].

Since most cases of NAS resolve spontaneously, treatment is often supportive and nonspecific. Headaches will frequently improve after corticosteroid therapy and/or lumbar puncture with CSF drainage [10, 37, 64]. The antihelminthics, albendazole and praziquantel, will cross the blood-brain barrier and are effective larvicides, but may precipitate an inflammatory host reaction to dying larvae that aggravates headache and meningismus [72]. Adjunctive corticosteroids may ameliorate this inflammatory response and improve headaches, but do not apparently alter the typically benign course of NAS. Repeated lumbar punctures and corticosteroid therapy did improve symptoms in two of three patients with severe headaches in the NAS outbreak series reported by Slom et al. [64].

In a recent randomized, prospective, placebo-controlled, double blind study of albendazole therapy for NAS, Jitpimolmard et al. in Thailand administered 15 mg/kg/day for two weeks to 34 study patients with EM from NAS and an identical placebo for two weeks to 32 control patients with EM from NAS [31]. The authors reported the following results: (1) the number of patients with persistent headaches was significantly less ($P = .08$) in the treatment group ($n = 7$) than in the control group ($n = 13$) [31]; (2) the mean duration of headache was significantly shorter ($p = 0.05$) in the treatment group ($n = 8.9$ days) than in the control group ($n = 16.2$ days) [31]; (3) no serious adverse drug reactions were observed [31]. The authors concluded that a two-week course of albendazole therapy may reduce the duration of severe headache in EM caused by NAS without serious sequelae from inflammatory host responses to dying larvae [31]. Although this study was compromised

by small sample size, it was very well designed, conducted in Thailand where *A. cantonensis* is epizootic and serodiagnostics are readily available, and suggested that albendazole therapy should not be withheld from patients with active NAS for fear of inducing host inflammatory reactions [31]. Nevertheless, NAS usually resolves spontaneously without specific pharmacotherapy with albendazole, and exhibits a much more benign course than BAS with the highest case fatality rate for helminthic EM.

3.6 The ecology and pathobiology of baylisascariasis

Baylisascaris species roundworms are common intestinal parasites of many wild vertebrates, with *Baylisascaris procyonis*, the raccoon roundworm, being a frequent parasite of raccoons in North America [16, 65]. All species require intermediate hosts, usually small mammals and birds that become infected after ingesting embryonated eggs in raccoon feces [16, 65]. The eggs then hatch and release larvae in the intestines of the intermediate or paratenic hosts and migrate to various tissues, including the CNS, but do not develop into adult worms. Only when raccoons eat paratenic hosts with encysted larvae do the larvae mature into adults in the raccoon intestinal tract, mate, and release their unembryonated eggs in raccoon feces. Within 2–4 weeks, the environmentally stable eggs embryonate and contain infective-stage larvae restarting the parasite's life cycle (Figure 2).

Humans, particularly infants and young children, may interrupt this life cycle by coming in contact with raccoon feces in communal latrine sites and inadvertently ingesting embryonated eggs containing infective *B. procyonis* larvae [4, 11, 20, 53]. Humans are dead-end hosts in which wandering larvae seek to mature to adulthood in the eyes and/or the CNS. These migrating larvae can cause ocular and/or neural larva migrans with eosinophilic meningoencephalitis and severe neurologic deficits, including blindness, seizures, and coma [46, 49].

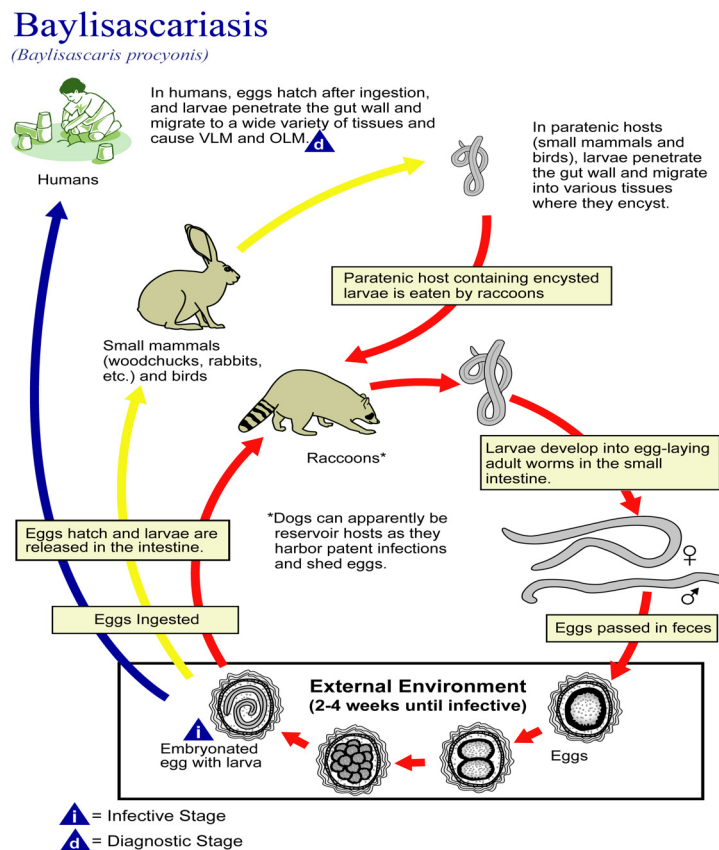


Figure 2: The life cycle of the raccoon roundworm, *Baylisascaris procyonis*. Source: CDC Public Health Image Library (PHIL), Image ID # 3381. No copyright permission required.

3.7 The epidemiology of baylisascariasis

The first report of *B. procyonis* infection in raccoons in the US was made in New York state in 1931 [44]. Although the earliest case of baylisascariasis (BAS) was reported from Missouri in 1975, the first fatal human case of BAS was reported in 10-month-old child from Pennsylvania in 1984 [4, 16, 28]. BAS is transmitted by the fecal-oral route and has occurred only in infants and children in raccoon-endemic areas with a median age of 13 months [20, 28]. Until 2003, most cases of BAS in the US were reported in the northern US from New York in the east to California in the west, with one case reported from the southern US in New Orleans, Louisiana (Table 2) [4, 11, 16, 20, 52, 53].

In 2003, Eberhard et al. reported that 11 (22%) of 50 raccoons trapped in DeKalb County, Georgia, within the Atlanta metropolitan area, during spring 2002 were intestinally infected with mating *B. procyonis* roundworms and had unembryonated eggs in their feces [15]. The authors concluded that the distribution of *B. procyonis*-infected raccoons had now extended into the southeastern US and posed significant risks of BAS in humans, especially

infants and young children, encountering raccoon latrine sites near residential neighborhoods, and inadvertently ingesting infective *B. procyonis* eggs [15].

In 2003, Sato et al. investigated the first outbreak of BAS in Japan in domestic rabbits in a small wildlife park and petting zoo (Table 2) [61]. The park also housed a 12-member North American raccoon population, one of which had been donated to the park by an exotic pet owner eight weeks prior to the BAS outbreak in rabbits [61]. The authors noted that the donated raccoon and two of the long-term resident raccoons were shedding *B. procyonis* eggs in their feces [61]. Despite immediate control methods including antihelminthic treatment of animals and rigorous environmental sanitation, recurrent ascarid infections occurred in three young raccoons three months after control methods were instituted [61].

The authors reached the following conclusions regarding the epidemiological aspects of the outbreak: (1) the North American raccoon donated by the exotic pet owner was the likely source of the outbreak, which spread quickly throughout other raccoons and rabbits in the wildlife park [61]; (2)

despite aggressive control strategies, the outbreak was difficult to contain environmentally and resulted in recurrent infections in raccoons [61]; (3) the outbreak posed a serious threat of zoonotic BAS to wild and domestic animals in Japan [61]; (4) the outbreak also posed a risk of human BAS to the park and its petting zoo visitors, especially infants and young children at greater risks of fecal-oral transmission of BAS [61]; (5) lastly, pet owners should be discouraged from owning imported exotic pets, such as North American raccoons, which are also zoonotic reservoirs of rabies [61].

Also in 2003, Roussere et al. assessed the potential for BAS in three northern California communities by collecting fecal samples from 215 raccoon latrine sites [58]. The authors reported that 44%–53% of the latrine sites in the 3 regions contained *B. procyonis* eggs and that 16%–33% contained environmentally stable, fully embryonated, and infective eggs, capable of causing BAS [58]. The authors made the following conclusions based on their findings: (1) the presence of *B. procyonis* eggs in raccoon latrines was very high [58]; (2) raccoon latrines were commonly located near residential sites, especially on rooftops, chimneys, lawns, tree stumps, tree forks, woodpiles, decks, and steps [58]; (3) humans living or visiting areas with high raccoon densities would have increased opportunities to come in contact with raccoon latrine sites containing infective *B. procyonis* eggs [58]; (4) public health authorities in areas of high *B. procyonis*-infected raccoon densities should consider informing the public about the risks of contracting BAS, reducing the availability of human food sources for raccoons near residences, such as outdoor pet food bowls and uncovered garbage, and decreasing raccoon densities in residential areas by trapping and relocation of raccoons [58]. Since raccoons are accustomed to humans and often visit home exteriors at night, visitors staying in rustic mountain cabins throughout North America are also likely to encounter raccoons and their latrines, and should practice frequent hand washing before eating and after trekking or gathering firewood.

Human cases of BAS with EM and/or ocular larva migrans have been steadily increasing in the US since the earlier reports of nonfatal and fatal BAS in 1975 and 1984, respectively [4,7,11,16,20,28,46,49,53]. To date, the case fatality rate for BAS is 29.4% ($n = 5$); the permanent neurologic morbidity rate is 70.5% ($n = 11$); there is only one case of full recovery from presumed BAS in a 4-year-old boy from a New Orleans, Louisiana neighborhood frequented by raccoons in 2004 [4,7,11,16,20,28,44,46,49,52,53]. Thus, BAS has the highest case fatality rate of the 3 reemerging causes of helminthic EM distributed by international commerce; has a large animal reservoir in indigenous, North American and imported, North American raccoons that are completely accustomed to living near humans, either in the wild or in petting zoos.

3.8 The clinical manifestations and management of baylisascariasis

Following a presumed incubation period of 1–3 weeks, neurotropic larvae emerge from infective eggs in the gastrointestinal tract, penetrate the circulatory system, and migrate to the CNS seeking to mature to adulthood, usually in the eyes or brain and causing intense peripheral and CSF eosinophilia. Infants will present initially with lethargy and obtundation, progressing to paralysis and coma. *B. procyonis* larvae have been observed in the retinas of patients with diffuse unilateral subacute neuroretinitis (DUSN), and in the brains of infants dying from BAS-associated EM [4,16,28,46]. Nevertheless, the definitive diagnosis of BAS can only be made by expert identification of the parasite in tissues and not simply by slit lamp observation in the retina [46]. Since the parasite does not mature and reproduces in humans, microscopic examination of stool specimens will be negative for the parasite's unembryonated eggs.

Neuroimaging findings in BAS are nonspecific and may manifest leptomeningeal enhancement, diffuse cerebral edema, and cerebellar edema [7,20,49,53,59]. The serological diagnosis of BAS-associated EM and diffuse unilateral subacute neuroretinitis (DUSN) may be presumed by identifying rising antibody titers in acute and convalescent sera and CSF samples using indirect immunofluorescence assays and enzyme-linked immunosorbent assays (ELISAs), which may not be uniformly available (Table 3) [5,16,19].

Treatment for BAS is both supportive with mannitol diuresis, corticosteroids, and hyperventilation for cerebral edema and specific with albendazole 10 mg/kg every 12 hours [7,15,20,28,49,53,58,59,61]. Early treatment with albendazole after egg ingestion, but before the onset of symptoms, has been shown to prevent the development of BAS in experimental animals [20]. As in other cases of EM from neural larva migrans, such as NAS, albendazole may worsen neurologic outcomes by increasing the host's inflammatory response to dying larvae and combined therapy with albendazole, and corticosteroids is usually recommended [7,20,49,53]. Since there has been only one case of complete neurological recovery in an infant with BAS, the outcomes of BAS even with intensive therapy have been poor [52].

3.9 The ecology and pathobiology of gnathostomiasis

Originally confined to Southeast Asia and Japan, gnathostomiasis (GNS) is acquired by eating raw or undercooked foods, infected with third-stage larvae of the roundworm, *Gnathostoma spinigerum* [12,32,47,60]. *G. spinigerum* is a common roundworm of wild and domestic cats, dogs, and other carnivores that coils within submucosal tumors in the stomach of definitive hosts, mates and releases eggs in the

host's feces. The eggs embryonate into first-stage larvae in fresh or brackish water ecosystems and are ingested by small crustacean intermediate hosts, which become prey for larger predators including fish, shrimp, crabs, crayfish, frogs, and snakes. The larvae mature into infective third-stage larvae in these transport or paratenic hosts, encyst in tissues, but do not develop into adults; unless the paratenic hosts are consumed by definitive carnivorous hosts. Once infective larvae are consumed by predators, they will mature into adults in the stomach and restart the parasite's life cycle (Figure 3). Since humans are not the natural definitive hosts, infective larvae consumed by humans in raw foods will not develop into adults, but will penetrate the gastrointestinal tract and migrate hematogenously causing cutaneous and/or visceral larva migrans in any organ system [12,32,47,60].

Typically, the most common foods containing infective larvae have included fish, shrimp, crab, crayfish, frog, snake, and chicken [15,28,47,58,59,61]. However, most human cases have followed consumption of raw (*sashimi*) or marinated (*ceviche*) fish or shellfish [15,28,47,58,59,61]. Today, the parasite's range of distribution is worldwide with cases reported from Australia, Bangladesh, China, Cuba and throughout the Caribbean, Europe, India, New Zealand, the US, and throughout Central America (notably Mexico) and South America (notably Ecuador) (Table 2) [12,32,47,60].

3.10 The epidemiology of gnathostomiasis

In 2003, Moore et al. first recognized GNS caused by *G. spinigerum* as an emerging imported helminthic infection in the UK in their case series of 16 patients treated over a 12-month period (April 1, 2000–March 31, 2001) at the Hospital for Tropical Diseases in London [47]. In their series, the median incubation period was 12 months; peripheral eosinophilia was present in seven (44%) of the sixteen patients and was not a reliable screening tool [47]. Cases presented with a myriad of symptoms ranging from migratory cutaneous swellings (also known as Yangtze edema in Asia, or nodular eosinophilic migratory panniculitis in the US) to eosinophilic gastritis [47]. The authors concluded that GNS was often misdiagnosed as rheumatic disease, demonstrated a prolonged incubation period due to the relapsing nature of the disease and was an emerging disease in international travelers as a direct result of adventurous eating habits in highly endemic regions, often popular tourist destinations [47].

Today, GNS remains common in southern China, Thailand, and Bangladesh. GNS is becoming more common throughout Latin America and the Caribbean and is most often described in the US in Southeast Asian immigrants and Mexican border residents (Table 2) [12,32,47,60]. A diagnosis of GNS should now be considered for all patients

with a history of travel to endemic regions and migratory cutaneous swellings, eosinophilic gastritis, or a combination of cutaneous swellings with any manifestations of neural larva migrans, especially eosinophilic meningoencephalitis and migratory radicular pain or radiculomyelitis [12,32,47,60].

3.11 The clinical manifestations and management of gnathostomiasis

The infective inoculum for GNS is small, often 1–2 larvae. As soon as the raw paratenic host containing infective larvae is ingested and reaches the stomach, a syndrome of severe epigastric pain, nausea, and vomiting begins and lasts for 2–3 weeks, before resolving completely [12,32,47,60]. This prodrome is often dismissed as transient food poisoning, misdiagnosed as acute appendicitis or mesenteric adenitis, and frequently under-reported, unless intestinal obstruction ensues [12,32,47,60]. The prodrome may be consistent with larval penetration of the intestinal wall and larval migration through the portal venous system to the liver [12,32,47,60]. A prolonged incubation period then ensues, with a median of 12 months (range 3 weeks to 5 years) in the case series reported by Moore et al. [47]. Ultimately, one or more larvae may reemerge seeking to mature in any tissue and causing cutaneous, visceral, ocular, or neural larva migrans or any combination of larva migrans [12,32,47,60].

In addition to a prolonged incubation period and the migratory nature of disease, another pathognomonic feature of GNS is a radiculomyelitis characterized by initial painful radiculopathy followed by paralysis of one or more extremities and felt due to larvae migrating to the spinal cord via spinal nerves [47,56]. Besides EM and radiculomyelitis, neural or cerebral GNA has also caused radiculomyeloencephalitis and subarachnoid hemorrhage [47,56,63,66].

Most fatal cases of GNS have been associated with neural larva migrans and EM with eosinophils comprising over 50% of the CSF cell count [47]. Peripheral eosinophilia, however, is not a constant finding in GNS [47]. Moore et al. reported peripheral eosinophilia in seven of sixteen patients (44%) treated for GNS and concluded that peripheral eosinophilia could not be relied upon as a screening tool for GNS, but could, instead, serve as a reliable marker of relapse in cases with eosinophilia at baseline [47]. In their series, peripheral eosinophilia preceded the onset of symptoms in 3 patients who required a second course of albendazole therapy for relapses [47].

G. spinigerum larvae are large, 2.5 mm–12.5 mm in length and 0.5–1.2 mm in width and can be visualized through the skin in cases of cutaneous larva migrans and in the retina in ocular larva migrans. The definitive diagnosis of GNS can only be made by recovery of the larvae or by expert

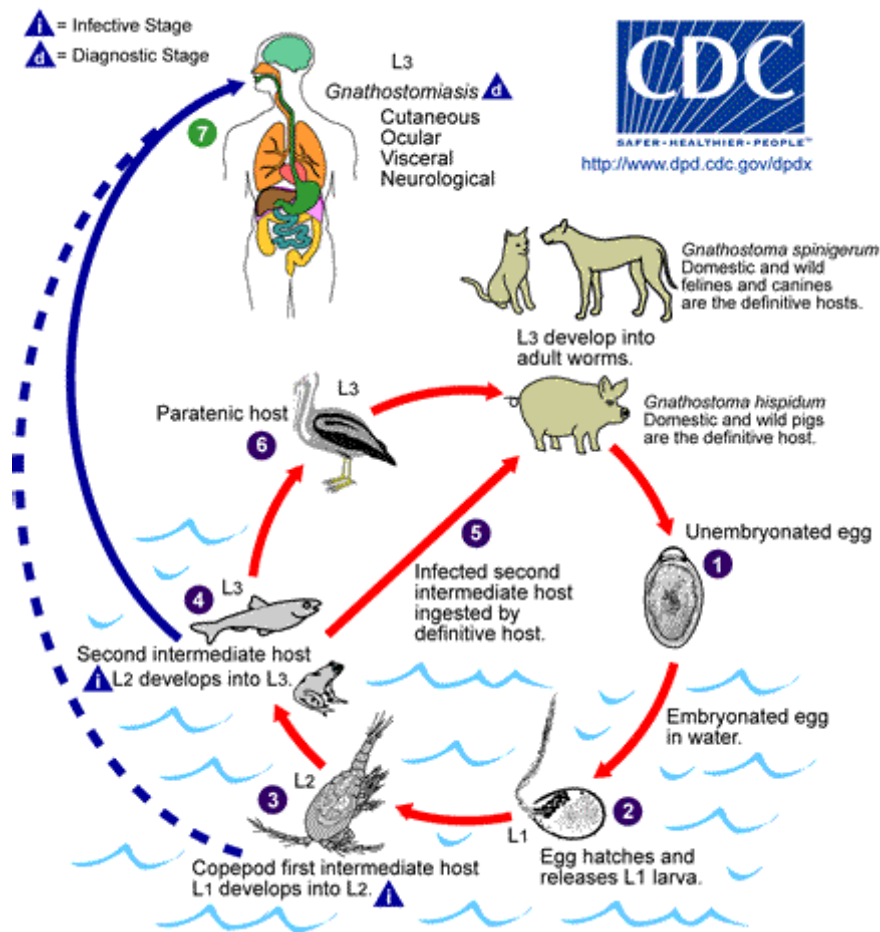


Figure 3: The life cycle of *Gnathostoma spinigerum*. Source: CDC Image, available at <http://www.dpd.cdc.gov/dpdx>. No copyright permission required.

identification of the larvae in tissues. Superficial larvae can be recovered from squamous epithelium for precise diagnosis by skin scrapings or snips, and subcutaneous larvae can be recovered from pruritic, indurated, and erythematous swellings by skin biopsies. These migratory subcutaneous swellings may mimic rheumatoid nodules or Calabar swellings of loiasis in travelers to sub-Saharan Africa, where parasite distribution ranges overlap [47]. In such cases, rheumatoid arthritis can be excluded by rheumatoid factor and antinuclear antibody tests and loiasis can be excluded by daytime peripheral blood smears for microfilaria or microfilarial ELISA [47]. In addition to recovery from skin, subcutaneous tissues, and CNS, *G. spinigerum* larvae have been recovered from the eyes, lungs, muscles, and gastrointestinal tract [47].

Neuroimaging studies are nonspecific and nonconfirmatory, but will compliment serological studies for presumptive diagnoses of gnathostomiasis [63,66]. Sithinamsuwan

and Chairangsaris reported multiple, noncontrast enhancing worm-like lesions in both cerebral hemispheres and the cerebellum on MRI of the brain in an 18-year-old man presenting with a one-month history of migratory skin swellings followed by headache, ataxia, and left-sided hemiparesis [63]. The CT of the brain was non-specific and demonstrated cerebral edema only [63]. The patient reported consuming raw freshwater fish in his diet, and the immunoblot assay of CSF identified reactive antibodies to a specific 24-kD antigenic polypeptide band diagnostic of gnathostomiasis (Table 3) [63]. The authors concluded that MRI may provide better neuroimaging of cerebral larval migration in GNS than CT and that a combination of positive neuroimaging and immunoblot studies would be required for presumptive diagnosis of GNS in cases in which larvae could not be recovered for definitive diagnosis [63]. Ribosomal DNA sequencing has been used to identify the *Gnathostoma* species that can cause gnathostomiasis in the Americas and may offer a more definitive diagnostic tool than neuroimaging and immunoblot assay [1]. Unfortunately, neither rDNA sequencing nor the 24-kD

immunoblot assays are uniformly available, and clinicians should rely on combinations of history of exposure in endemic regions, positive neuroimaging, and parasite identification for definitive diagnoses of GNS in most cases (Table 3).

The treatment of GNS with albendazole is usually straightforward except in cases of neural larval migrans or cerebral GNS, where brain edema could be aggravated by the host's inflammatory response to dying larvae [12,32,47,60]. In such cases, corticosteroids may be administered alone (prednisolone, 60 mg per day for seven days) as the larvae migrate and then die naturally [12,32,60]. The reported efficacy of albendazole, 400 mg twice a day for 21 days, in the treatment of gnathostomiasis is over 90%, and a similar therapeutic efficacy has been reported for ivermectin [12,32,47,60]. As in the case series reported by Moore et al. some patients may relapse and require a second course of albendazole therapy with relapses often heralded by peripheral eosinophilia [47]. Moore et al. concluded that a lack of migratory symptom recurrence within a median incubation period of 12 months and the resolution of peripheral and CSF eosinophilia should be accepted as presumptive evidence of cure of GNS [47].

4 The control and prevention of helminthic eosinophilic meningoencephalitis

There are no human or veterinary vaccines for the primary prevention of the helminthic diseases that can cause EM. Screening tests for helminthic diseases, such as neuroimaging, serological assays, such as ELISAs and immunoblots, and DNA sequencing are expensive and not uniformly available (Table 3). The wild animal reservoirs for some of the helminthic diseases that can cause EM may be difficult to monitor and to contain, such as the raccoon reservoir of *B. procyonis* and the rodent reservoir of *A. cantonensis*.

Current "survivor" television programs and movies often feature the consumption of raw amphibians, fish, mollusks, reptiles, and unwashed fruits and vegetables that can serve as paratenic hosts or conceal the paratenic hosts that can cause helminthic EM. In addition to popular "survivor" programming, adventurous and exotic eating habits, including the consumption of marinated (*ceviche*) or raw (*sashimi*) crustaceans and fish may also expose individuals to the paratenic hosts that cause helminthic EM. Finally, juvenile behavior, as promoted on cartoon and adolescent television networks, may prompt individuals to consume raw amphibians, fish, and mollusks on a dare or a bet and may unnecessarily expose people to the risks of helminthic EM, as reported in two NAS cases in Louisiana [6,50].

The best methods to prevent and to control the helminthic causes of EM will include informing residents and travelers of regional hyperendemic disease risks, educating the public about proper food washing and cooking,

and reducing risk factors for fecal-oral transmission in infants and children (Table 2). For example, effective prevention and control strategies for NAS include the following: (1) educating citizens and travelers in endemic areas that snails, slugs, freshwater fish and shrimp, frogs, and crabs must be cooked thoroughly, not simply marinated or refrigerated before being eaten; (2) washing all fruits and vegetables before eating them uncooked; (3) washing hands after handling pet African land snails (*Achatina fulica*) or cleaning out their terrariums; (4) reducing and controlling the definitive host rodent populations with rodenticides; (5) reducing and controlling snail and slug paratenic host populations with molluscicides.

Prevention and control strategies for BAS include the following: (1) informing the public about the frequent risks of encountering raccoons and their latrines filled with infective eggs often located close to residential areas, where food is plentiful; (2) discouraging raccoon access to home sites and neighborhoods by not leaving pet food outdoors and keeping outdoor garbage in sealed containers; (3) discouraging keeping raccoons as domestic pets or importing raccoons as exotic pets; (4) recognizing the risks of hand-to-mouth behaviors in infants and young children while outdoors and practicing frequent hand washing; (5) recognizing that infective eggs are environmentally stable and resistant to common household disinfectants including ammonia, bleach, and chlorhexidine and can only be removed from the hands by vigorous soap and water washing and not simply by hand sanitizers [58]; (6) controlling raccoon populations in residential areas with trapping and relocation programs.

Prevention and control strategies for GNS include the following: (1) educating citizens and travelers in endemic areas that fish, shrimp, crayfish, frogs, crabs, and chicken must be cooked thoroughly first and not eaten raw, marinated, or refrigerated; (2) seeking medical care immediately for evaluation of persistent nonspecific gastrointestinal illnesses or migratory subcutaneous swellings.

5 Conclusions

The helminthic causes of EM today are primarily the result of emerging epizoonoses that have now been distributed worldwide by international commerce and travel. Other factors responsible for these emerging helminthic infections of the CNS include mass immigration, lifestyle and place of residence choices, food preferences, eating habits, world travel, and human behaviors. Frequent travelers may be predisposed to helminthic EM by several unique behavioral factors including (1) their exotic eating habits abroad and a willingness to eat unfamiliar cuisine raw or undercooked; (2) a relaxing of sanitary habits practiced at home, especially frequent hand washing; (3) unfamiliarity with local zoonotic reservoirs of infectious diseases; (4)

a preference for wilderness, tropical island, and isolated beach resorts that are also home to rodent and other zoonotic reservoir hosts of EM-causing helminths.

Although intracranial hardware and appliances, especially VP shunts, are the most common causes of EM, clinicians should include the emerging helminthic causes of EM in their differential diagnosis of EM. In addition, clinicians should order appropriate neuroimaging and immunological studies and consider early supportive, specific, and adjunctive pharmacotherapy to improve neurological outcomes (Table 3). Public health authorities must upgrade surveillance programs for zoonotic diseases, monitor the exotic animal trade, improve rodent and wild animal control programs, and discourage adventurous eating habits and risky “survivor”-like behaviors, especially in frequent travelers.

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